ORGANIC REACTION MECHANISMS · 2006

An annual survey covering the literature dated January to December 2006

Edited by

A. C. Knipe

University of Ulster

Northern Ireland

An Interscience® Publication

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Preface

The present volume, the forty-second in the series, surveys research on organic reaction mechanisms described in the available literature dated 2006. In order to limit the size of the volume, it is necessary to exclude or restrict overlap with other publications which review specialist areas (e.g. photochemical reactions, biosynthesis, electrochemistry, organometallic chemistry, surface chemistry and heterogeneous catalysis). In order to minimize duplication, while ensuring a comprehensive coverage, the editor conducts a survey of all relevant literature and allocates publications to appropriate chapters. While a particular reference may be allocated to more than one chapter, it is assumed that readers will be aware of the alternative chapters to which a borderline topic of interest may have been preferentially assigned.

In view of the considerable interest in application of stereoselective reactions to organic synthesis, we now provide indication, in the margin, of reactions which occur with significant diastereomeric or enantiomeric excess (*de* or *ee*).

Unfortunately the personal circumstances of an author resulted in an unexpected delay in publication of this volume, for which we apologise. The next volume is expected to be published in the same year and steps have been taken to ensure that the delay between title year and publication date will be further reduced thereafter.

I wish to thank the production staff of John Wiley and Sons and the team of experienced contributors for their efforts to ensure that the review standards of this series are sustained.

CONTENTS

CHAPTER 1

Reactions of Aldehydes and Ketones and their Derivatives

B. A. MURRAY

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Organic Reaction Mechanisms 2006. Edited by A. C. Knipe

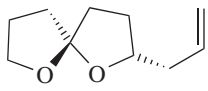
Formation and Reactions of Acetals and Related Species

Chemoselectivities in the acetalization of *p*-nitro- and *p*-hydroxy-benzaldehyde have been studied for a range of bisnucleophiles, XCH_2CH_2Y (X, Y = OH, OH; SH, SH; SH, OH; and SH, NH).[1] The relative yields of products have been analysed in terms of atomic charges, Parr's global electrophilicity descriptor (w), and Pearson's hard–soft acid–base concept; such a global electrophilicity descriptor has also been used to explain acetalizations and thioacetalizations of substituted benzaldehydes, although it cannot handle steric factors.[2]

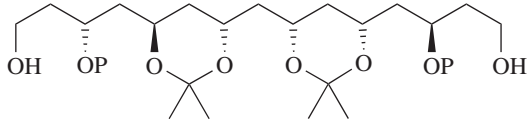
Pd[(−)-sparteine]Cl_2 catalyses the conversion of styrenes to their Markovnikov dialkyl acetals.[3] Deuterium labelling studies suggest an enol ether mechanism involving a Pd–H species.

The Eberlin reaction – polar acetalization and transacetalization in the gas phase – has been reviewed (249 references).[4] In addition to a detailed mechanistic treatment, several analytical applications are described, as are atmospheric pressure variants, relationships with condensed-phase reactions, and other gas-phase processes closely related to acetalization. Another review covers similar ground.[5]

Enantiopure 1,6-dioxaspiro[4.4]nonanes [e.g. (**1**)] have been prepared from an *α*-hydroxy-*ω*-ene ketone, using a camphor–selenide auxiliary.[6] (*de*) (*ee*)



(**1**)



(**2**)

Differentiation of 1,3-*anti*- and -*syn*-diols has been achieved via the selective hydrolysis of an *anti*-1,3-acetonide (**2**) containing an adjacent *syn*-acetonide.[7] (*de*)

Gallium(III) chloride catalyses two useful reactions that employ isocyanides as a C_1 source: (i) an insertion into a C−O bond of an acetal and (ii) a 4 + 1-cycloaddition of *α*,*β*-unsaturated carbonyl compounds. The catalysis appears to depend on the low affinity of $GaCl_3$ for heteroatoms.[8]

The reagent $BH_3.NMe_3$–$AlCl_3$ has been used to bring about reductive opening of acetals.[9] With mixed phenolic–benzylic acetal as reactant, the reagent acts regioselec-

tively (in THF at 0 °C), yielding a benzylic ether and free phenol, probably because the borane first associates with the more basic benzylic oxygen. Conditions to bring about the inverse opening are being sought.

Reactions of Glucosides and Nucleosides

A detailed experimental and computational study of the anomerization of glucose in water has been undertaken.[10] Following measurement of kinetic isotope effects (KIE) on rate constants for approach of α-glucopyranose to its equilibrium with the β-anomer, these were converted into unidirectional KIEs using equilibrium isotope effects. Saturation transfer ^{13}C NMR spectroscopy then yielded the relative free energies of the transition states (TS) involved. Modelling, constrained by all the KIEs measured, then gave the anomerization TSs. Key findings include the observation that only one water molecule is required to participate, and that it must not hydrogen bridge OH(1) and O(5) simultaneously in either TS.

The mechanistic role of nucleotides in directing the growth of IR-emitting semiconductor nanocrystals has been investigated for a range of nucleotides, concentrations, stoichiometries, and temperatures.[11]

Reactions of Ketenes and Ketenimines

A short review of the first 100 years of ketene chemistry covers haloketenes, Wolff rearrangements, stereoselective nucleophilic attack, dimerization, cycloadditions, ketene-Claisen and -Cope reactions, bisketenes, and free radical processes.[12] (*de*) (*ee*)

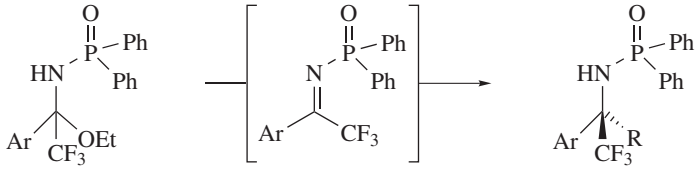
Two series of ketenimines, Ph–CH=C=N–Ph–*p*-R and *p*-R–Ph–CH=C=N–*i*-Pr, have been aminated with butylamine, with UV monitoring allowing rate measurement and hence construction of Hammett plots for each ring system.[13] Addition to the C=N bond to give vinylidenediamine intermediate is followed by tautomerization to amidine product. A switchover in rate-determining step is observed. Calculations indicate that the *N*-aromatic group provides significant electronic stabilization to the first TS.[14]

Formation and Reactions of Nitrogen Derivatives

Imines: Synthesis and Tautomerism

Erbium(III) triflate is an efficient catalyst in the synthesis of aldimines, ketoimines, and enaminones.[15] For aromatic imines, the problem of Michael addition found with the $CeCl_3$/NaI-catalysed addition to unsaturated aldehydes is avoided.

An *N*-phosphinoylhemiaminal (**3**) has been used as a precursor to trifluoromethylketimines (**4**); *in situ* alkylation with a dialkylzinc in the presence of a diphosphine monoxide auxiliary gives chiral α,α,α-trifluoromethylamines (**5**) in high yield and *ee* up to 99%.[16]

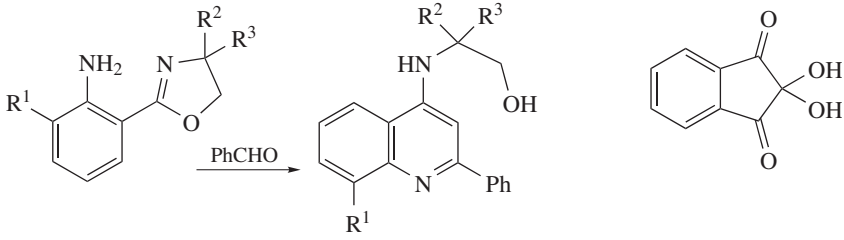


(**3**) (**4**) (**5**)

The Skraup–Doebner–Von Miller synthesis of quinolines – involving condensation of an aniline with an α,β-unsaturated ketone – has been investigated using ^{13}C-labelled ketones in cross-over experiments: a complex fragmentation–recombination mechanism involving imine intermediates is indicated.[17]

In another synthesis of quinolines involving imine intermediates, *o*-oxazoline-substituted anilines (**6**) react with ketones in dry butanol reflux to give 4-amino-substituted quinolines [e.g. (**7**)], or 4-quinolones, using tosic acid as catalyst.[18] A mechanism involving ketoimine formation with subsequent tautomerization to give an enamine which attacks the oxazoline ring is discussed.

A related one-pot, three-component synthesis of β-amino carbonyl compounds has been achieved using a cascade reaction of anilines with aromatic aldehydes and carbonyl compounds, catalysed by zinc triflate.[19] (*de*)



(**6**) (**7**) (**8**)

An enantioselective one-pot, three-component imino-Reformatsky reaction has been reported.[20] Combining a benzaldehyde, an aniline, and an alkyl bromoacetate ester, *ee*s of up to 92% have been achieved in the β-amino ester product, using a recyclable *N*-methylephedrine as auxiliary. A nickel(II) salt and dimethylzinc are employed: the latter serves as dehydrating agent, reductant, and coordinating metal. (*ee*)

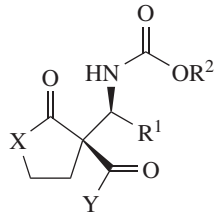
The kinetics and mechanism of the reaction of glycylglycine[21] and of valine[22] with ninhydrin (**8**) have been studied in aqueous micellar media.

Cis–trans isomerization in benzylideneaniline (PhCH=NPh) has been found by computation to involve a single TS, and conformers leading to each isomer have been identified. However, kinetic selectivity of the two conformers depends on the reaction dynamics.[23]

The Mannich Reaction

Most reports in this category deal with asymmetric processes. For example, classic Mannich reaction of unmodified ketones, aqueous formaldehyde, and aromatic amines produces α-aminomethylation of the ketones in >99% *ee*, using L-proline as catalyst.[24] (*ee*) Methyl ketones regioselectively reacted on the methylene carbon. The method is simple, using wet solvents in the presence of air.

Direct Mannich reactions of cyclic 1,3-dicarbonyls with acyl imines, R^1–CH=N–CO_2R^2, gives α-quaternary-carbon-bearing products (**9**; X = CH_2, O; Y = Me, OMe, OEt) with yield/*de*/*ee* up to 98/90/99%, using cinchona alkaloid catalysts.[25] (*de*) (*ee*)



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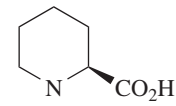
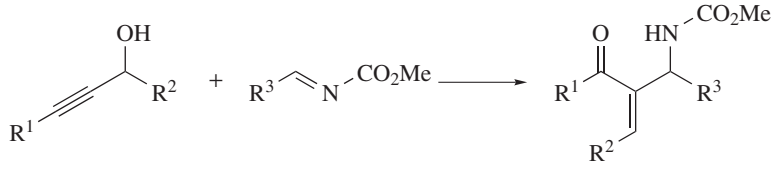


(**10**)

Mannich reactions between aldehydes and *N*-*p*-methoxyphenyl-protected α-imino ethyl glyoxylate (PMP−N=CH−CO_2Et) give high *ee*s using (*S*)-pipecolic acid (**10**) as catalyst, but low *de*s.[26] (*S*)-Proline also gives high *ee*, but also predominantly *syn* product. Calculations indicate that the transition structures involving the s-*cis*- and s-*trans*-enamine intermediates are much closer in energy in the case of catalyst (**10**). (*de*) (*ee*)

A highly enantioselective direct Mannich reaction of simple *N*-Boc-aryl and alkyl-imines with malonates and β-keto esters has been reported.[27] Catalysed by cinchona alkaloids with a pendant urea moiety, bifunctional catalysis is achieved, with the urea providing cooperative hydrogen bonding, and the alkaloid giving chiral induction. With yields and *ee*s up to 99% in dichloromethane (DCM) solvent, the mild air- and moisture-tolerant method opens up a convenient route to *N*-Boc-amino acids. (*ee*)

Several other asymmetric Mannich-type processes have been described. Propargyl alcohols (**11**) undergo an addition to imines (**12**), to give 2-acylallylic carbamates (**13**), using an oxovanadium catalyst.[28] The reaction always gave the (*Z*)-enone, but a trial with a chiral propargyl alcohol showed virtually no enantioselectivity. (*ee*)



(**11**) (**12**) (**13**)

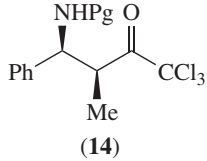
N-Sulfonylaldimines undergo Mannich-type addition to silyl enol ethers of ketones, giving β-amino carbonyl derivatives in up to 93% *ee* in the presence of a chiral ferrocene bearing *S*- and *P*-substituents complexed to copper(II).[29] (*ee*)

β-Aminocarbonyl compounds have been prepared via Lewis base-catalysed Mannich reaction of TMS enol ethers and *N*-tosylaldimines, ArCH=N−Ts, with excellent *anti* selectivity in some cases.[30] (*de*)

A zinc–bis(BINOL) complex has been employed to effect chemoselective enolate formation from an α-hydroxy ketone (in the presence of an isomerizable imine) to give a Mannich-type product in high *ee*.[31] (*de*) (*ee*)

Chiral *syn*-β-amino esters have been prepared by addition of titanium ester enolates to aldimines containing an (*R*)-α-methylbenzylamine moiety.[32] (*de*)

Benzaldimines bearing *N*-protection react diastereoselectively in a direct catalytic Mannich-type transformation with a trichloromethyl ketone donor, Me–CH_2–C(=O)–CCl_3, using a Lewis base catalyst, lithium *p*-methoxyphenoxide, to give *syn*-amino ketone (**14**, in protected form).[33] Subsequent carbonyl reduction of (**14**) to give the carbinol sets up ring closure to azetidines, with the trichloromethyl moiety as the leaving group. (*de*)



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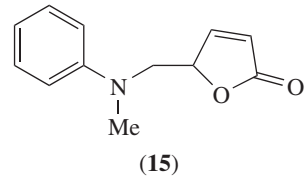


(**15**)

Two redox-Mannich conversions have been described. A direct asymmmetric reductive reaction produces three contiguous stereocentres with high chemo-, diastereo-, and enantio-selectivity.[34] An oxidative Mannich reaction has been employed to form a γ-aminoalkylbutenolide (**15**).[35] Starting with *N*,*N*-dimethylaniline, C−H oxidation yields iminium ion, which is then intercepted with 2-triisopropylsilylfuran as nucleophile. Carried out in T-HYDRO reagent (70% *t*-BuOOH in water) in the presence of air, dirhodium caprolactamate [$Rh_2(cap)_4$] catalyses the reaction, giving yields of up to 95% in a few hours, using methanol co-solvent at 60 °C. Evidence for the intermediacy of the iminium ion includes rapid formation of α-methoxyamine in the absence of the furan nucleophile. (*de*) (*ee*)

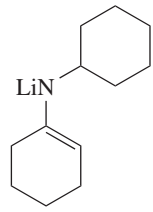
Addition of Organometallics

Schiff bases, Ar^1–CH=N–Ar^2, that are unreactive with triethylaluminium alone undergo ethylation in the presence of cerium(IV); the reaction site is the methine.[36] The sterically sensitive reaction is favoured by electron-donating substituents. Excess Et_3Al is required, or cleavage to aldehyde and amine results.

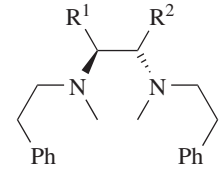
The structure of lithiated cyclohexanone *N*-cyclohexylimine (**16**) and its reactivity towards *C*-alkylation has been investigated experimentally and by DFT calculations.[37]

Formed from the imine using LDA in hexane, NMR studies reveal complex solvent-dependent distributions of monomers, dimers, and trimers in several ethereal solvents, although a mono-solvated dimer can be selected by appropriate choice of solvent. Study of *C*-alkylation rates suggests that both monomer- and dimer-based mechanisms operate. The lithioimines were compared with the isostructural lithium dialkylamides, but were shown to be *not* simply vinylogous analogues thereof.

(*S*)-*t*-Butylsulfinylferrocene has been added to a range of aryl- and alkyl-imines, via *o*-lithiation: some imines gave complete stereocontrol of the three stereocentres in the product, as shown by single-crystal X-ray analysis.[38] (*de*)



(**16**)



(**17**)

A pseudo-C_2-symmetric tertiary diamine derived from (1*S*,2*S*)-(+)-pseudoephedrine (**17**, R^1 = Me, R^2 = Ph) has been prepared and tested in the enantioselective addition of methyllithium to aromatic imines.[39] It shows comparable *ee* and better reactivity than a genuinely C_2-symmetric relative [**17**, R^1, R^2 = $-(CH_2)_4-$]. (*ee*)

A chiral rhodium(I)–diene complex catalyses the addition of dimethylzinc to *N*-tosylarylimines, ArCH=NTs, with *ee*s up to 98%.[40] (*ee*)

α-Aldiminoesters, R^1–N=CH–CO_2R^2, undergo diethylzinc addition to give the corresponding α-amino esters in high *ee* in the presence of a chiral titanium(IV) Lewis acid–Lewis base bifunctional catalyst.[41] (*ee*)

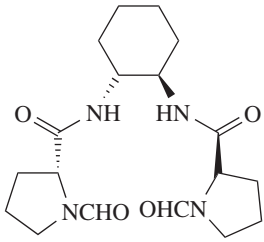
Other Alkylations and Allylations of Imines

Primary alkyl radicals have been generated from alkyl iodides (RCH_2I) using dimethylzinc and air as initiator; the radicals can then be used to alkylate *N*-tosylimines, ArCH=NTs, to give the corresponding amines, $ArCH(CH_2R)NHTs$.[42] The latter process is promoted by BF_3 etherate and catalysed by copper(II).

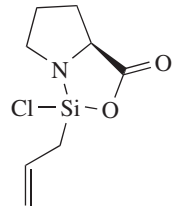
Di(*t*-butyl) tartrate has been used as an auxiliary to give asymmetric addition of alkynylzincs to nitrones, yielding optically active α-substituted propargylic *N*-hydroxylamines.[43] Addition of product-like *N*-hydroxylamine boosted *ee*s up to 95%. (*ee*)

A C_2-chiral bisformamide (**18**) derived from diaminocyclohexane catalyses the enantioselective allylation of simple aldimines, using allyltrichlorosilane in the presence of L-proline.[44] The more immediate allylating agent is, in fact, L-proline derivative (**19**), formed *in situ*, and observed by NMR and MS. (*ee*)

Phenols have been employed as directing groups in the enantioselective allylation of aldimines and ketimines using allylchlorosilane reagents.[45] (*ee*)



(**18**)



(**19**)

Ketoimines, including aromatic, heteroaromatic, and enolizable cases, have been allylated in a catalytic enantioselective process using CuF complexed with an axially chiral DuPHOS ligand and a non-toxic allylboronic pinacol ester as nucleophile.[46] Lithium isopropanoxide catalyses the reaction, and extensive ^{11}B NMR studies indicate that it does so by boosting formation of a copper alkoxyallylborate, $H_2C{=}CH{-}CH_2{-}B(pinacol)^{-}{-}^{+}OR$ (R = *i*-Pr), which then reacts with copper(I) to generate allylcopper, $H_2C{=}CH{-}CH_2{-}Cu$, as immediate nucleophile. Addition of *t*-butanol gives even better results, through formation of a similar intermediate with R = *t*-Bu. (*ee*)

Regio- and stereo-selective allylation of sulfonylimines has been carried out with trifluoro(allyl)borates and allylstannanes, using 'palladium-pincer' complexes as catalysts.[47] *Syn* products predominate, in contrast to the corresponding reaction of aldehyde electrophiles; DFT calculations have been employed to probe the mechanistic differences. (*de*)

Reduction of Imines

Ruthenium and iridium are commonly used in catalysts for this reaction. A selectively deuterated hydroxycyclopentadienyl ruthenium hydride catalyst has been employed to probe the mechanism.[48] The relative rates of different steps determine whether the process is stereospecific (typically *trans*) or stereorandom.

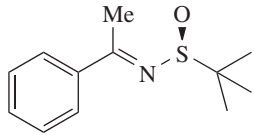
A water-soluble, recyclable ruthenium(II) complex including a chiral diamine ligand has been used for asymmetric transfer hydrogenation of cyclic imines and iminiums in water, with yields and *ee* up to 99%.[49] (*ee*)

Homogeneous catalytic hydrogenation of imines has been carried out using cationic iridium hydride catalysts.[50] The mechanistic possibilities are compared and contrasted with C=O hydrogenations.

A new class of chiral phosphine–oxazolines act as ligands in iridium-catalysed asymmetric hydrogenation of imines, and of alkenes, giving *ee*s up to 99%.[51] (*ee*)

Acyclic aromatic *N*-arylimines, $Ar^1{-}C(Me){=}N{-}Ar^2$, have been reduced to the corresponding amine with up to 99% *ee*, using 1 atm of hydrogen and an iridium(I) catalyst bearing a chiral diphosphinoethane chelating ligand.[52] (*ee*)

Using cheaper metals, electron-deficient imines such as sulfinylimine (**20**) can be reduced by diethylzinc, using a chiral nickel(II) catalyst; yields and *de*s >90% can be achieved.[53] Interestingly, ketones are unaffected by the process; many common reducing agents cannot so discriminate. ^{1}H NMR profiling indicates ethylene production, a (*de*)



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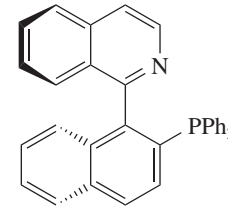


(**21**)

finding which supports an Et–Zn–N–C–Ni–Et intermediate, which eliminates the gas to give a nickel hydride which acts as immediate reductant of the carbon.

Formamides derived from L-pipecolinic acid act as Lewis base organocatalysts for reduction of *N*-arylimines with trichlorosilane, giving yields and *ee*s in the high 90s for a wide range of imine substrates.[54] (*ee*)

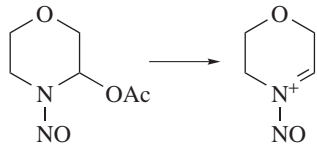
Iminium Species

A QUINAP auxiliary (**21**), bound to copper(I), gives excellent enantioselectivity in the addition of terminal alkynes to isolated isoquinoline iminium cations.[55] (*ee*)

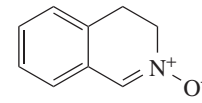
DFT calculations have been used to follow the formation of iminium ions from secondary amines and acrolein.[56] Energy barriers in the process can be lowered by incorporation of a heteroatom (N or O) in the α-position of the amine, or an electron-withdrawing group (carbonyl or thiocarbonyl) in the β-position.

Pentafluorophenylation of iminium cations has been studied by DFT methods, and the experimental conditions have also been optimized.[57] Silane reagents, $(F_5C_6)_{4-n}SiF_n$ ($n = 1, 3$) have been investigated, particularly with reference to their activation by weak Lewis bases. Pentafluorophenyl significantly stabilizes pentacoordinate silicon species, but as a group it is much more reactive in an apical than an equatorial position.

The synthesis and aqueous chemistry of α-acetoxy-*N*-nitrosomorpholine (**22**) has been described.[58] It decomposes cleanly, with first-order kinetics, via an *N*-nitroso-iminium ion intermediate (**23**), with the pH–rate profile showing acid- and base-catalysed regions, and an extensive pH-independent region between 3 and 9, the latter being ca 100 times slower than its *C*-analogue, the corresponding piperidine derivative. Implications for the interaction of *N*-nitrosomorpholine with DNA are discussed.



(**22**) (**23**)



(**24**)

Vinylzinc reagents have been added to 3,4-dihydroisoquinoline *N*-oxide (**24**) in up to 95% *ee*, using a chiral 2-aminoamide as auxiliary.[59] (*ee*)

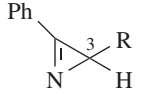
Asymmetric catalysis of carbonyl transformations via iminium ion and enamine intermediates have been reviewed (35 references), including their recent merger in tandem iminium–enamine sequences.[60] (ee)

Other Reactions of Imines

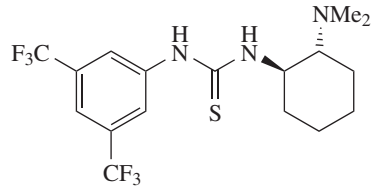
Several of preparations of aziridines have been reported. The aza-Darzens reaction of an *N*-bromoacylcamphorsultam with *N*-diphenylphosphinylimines, ArCH=N−P-(=O)Ph_2, gives *cis*-aziridine derivatives, except if the aryl is *o*-substituted, which gives significant *trans* product, and even 100% *trans*- with *o*-CF_3.[61] While steric factors play a role in this inversion of selectivity, electronic effects are also important: *o*-methyl gives a 50:50 ratio of products. (de)

A computational study has probed the origin of the diastereoselectivity in aziridine formation from sulfur ylides, Me_2S^+–CH^-–R, and imines.[62] For semi-stabilized cases (R = Ph), betaine formation is non-reversible, so that selectivity is determined in the initial addition step. In contrast, for stabilized ylides (R = CO_2Me), betaine formation is endothermic, and the elimination step becomes rate and selectivity determining. (de)

Allylaziridines have been prepared in good yield by the action of allylindium reagents on azirines (e.g. **25**).[63] The C(3) substituent can control stereochemistry: hydroxy- (or acetoxy-) -methyl gives *cis*-allylation (via chelation with the indium reagent), whereas R = Me/Ph/CO_2Et gives a *trans* result, presumably due to steric repulsion. (de)



(**25**)



(**26**)

Enantioselective nucleophilic addition to imines has been carried out with a planar-chiral Lewis acid based on a 1,2-azaborolyl framework.[64] (ee)

Addition and cyclization reactions of imines, catalysed by Brønsted acids, have been reviewed, including examples in water solvent and enantioselective cases.[65] Another review examines stereoselective nucleophilic additions to the C=N bond of aromatic azines (60 references).[66] (ee) (ee)

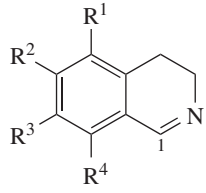
An enantioselective Strecker reaction involving Brønsted acid catalysis uses a BINOL-phosphoric acid, which affords *ee*s up to 93% in hydrocyanations of aromatic aldimines in toluene at −40 °C.[67] The asymmetric induction processes in the stereoselective synthesis of both optically active *cis*- and *trans*-1-amino-2-hydroxycyclohexane-1-carboxylic acids via a Strecker reaction have been investigated.[68] A 2-pyridylsulfonyl group has been used as a novel stereocontroller in a Strecker-type process: *ee*s up to 94% are suggested to arise from the ability of a chiral Lewis acid to coordinate to one of the sulfonyl oxygens.[69] (ee) (de) (ee) (ee)

The Strecker reaction of silyl cyanide (H_3SiCN) with benzaldehyde *N*-methylimine (PhCH=NMe), catalysed by an axially chiral 2,2′-bipyridine *N*,*N*′-dioxide has been explored computationally as a model for the corresponding reaction using TMSCN, $PhCH{=}NCH_2Ph$, and a biquinoline dioxide.[70] The non-catalysed reaction is found to be concerted (via a five-membered ring TS), whereas the catalysis is stepwise, via a hexacoordinate hypervalent silicate. (*ee*)

A thiourea derived from hydroquinine (a cinchona alkaloid) acts as a general organic catalyst for asymmetric addition of stabilized nucleophiles to acylimines, giving secondary amine adducts in high *ee* and *de*. Sample reactions catalysed include asymmetric nitro-aldol and aza-Henry reactions.[71] Chiral thiourea (**26**) catalyses aza-Henry reactions of *N*-Boc-aldimines with nitroalkanes, giving *syn*-*β*-nitroamines in high yield, *de*, and *ee*.[72] A bifunctional catalysis, with the thiourea N–Hs binding the nitro group and activating C−H deprotonation via the tertiary amine substituent, is discussed. (*de*) (*ee*) (*de*) (*ee*)

A cheap and efficient enantioselective aza-Henry reaction of nitromethane with a variety of *N*-protected arylaldimines has been reported.[73] Using zinc triflate and (−)-*N*-methylephedrine at −20 °C, yields and *ee*s of up to 99% have been achieved with wide tolerance of aryl substituent in terms of both electronic nature and position. The auxiliary is also easily recycled. (*ee*)

Among addition reactions of imines, malonate esters have been added to dihydroisoquinolines (**27**) at C(1), to give the corresponding tetrahydro derivatives in high *ee*,[74] and enantiopure aromatic sulfoxides (prepared by *o*-directed metallation) have been added enantioselectively to imines.[75] (*ee*) (*ee*)



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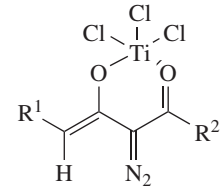


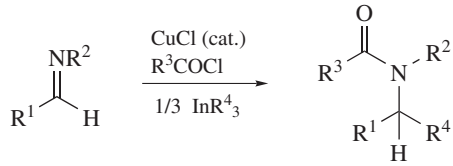
(**28**)

Titanium(IV) enolates derived from *α*-diazo-*β*-keto esters or ketones (**28**) efficiently add to $TiCl_4$-activated *N*-tosylimines to give the corresponding *δ*-*N*-tosylamino derivative.[76] Subsequent diazo decomposition – catalysed by rhodium(II) or light – yields useful pyrroles or *γ*-lactams, respectively.

Scandium triflate catalyses a highly diastereoselective addition of imines to 1,1-cyclopropane diesters to give multi-substituted pyrrolidines.[77] (*de*)

Non-activated imines have been pentafluorophenylated with $(F_5C_6)_3SiF$; protonation activates the imine, and chloride ions activate the silane.[78]

Highly substituted amides (**29**) have been prepared in a three-component reaction of an imine, an acid chloride, and trialkylindium.[79] Proceeding under mild conditions and high metal efficiency, the ‘alkyl’ group on indium can also be aryl, heteroaryl, or vinyl.

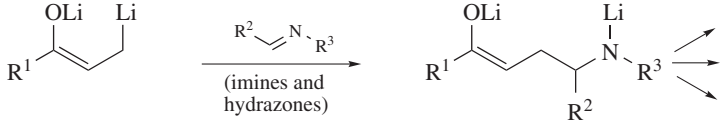


(**29**)

Carbonyls protected as azines or other C=N derivatives can be deprotected in seconds using HOF.MeCN, a reagent easily generated from dilute fluorine in water.[80] Sensitive groups such as cyclic acetals of ketones elsewhere in the substrate often survive. As the electrophilic oxygen in the reagent is derived from water, the method is easily adapted to produce isotopic oxygen labelling in carbonyls.

A study of the Staudinger synthesis of β-lactams from a diazo ketone, an acid chloride, and an imine (under basic conditions) has explored the *cis/trans* selectivity as a function of time, temperature, solvent, and the order of addition of reagents.[81]

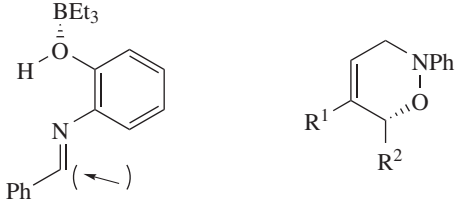
Ketone dilithio-α,β-dianions (**30**, formed by treatment of β-stannylketones, $RCOCH_2$-$CH_2SnBuCl_2$, with 4 equiv. of BuLi) react with imines and hydrazone selectively at the β-anion portion to give dilithium enolate amides (**31**).[82] Subsequent reaction with electrophiles gives γ-amino ketones and related heterocycles.



(**30**) (**31**)

Among reports related to radicals, *ab initio* calculations have been used to model intramolecular additions of acyl radicals to imines.[83] Imines and oxazolines bearing a pendant acyl radical at carbon have been cyclized to give 2-piperidones through a selective 6-*endo*-cyclization at nitrogen.[84] The acyl radical is generated via CO insertion into a suitable precursor. A diastereoselective example is also reported. (*de*)

Nucleophilic carbon radicals can *C*-alkylate imines, a process which is found to be substantially facilitated by an *o*-phenolic substituent as in e.g. (**32**).[85] The hydroxyl is presumed to stabilize an intermediate aminyl radical. An enantioselective version of the reaction is also reported. (*ee*)



(**32**) (**33**)

Oximes, Hydrazones, and Related Species

The Beckmann rearrangement of cyclohexanone oxime has been modelled kinetically, focusing on simulation of industrial conditions, and taking into account self-catalysis and the role of polymorphs.[86]

Chiral 1,2-oxazines (**33**) have been prepared from achiral ketones, R^1–CO–CH_2–R^2, via an α-oximation step (with a tetrazolylpyrrolidine organocatalyst), followed by a Wittig reaction.[87] Subsequent N−O cleavage yields enantiopure *cis*-allylic alcohols (*ee*) bearing a pendant amine.

Aryl alkyl ketoxime ethers, Ar–C(R^1)=N–OR^2, have been reduced with borane-THF at ca 0 °C to give amines, Ar–*CH(R^1)–NH_2.[88] A chiral BINAP with an O_3BN (*ee*) framework gives up to 98% *ee*.

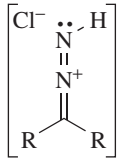
The kinetics of oxidative deoximation of aldo- and keto-oximes by 2,2′-bipyridinium chlorochromate (back to the parent carbonyl compounds) have been studied in DMSO, where the reaction is found to be first order in both oxime and oxidant.[89] The aldoximes proved more reactive, and rates correlated well with the Pavelich–Taft dual substituent equation. Following extension of the study to hindered cases, and to 18 other solvents (analysed by Taft and Swain multi-parametrics), a cyclic intermediate is proposed for the rate-determining step. The same reaction order behaviour is found using the pyridinium version, and again electronic, steric, and solvent effects were examined.[90]

Electroanalytical techniques indicate the formation of two carbinolamine intermediates and one monohydrazone in the reaction of terephthalaldehyde with hydrazine at pH 7.3.[91]

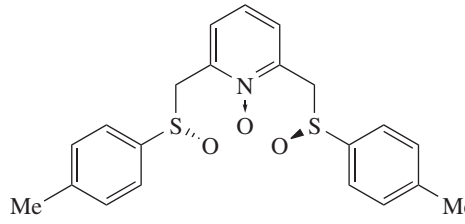
Reaction of hydrazones with iodine under basic conditions, to give azines, shows evidence of diazo intermediates that can be trapped with an internal alkene or alkyne function.[92]

Unsubstituted hydrazones of aromatic ketones and aldehydes have been converted in high yield to alkyl chlorides under Swern oxidation conditions, although the substrate actually undergoes a net reduction.[93] When the hydrazone is dideuterated, a deuterium ends up on the carbon, supporting the proposed intermediacy of cation (**34**), which tautomerizes and loses N_2, to give a carbocation which combines with the chloride. This experiment also suggests a convenient method to produce deuterium-labelled alkyl chloride from the corresponding aldehyde/ketone.

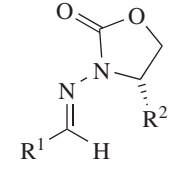
A new C_2-symmetric bis-sulfoxide/*N*-oxide (**35**; *R*,*R*-) promotes allylation of *N*- (*ee*) benzoylhydrazones with allyltrichlorosilane in up to 76% *ee*.[94]



(**34**)



(**35**)



(**36**)

Chiral *N*-acylhydrazones (**36**) – derived from an aldehyde (RCHO) and 4-benzyl-2-oxazolidinone – are sufficiently conformationally restricted to impart facial selectivity to C=N bond addition.[95] Using indium(III) triflate, they undergo highly diastereoselective fluoride-initiated allylsilane addition, i.e. the aza-Sakurai reaction. Mechanistic investigation suggests a dual activation process in which the hydrazone is electrophilically activated via formation of its indium complex, followed by nucleophilic attack by an allylfluorosilicate species, $[(allyl)_4SiF^-]$, leading to homoallylic amine adducts. (*de*)

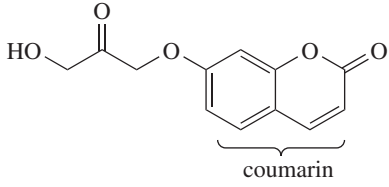
C–C Bond Formation and Fission: Aldol and Related Reactions

Stereoselective Aldol Reactions Using Proline Organocatalysts

The use of L-proline, amides derived from it, and related amino acids and small peptides as asymmetric organocatalysts for aldols – and indeed many other reactions mentioned elsewhere in this chapter – expanded hugely in 2006. A review deals with the direct aldol case.[96] (*ee*)

L-Proline catalyses direct aldols of trifluoroacetaldehyde ethyl (hemi)acetals, $F_3C-CH(OH)-OX$ (X = H, CH_2CH_3, CH_2CF_3), with ketones at room temperature to produce β-hydroxy-β-fluoromethylated ketones with *de*s up to 96% and *ee*s up to 91%.[97] (*de*) (*ee*)

Many reactions have also been carried out in water. The mechanisms of the reactions of acetone and 1,3-dihydroxyacetone using zinc–proline and related catalysts have been probed kinetically.[98] The former exhibits an enamine route, whereas the latter involves rate-limiting deprotonation of the α-carbon and formation of an enolate. An umbelliferyl ether of dihydroxyacetone (**37**) has been used as a fluorogenic probe for enolization, which may prove useful in screening of aldolases in water. (*ee*)



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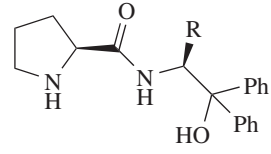


(**38**)

trans-4-Hydroxyproline is readily available in both enantiomeric forms. It catalyses direct aldols in water with high *de* and *ee*, as do several of its silyloxy analogues.[99] (*de*)

The first asymmetric direct aldol of 1,2-diketones and ketones, to give 2-hydroxy-1,4-diketones, has been reported.[100] L-Proline derivatives give high regio-, diastereo-, and enantio-selectivity in the reaction of 1-arylpropane-1,2-diones with simple ketones. (*ee*)

Several reports describe additives: for example, tertiary amine bases, weak acids, and strong acids have been examined, with limited effect, except for the strong acids, which stop the reaction completely.[101] C_2-symmetric chiral diols substantially improve proline-catalysed *ee*, conversion efficiency, and yield in the reaction of acetone with benzaldehyde, with addition of (*S*)-BINOL giving further improvement.[102] (*ee*)

PEG [poly(ethylene glycol)] – a non-toxic and widely used solvent – has been successfully used with proline; no loss of activity was found when both PEG and proline were recycled 10 times.[103] (*ee*)

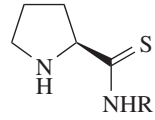
Several prolinamides have been examined: (**38**) catalyses the reactions of acetone with both aliphatic and aromatic aldehydes with *ee*s up to 97%.[104] It is proposed that amide and alcohol groups simultaneously donate hydrogen bonds to the aldehyde, while the *gem*-diphenyl moiety's bulk orients the aldehyde's approach. (*ee*)

An L-prolinamide gives high regio-, diastereo-, and enantio-selectivity in direct aldols of *p*-nitrobenzaldehyde with chloroacetone, giving *anti*-α-chloro-β-hydroxy ketones;[105] prolinamides with groups such as tetrazole or benzimidazole attached (via a methylene) to the amide nitrogen give *ee*s up to 96% for acetone reacting with electron-deficient aromatic aldehydes.[106] (*de*) (*ee*) (*ee*)

A range of prolinamides, some bearing one or more additional amino groups, have been developed as catalysts in water;[107] *o*-hydroxyaromatic substituents likewise give high selectivity in this solvent (and in neat ketone solution) for direct aldols of aralde-hydes with ketones.[108] (*ee*) (*de*)

Sterically and electronically tuneable and bifunctional organocatalysts based on diamides derived from proline are particularly selective in reactions of heterocyclic ketones with aldehydes.[109] (*de*) (*ee*)

L-Prolinethioamides (**39**, R = alkyl including chiral alkyl), prepared from proline and amines, are effective in acetone–benzaldehyde reactions.[110] Mechanistic studies focused in particular on suppression of non-enantioselective side-reactions, and also on the role of the side-chain of the catalyst acting as hydrogen bond donor, especially as the thioamides (with their more acidic N–H protons) are more catalytic than their amide analogues. (*ee*)



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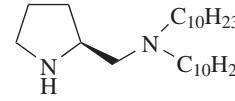
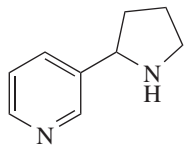


(**40**)

A range of proline derivatives have been employed as enamine-based organocatalysts of direct aldols in water, without organic co-solvent.[111] Using the reaction of cyclohexanone with benzaldehydes as a test bed, lipophilic diamine (**40**) in the presence of TFA proved to be an excellent bifunctional catalyst system, giving performance up to 99/90/99% in terms of conversion/*de*/*ee*. Alkyl chains of (**40**) make an organic microphase likely. (*ee*) (*de*)

A computationally derived model for catalysis of the aqueous aldol by nornicotine (**41**) has been tested (by the same authors) via kinetic isotope effects (KIEs) and thermodynamic measurements.[112] A proton inventory indicates that the computational results are not conclusive, and a water molecule is involved in or before the rate-determining step.

New chiral α-aminophosphonates related to proline catalyse enantioselective direct aldols; *syn* selectivity is also achieved on addition of bases such as DBU or DBN.[113] (*de*) (*ee*)



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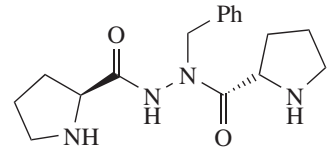


(**42**)

N′-Benzyl-*N′*-prolylhydrazide (**42**), in its protonated form, gives high *ee* in the acetone–benzaldehyde reaction.[114] (*ee*)

A dendrimer bearing *N*-prolylsulfonamide catalytic groups achieves up to 99% yield, *de*, and *ee* in direct aldols in water.[115] (*de*) (*ee*)

BINAM – the diamino analogue of BINOL – has been converted to its C_2-symmetric bis(prolinamide).[116] The latter acts as a recoverable catalyst of direct aldols in DMF–H_2O at 0 °C, giving high *de*s and *ee*s. Butan-2-one showed significant regioselectivity, giving predominantly the iso product. (*de*) (*ee*)

Multi-functional enantioselective catalysts for direct aldol and Mannich reactions have been prepared from (*S*)-proline and 2,2′-diaminoBINAP.[117] (*ee*)

Among the uses of other amino acids, L-tryptophan gives high *ee*s and *de*s in direct aldols of cyclic ketones and benzaldehydes in water;[118] hydrophobic and aryl-stacking effects have been considered in explaining the selectivities. (*de*) (*ee*)

β-Homoamino acids have been tested as enantioselective catalysts of intra- and inter-molecular aldols.[119] (*ee*)

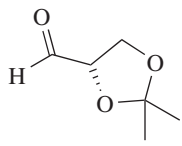
α- and *β*-amino acids, chiral primary amines, and small peptides have been investigated as organocatalysts of direct aldols in non-aqueous systems, with *ee*s up to 99% in some cases.[120] Enantioselectivities were raised in some instances by the addition of water, suggesting a significant role for hydrogen bonding. The implications for the evolution of homochirality in sugars are discussed. (*ee*)

Small peptides – simple di- and tri-peptides with a primary amine at the N-terminus – catalyse the aqueous aldol between unmodified ketones and aldehydes with up to 86% *ee*.[121] This is dramatically different from the corresponding amino acid-catalysed reaction, suggesting that peptide formation may have been significant in the evolution of asymmetric synthesis. Addition of *α*-cyclodextrin raised the *ee* further through the hydrophobic effect. (*ee*)

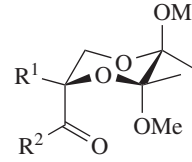
Other Stereoselective Aldol Reactions

To address limitations in the use of glyceraldehyde acetonide (**43**) as a three-carbon chiral building block, butane-2,3-diacetal-protected glyceraldehyde (**44**, $R^1 = R^2 = H$) has been prepared. It undergoes diastereoselective aldol reactions with a range of carbonyl compounds: esters, thioesters, and ketones. The work has been extended to other derivatives such as the *α*-substituted aldehyde (**44**, R^1 = Me, allyl) and the methyl ketone (**44**, R^2 = Me).[122a,b] (*de*)

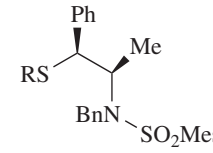
A highly diastereoselective aldol of an *α*-CF_3-substituted enolate has opened up a new route to trifluoromethyl-substituted chiral centres.[123] (*de*)



(**43**)



(**44**)

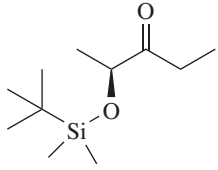


(**45**)

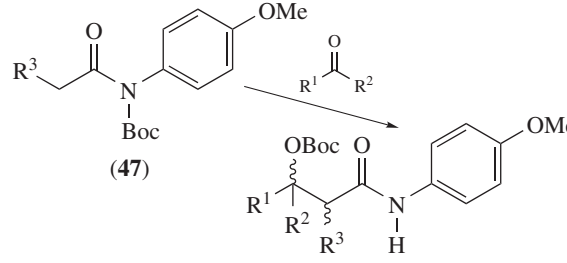
A new thiol auxiliary (**45**, R = COEt) participates in boron-mediated *anti*-aldol reactions with aldehydes with high yield and *de*.[124] Reaction of the product with nucleophiles displaces it (in the form of the thiol, **45**; R = H), converting the aldol product under mild conditions into esters, thiolates, phosphonates, alcohols, or acids. (*de*)

Hydrogen bonding and steric effects have been investigated in a theoretical study of the origin of the diastereoselectivity in the remote 1,5-stereoinduction of boron aldol reactions of β-alkoxy methyl ketones;[125] high levels of 1,5-*anti*-stereocontrol have been achieved in such reactions of α-methyl-α-alkoxy methyl ketones, giving both Felkin and anti-Felkin products.[126] (*de*) (*de*)

(*S*)-2-*t*-Butyldimethylsilyloxypentan-3-one (**46**), a lactate-derived chiral ketone, undergoes titanium-mediated aldols giving all-*syn* products in high *de*.[127] Low-temperature ^{1}H and ^{13}C NMR evidence suggests a likely TS to account for the selectivity. (*de*)



(**46**)



(**47**)

(**48**)

A highly *anti*-selective catalytic aldol reaction of amides with aldehydes has been reported.[128] The amide – specifically an *N*-Boc-anisidide (**47**) – gives the aldol product (**48**) with the Boc group transferred to oxygen. Catalysed by barium phenoxides, the reduction proceeds under mild, convenient conditions (THF, 0 °C, 24–48 h), giving high yields and *de*s. A wide variety of aldehyde types work (though aliphatics give low yields), and a trifluoromethyl ketone example is also reported, as are initial investigations of enantioselective cases. (*de*) (*ee*)

A catalytic enantio- and diastereo-selective aldol reaction of ketones with ketene silyl acetals, $H_2C{=}C(OTMS){-}OMe$, gives fair to good yields and *ee*.[129] With further substitution of the vinyl function, the reaction is diastereoselective, up to 97%. A highly developed catalyst/promoter protocol is employed: a copper(I) fluoride complex is combined with a Taniaphos auxiliary (a chiral ferrocenyldiphosphine), plus $(EtO)_3SiF$. Evidence for the formation of species $(EtO)_{4-n}SiF_n$ ($n \geq 2$) as active (*de*) (*ee*)

trapping silyl agents is presented. These intermediates appear to form more rapidly when K^+ $PhBF_3^-$ is added, by direct reaction with $(EtO)_3SiF$.

A systematic study of methyl ketone aldol additions with α-alkoxy and α,β-bisalkoxy aldehydes has been undertaken, under non-chelating conditions.[130] With a single α-alkoxy stereocentre, diastereoselectivity generally follows Cornforth/polar Felkin–Anh models. With an additional β-alkoxy stereocentre, π-facial selectivity is dramatically dependent on the relative configuration at α- and β-centres: if they are *anti*, high *de* results, but not if they are *syn*. A model for such acyclic stereocontrol is proposed in which the β-alkoxy substituent determines the position in space of the α-alkoxy relative to the carbonyl, thus determining the π-facial selectivity. (*de*)

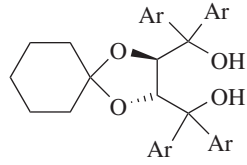
Mukaiyama and Vinylogous Aldols

An aldol reaction of a trimethoxysilyl enol ether, catalysed by a lithium binaphtholate, shows *anti* diastereoselectivity and modest *ee*s under dry conditions, but addition of water brings about *syn* adduct formation, with higher *ee*.[131] (*de*) (*ee*)

Silyl Lewis acid-induced Mukaiyama aldol reactions have attracted considerable mechanistic attention lately.[132] In a study which considers five mechanisms (including a new one), the effect of the conjugate base of the Lewis acid is examined. Considering three cases, $^-NTf_2$, $^-CTf_3$, and ^-OTf, the catalytic cycles are suggested to be significantly different between the low-nucleophilicity cases (the first two) and the relatively highly nucleophilic ^-OTf. (*de*)

Scandium(III) and lutetium(III)[133] and zinc[134] complexes of C_2-symmetric pyridine–bis(oxazoline) (PYBOX) ligands are highly effective enantioselective catalysts of Mukaiyama aldol reactions. (*de*) (*ee*)

A TADDOL derivative (**49**, Ar = 1-naphthyl) is a potent diastereo- and enantioselective catalyst; an X-ray structure of a complex of (**49**) with an aldehyde indicates (i) an intramolecular hydrogen bond in the catalyst and (ii) a hydrogen bond from catalyst to aldehyde.[135] It is therefore proposed that the asymmetric activation of the aldehyde arises from hydrogen bonding to a pre-organized catalyst. (*de*) (*ee*)



(**49**)

A chiral silver-based catalyst – formed from an amino acid and AgF_2 – promotes efficient enantioselective addition of enolsilanes to α-keto esters in THF at temperatures as low as $-30\,^\circ C$, with yields and *ee*s in the high 90s.[136] (*ee*)

Chiral sulfoximines liganded to copper(II) give highly enantioselective vinylogous Mukaiyama-type aldol reactions under mild conditions.[137] A chiral sulfinyl group has been used to achieve 1,5- and 1,6-asymmetric induction in Mukaiyama aldols, using $Yb(OTf)_3$ catalysis.[138] (*ee*) (*de*)

The Aldol-Tishchenko Reaction

A short review examines the current status and prospects for the direct asymmetric aldol-Tishchenko reaction, a process which allows for stereocontrol of three contiguous chiral centres in 'three-aldehyde' or 'aldehyde–ketone–aldehyde' reactant combinations.[139] (*ee*)

anti-1,3-Diols have been prepared in good yield and enantioselectivity, and high diastereoselectivity, by reaction of aromatic aldehydes with aliphatic or aromatic ketones.[140] The chiral ytterbium catalyst employed – derived from Yb(III) triflate and an ephedrine – promotes both the aldol reaction (through enolization) and the Evans–Tishchenko reduction of the aldol intermediate. (*de*) (*ee*)

Nitro and Nitroso Aldols

The catalytic asymmetric Henry reaction has been reviewed.[141,142]

Chiral iminopyridines catalyse nitro aldol reactions with good *ee*s in the presence of copper(II) acetate, without the need for exclusion of air or moisture.[143] A phenylalanine-derived Schiff base – also complexed to copper(II) – is also effective, with the advantage that product configuration is easily reversed (by using the enantiomeric phenylalanine).[144] (*de*) (*ee*) (*ee*)

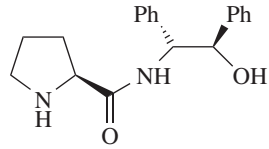
β,γ-Unsaturated α-keto esters such as *trans*-MeCH=CHCOCO$_2$Et undergo enantioselective reaction with nitromethane, using new catalytic auxiliaries based on cinchona alkaloids.[145] Carried out at $-20\,^{\circ}$C in DCM, the organocatalysts give high conversion, predominantly reaction at ketone only (typically <5% of product involves simultaneous addition to the alkene), and up to 97% *ee*. (*ee*)

A diastereomeric guanidine–bisthiourea bifunctional organocatalyst gives high *ee*s and *de*s in nitroaldols in a biphasic system: toluene–water at $0\,^{\circ}$C.[146] (*de*)

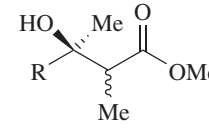
A dichloro[(−)-sparteine-*N*,*N*′]copper(II) catalyst in cold MeOH–Et$_3$N gives good yields and *ee*s of 73–79%.[147] (*ee*)

While metal–phosphine complexes can apparently catalyse the nitroaldol, it may be the free phosphine that is involved.[148] Testing of phosphines under metal-free conditions, and addition of extra phosphine in the presence of metal–phosphine complexes, have both been shown to catalyse the reaction.

In direct nitroso aldol reactions of α-branched aldehydes, an L-prolinamide (**50**) catalyses to give α-hydroxyamino carbonyl compounds which are otherwise disfavoured; *ee*s up to 64% were found.[149] Another prolinamide derivative gives similar results in a nitrosobenzene reaction.[150] For proline-catalysed cases involving highly substituted cyclohexanones, DFT calculations have highlighted the roles of electrostatic and dipole–dipole interactions in the level of *de* achieved.[151] (*ee*) (*ee*) (*ee*) (*de*)



(**50**)



(**51**)

Other Aldol-type Reactions

Migration of silyl groups from α- to β-oxygen in a sodium aldol reaction has been reported.[152]

A cationic rhodium complex, $[(Me_5Cp)Rh(\eta^6\text{-benzene})]^{2+}$, catalyses direct aldol condensation of ketones.[153]

A DFT study of enolborane addition of α-heteroatom-substituted aldehydes has focused on the relevance of the Cornforth and polar Felkin–Anh (PKA) models for asymmetric induction.[154] Using chiral substrates, MeCH(X)CHO, polar (X = F, Cl, OMe) and less polar (X = SMe, NMe_2, PMe_2) substituents have been examined. The former favour Cornforth TS structures, the latter PKA. TS preferences have been correlated with the relative energy of the corresponding rotamer of the uncomplexed aldehyde. An in-depth study of addition of (*E*)- and (*Z*)-enolborane nucleophiles to 2-methoxypropanal successfully predicts experimentally determined diastereofacial selectivities. (*de*)

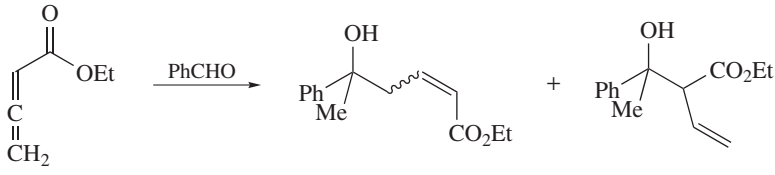
Direct aldol-type condensations of aldehydes with ethyl diazoacetate to give β-hydroxy-α-diazocarbonyl compounds, R–CH(OH)–C(=N_2)–CO_2Et, are catalysed by tetrabutylammonium hydroxide.[155]

A nickel hydride complex, NiHCl(diphenylphosphinoethane), catalyses the tandem isomerization–aldolization reaction of allylic alcohols with aldehydes.[156] The atom-efficient process proceeds at or below ambient temperature with low catalyst loading, and works well even for bulky aldehydes. Magnesium bromide acts as a co-catalyst, and mechanistic investigations suggest that a free enol is formed, which then adds to the aldehyde in a 'hydroxyl–carbonyl–ene'-type reaction. (*de*)

A domino reduction–aldol reaction of ketones with methyl acrylate produces tertiary alcohols bearing an ester group (**51**) in high *ee* and *de*.[157] Using a diphosphine-modified copper(I) fluoride complex in the presence of phenylsilane, the method avoids having to preactivate the nucleophile prior to the C−C bond-forming step. (*de*) (*ee*)

Three types of one-pot catalytic enantioselective reductive aldol reactions of ketones have been described,[158] giving fair to excellent *ee*s with a BINAP auxiliary. (*ee*)

Reductive aldol reaction of an allenic ester (**52**) to a ketone such as acetophenone can give γ- (**53**-γ) or α-product (**53**-α).[159] Using as catalysts a copper salt and a range of chiral phosphines, together with phosphine additives such as the triphenyl or tricyclohexyl compounds, a highly selective set of outcomes can be achieved, e.g. (**53**-γ) almost exclusively *cis*- with 99% *ee*, or – without additive – significant amounts of (**53**-α) can be formed (as a *syn–anti* mixture). A diastereoselective implementation of the latter has also been developed. (*de*) (*ee*)

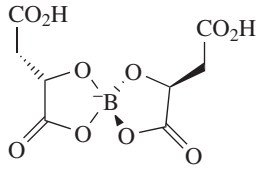


(**52**) (**53**-γ) (**53**-α)

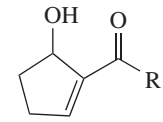
New 4-substituted phenyl(bisoxazoline) ligands (PHEBOX ligands) have been complexed with rhodium and examined as enantioselective catalysts of the reductive aldol of acrylates and aldehydes.[160] The results have been compared with the corresponding pyridine-centred (PYBOX) ligand complexes. (de) (ee)

The Aza and Morita Variants of the Baylis–Hillman Reaction

Chiral solvents rarely induce significant enantioselectivity, but *ee*s up to 84% have been achieved in an aza-Baylis–Hillman reaction.[161] Using an ionic liquid (IL), the anion of which is a dimalatoborate (**54**), it is suggested that the high enantioselectivity arises from strong ion-pair and hydrogen bond interactions with the zwitterionic intermediate of the reaction, i.e. IL–B^- ··· R_3P^+–CH_2–CH=C(Me)–O^- ··· HO–IL. (ee)



(**54**)



(**55**)

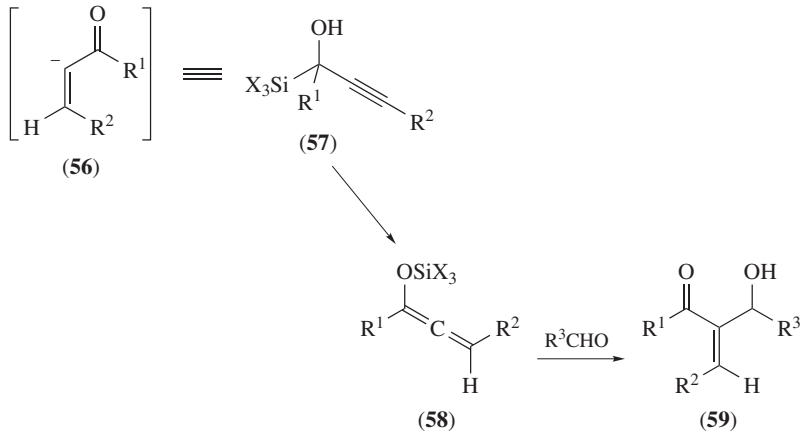
Chiral thiourea derivatives have been employed as catalysts; although yields are modest, *ee*s up to 99% have been recorded.[162] For the DABCO-promoted reaction of an *N*-*p*-nitrobenzenesulfonylimine with methyl acrylate, a DABCO–acrylate–imine adduct was isolated as a key intermediate. (ee)

A new tandem Michael–aldol reaction of α,β-unsaturated compounds bearing a chalcogenide or thioamide group with electrophiles has been reviewed.[163] The product α-(α-hydroxyalkyl)enones – Morita–Baylis–Hillman (MBH) adducts – can be formed with significant stereocontrol when an optically active thione is used. (de) (ee)

Enones with a pendant aldehyde, RC(=O)–CH=CH–$(CH_2)_2$–CHO, have been cyclized via an intramolecular MBH reaction in a study of the influence of Michael acceptor stereochemistry on yield.[164] Using triphenylphosphine as catalyst, the *Z*-isomer consistently gave 2.5–8.5 times higher yield of the product (**55**), using reaction times of 1–3 days. It is unclear whether this is due to the relative accessibility of the β-positions of the isomers to the nucleophilic catalyst, or differential stability in the enolate intermediates.

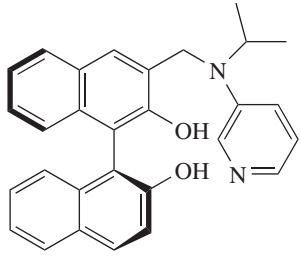
A new ionic liquid – a dinaphthalene imidazolium salt – catalyses the MBH reaction.[165]

As an alternative to the MBH generation of α-acylvinyl anions (**56**), α-hydroxypropargylsilanes (**57**) can be used: 1,2-Brook rearrangement converts them to the corresponding silyloxyallene (**58**), using *n*-BuLi, and subsequent reaction with an aldehyde gives the highly functionalized α,β-unsaturated carbonyl compound (**59**).[166] Using Lewis acid catalysts in DCM at $-78\,^{\circ}C$, highly selective versions of this reaction have been developed: with scandium(III) triflate, near-quantitative yields with an *E:Z* ratio of 1:20 result, and a chiral (salen)chromium(III) auxiliary gave 92% *ee*. (ee)

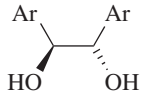


(**56**) (**57**) (**58**) (**59**)

Chiral BINOL (**60**) is a bifunctional organocatalyst: in addition to the phenolic Brønsted acid groups, it has a Lewis base unit attached via a spacer moiety.[167] This particular combination holds the groups in a conformational lock, where they can doubly activate a substrate while giving a high level of stereocontrol. For this example of an aza-Morita–Baylis–Hillman reaction of an enone and an imine, yields up to 100% and *ee*s up to 96% have been achieved. (*ee*)



(**60**)



(**61**)

Allylation and Related Reactions

Camphor-derived glyoxylic oxime ethers have been allylated in high yield and *de* using allyltributyltin–$Sn(OTf)_2$.[168] A diastereoselective allylation of an α-ketoamide bearing a camphor-derived auxiliary, again promoted by tin(II) triflate, undergoes a *de* reversal when palladium(II) chloride is employed, as indicated by ^{13}C NMR and IR spectra.[169] Tin(II) chloride-mediated allylation of aldehydes and ketones has been found to be significantly more straightforward in an ionic liquid.[170] (*de*) (*de*)

Chiral (salen)chromium(III) complexes catalyse the asymmetric allylation of a range of aldehyde types, using allylstannane reagents.[171] (*ee*)

BINOL-derived phosphoramidites are versatile ligands in palladium-catalysed umpolung allylation of aryl aldehydes mediated by diethylzinc.[172] The possible roles of allyl-zinc and -palladium species in the mechanism are discussed in detail. (*ee*)

A homoallyl alcohol has been used to generate an allylrhodium species via retro-allylation.[173] Subsequent reaction with an aldehyde (RCHO) yields the corresponding secondary alcohol, R–CH(OH)CH_2–C(Me)=CH_2, *in situ*. This can be isomerized in the same pot to yield saturated ketone, R–C(=O)CH_2–$CHMe_2$.

Pinacols (**61**) derived from a variety of aromatic aldehydes have been employed in enantio- and diastereo-selective allylations of aliphatic aldehydes.[174] Their allylboronate derivatives react under Lewis acid conditions ($SnCl_4$) with a variety of aldehyde types, in good yield and *ee*. Even better results are obtained by addition of (**61**) as a Brønsted acid (auto)catalyst, via coordination/activation of the tin catalyst. (*de*) (*ee*)

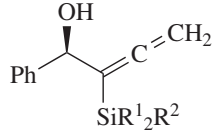
A combined experimental and computational approach has been undertaken to identify the origin of *syn*/*anti* diastereoselectivity in two types of crotylation reactions of aldehydes and ketones: (i) multi-component crotylations of simple aldehydes/ketones and (ii) acetal substitution reactions of aldehyde dimethyl acetals with *E*- and *Z*-configured crotyltrimethylsilane.[175] The stereochemical outcome is nearly identical in the two reactions, and the computational results suggest that this is due to near identical mechanisms: an S_N1 process involving attack of *O*-methyl-substituted carboxenium ions by crotylsilane. (*de*)

Chiral phosphoramides have been developed as catalysts for asymmetric addition of allylic trichlorosilanes to aldehydes.[176] Although some *de*s were high, *ee*s were modest. Kinetic studies suggest dual mechanisms, and thus a route to the design of more highly selective catalysts. (*de*) (*ee*)

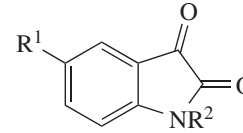
1,3-Dimethylallylation of (−)-menthone provides an allyl transfer agent for the highly enantio- and diastereo-selective pentenylation of aldehydes.[177] (*de*) (*ee*)

Trifluoromethyl ketones have been alkenylated, alkynylated, and phenylated in high *ee* using silane reagents and a chiral copper(I)–diphosphine complex.[178] (*ee*)

A chiral bis-oxazoline catalyses asymmetric Nozaki–Hiyama allenylation of aldehydes.[179] For example, benzaldehyde is converted to silylated allene (**62**) using a bromoalkynylsilane, $BrCH_2$–C ≡ C–$SiR^1{}_2R^2$; the product is readily desilylated quantitatively without loss of *ee*. (*ee*)



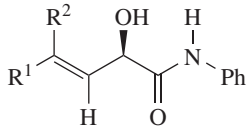
(**62**)



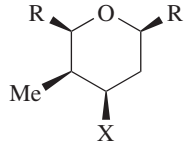
(**63**)

The ketone carbonyl of a series of isatins (**63**) undergoes enantioselective addition of aryl- and alkenyl-boronic acids, using a rhodium catalyst and a chiral phosphine.[180] (*ee*)

Enantiopure amide derivatives (**64**) of β,γ-unsaturated α-hydroxy acids have been made by addition of a vinylsilane, $R^2R^1C{=}CHSiMe_3$, to *N*-phenylglyoxamide.[181] The reaction is catalysed by scandium(III) triflate complexed to a C_2-symmetric PYBOX ligand derived from (*R*)-norephedrine. (*ee*)



(**64**)



(**65**)

Optically active homoallylic alcohols, $R^1CH(OH)CH_2CH{=}CHMe$, react with aldehydes (R^2CHO) to give 2,3,4,6-tetrasubstituted tetrahydropyrans (e.g. **65**, R = R^1 and/or R^2; X = OH, OAc, F, Cl, OTs) in the presence of an acid catalyst, HX, via Prins cyclization.[182] (*de*) (*ee*)

New hydrophobic Brønsted acidic ionic liquids (HBAILs) have been prepared and used as organic catalysts of dehydration reactions in water, e.g. Prins cyclization of styrene derivatives with aqueous formaldehyde, to give 1,3-dioxanes.[183]

Syn- and *anti*-selective halo-Prins cyclizations of δ,ε-unsaturated ketones to give 1,3-halohydrins have been catalysed by Lewis acids, with *syn* selectivity correlating with acid strength.[184] (*de*)

In a carbonyl–ene reaction of ethyl glyoxylate with α-methylstyrene catalysed by copper triflate–bisoxazoline complexes, *ee*s of up to 100% have been achieved, but a dramatic switchover in stereochemistry is seen for an apparently minor change in bisoxazoline structure.[185] A change in the metal geometry is implicated. (*ee*)

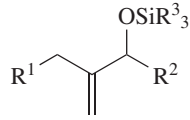
Olefinations

Ruthenium(II)–salen complexes catalyse olefination of aldehydes by ethyl diazoacetate: yields and *E*-selectivities are good, with electron-deficient aldehydes reacting faster.[186]

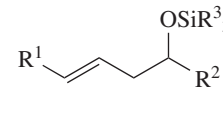
A new synthesis of sterically hindered *o*-substituted tetraphenylethenes via McMurry olefination of the corresponding 2,2′-disubstituted benzophenones exploits electronic effects that dominate over steric considerations.[187]

Two recently developed coupling reactions of an alkene ($R^1CH_2CH{=}CH_2$), an aldehyde (R^2CHO), and a silyl triflate ($R^3{}_3SiOTf$) yield an allylic (**66**) or homoallylic (**67**) alcohol (in protected form).[188] Employing nickel–phosphine catalysts, either product can be selected by small changes in the phosphine component. A mechanism distinct from that of Lewis acid-catalysed carbonyl–ene reactions is proposed and discussed.

Aldehydes, RCHO, have been reductively olefinated (to *trans*-RCH=CHR) using chromium dichloride and trichlorosilane, apparently via a novel chromium Brook rearrangement.[189] In one case, a *trans*-1,2-diol (a putative intermediate in such a mechanism) was isolated.



(**66**)



(**67**)

Alkynylations

A C_2-symmetric bisoxazolidine–zinc complex catalyses alkynylation of aldehydes, giving propargyl alcohols in high yield and *ee*.[190] (*ee*)

Aldehydes and alkynes (RC≡CH) have been reductively coupled via formal hydrochromation of the alkyne to give a 1-substituted ethenylchromium reagent, $H_2C{=}C(R)Cr(III)$, using a low-valent metal reagent, $CrCl_2$, in aqueous DMF.[191] Catalytic nickel(II)–PPh_3 is required to generate the organochromium species, probably through formation and transmetalation of $H_2C{=}C(R)Ni(II)$. Subsequent reaction with an aldehyde gives linear and branched β,γ-unsaturated alcohols.

Zinc-catalysed asymmetric alkynylation of α,β-unsaturated aldehydes giving high yields and *ee*s has been reported.[192] A dinuclear complex is proposed. (*ee*)

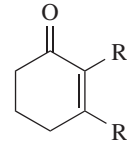
Carbonyl compounds have been alkynylated to give the corresponding propargyl alcohols, using TMS-alkynes and a base such as acetate or phenoxide ion.[193]

Ketones and aldehydes, including activated and enolizable substrates and those containing alcohol or carboxylic acid substituents, can be alkynylated using a rhodium(II) catalyst complexed with a bulky phosphine.[194]

A new cascade reaction of aromatic aldehydes with terminal conjugated alkynes produces a range of polycyclic aromatic hydrocarbons.[195] The effect of temperature on regioselectivity is discussed.

A complex of nickel(0) with an *N*-heterocyclic carbene catalyses coupling of α-silyloxyaldehydes with alkynylsilanes, giving (deprotected) *anti*-1,2-diols in good yield and *de* >96%.[196] (*de*)

Cyclobutanones can act as 1-oxobutane-1,4-diyl units: they undergo intermolecular alkyne (RC≡CR) insertion to give cyclohexanones (**68**), catalysed by $Ni(cod)_2$, apparently via a seven-membered nickelacycle.[197]



(**68**)

Reductive couplings of 1,6-enynes and aldehydes, catalysed by $Ni(cod)_2$, show regioselectivity effects that are switchable via addition of a phosphine.[198] Chelation control and steering effects due to the alkene tether have been invoked to explain this. (*de*)

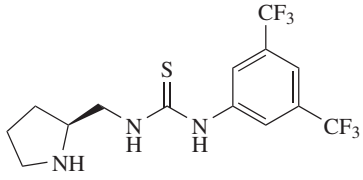
Favorskii ethynylation of acetone with acetylene in the presence of KOH is inhibited by dibenzo-18-crown-6, but not due to deactivation of acetone, as its aldol-like

condensation is accelerated under such conditions.[199] Rather, activation of acetylene by potassium cation is suggested to play an important role.

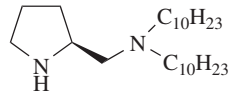
Michael Additions

Direct catalytic Michael addition of aldehydes to nitrostyrenes proceeds in good yield, *syn* diastereoselectivity, and enantioselectivity (up to 82/90/99%, respectively) using a recyclable dendritic catalyst bearing chiral pyrrolidine moieties.[200] High-yielding enantio- and diastereo-selective direct Michael addition of ketones to nitroalkenes to give aldol products employ modular acyclic primary amino acid derivatives as catalysts.[201]

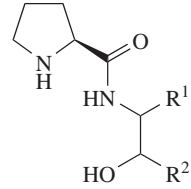
A pyrrolidine–thiourea organocatalyst (**69**) facilitates Michael addition of cyclohexanone to both aryl and alkyl nitroalkenes with up to 98% *de* and *ee*.[202] The bifunctional catalyst (**69**) can doubly hydrogen bond to the nitro group, leaving the chiral heterocycles positioned for cyclohexyl enamine formation over one face of the alkene.



(**69**)



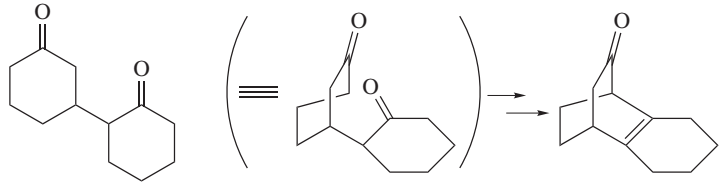
(**70**)



(**71**)

A direct organocatalytic Michael reaction of ketones or aldehydes with β-nitrostyrene has been reported in brine solution, using a bifunctional catalyst system: proline-derived diamine (**70**) and TFA.[203] In some cases the conversion, yield, *de*, and *ee* all exceeded 95%. Results in water were poor, mainly due to polymerization, which is catalysed by amines. It is proposed that sodium cations stabilize the anionic intermediate formed from (**70**) and β-nitrostyrene, thus minimizing polymer formation. While organic co-solvent is not required, an organic-rich phase is proposed to concentrate the Michael reactants and catalysts, thus accelerating the reaction.

L-Prolinamides (**71**) with a pendant alcohol act as recoverable bifunctional catalysts of direct nitro-Michael addition of ketones to β-nitrostyrenes, giving *syn-de*s up to 94% and *ee*s up to 80%.[204] The pyrrolidine provides enamine catalysis, and the side-chain donors can hydrogen-bond the nitro oxygens.



(**72**) (**73**)

Diketone (**72**) undergoes an acid-catalysed Michael–aldol reaction to give tricyclic ketone (**73**).[205]

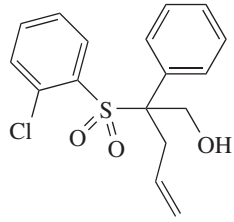
Other Addition Reactions

General and Theoretical

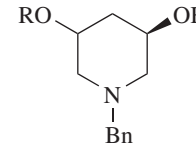
Recent developments in the asymmetric addition of aldehydes have been reviewed,[206] as have asymmetric catalysis using metal complexes[207] and nucleophile isotope effects.[208] (*ee*)

Natural bond orbital analysis of early and late TSs has been carried out to explore the factors involved in π-selectivity of nucleophilic addition to carbonyls.[209] Cieplak's $\sigma \rightarrow \sigma^*\#$ hyperconjugation hypothesis (where $\sigma\#$ is the incipient bond) is *not* supported by the results for early TSs, and evidence in favour of Felkin–Anh's $\sigma\# \rightarrow \sigma^*$ hypothesis is weak. Late TSs are devoid of $\sigma \rightarrow \pi^*_{C=O}$ interactions: here, the Cieplak model may be applicable. (*de*)

Alcohol (**74**) undergoes an unusual extrusion of its hydroxymethyl group in the presence of sodium hydride.[210] That it is a reverse reaction of nucleophilic addition to formaldehyde was confirmed by trapping experiments for the latter. Relief of steric congestion is a likely cause, with the sulfinyl also helping to stabilize the incipient carbanion. The two factors combined help to reverse the equilibrium which normally favours attack on formaldehyde.



(**74**)



(**75**)

The atmospheric chemical kinetics of linear perfluorinated aldehyde hydrates, $C_xF_{2x+1}CH(OH)_2$, have been measured for $x = 1$, 3, and 4, focusing on formation (from aldehyde, by hydration), dehydration, and chlorine atom- and hydroxyl radical-initiated oxidation.[211] The latter reaction is implicated as a significant source of perfluorinated carboxylic acids in the environment.

Addition of Organozincs

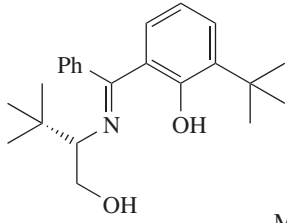
Most papers deal with diethylzinc. Chiral (3*R*,5*R*)-dihydroxypiperidines (**75**), derived from *trans*-4-hydroxy-L-proline, give up to 98% *ee* in its additions to benzaldehyde and heptanal.[212] (*ee*)

Cyclohexanols bearing 1-phenylethylamine attached via nitrogen in the α-position have been tested as enantioselective catalysts of diethylzinc addition to benzaldehyde.[213] (*ee*)

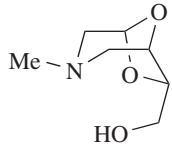
A range of chiral bridged resorcinarene 'bowls' also catalyse this reaction: a mechanistic model suggests that the axial chirality of the receptor cavity, rather than a central chirality in the bridge, is responsible.[214] Theoretical predictions for the reaction have been calculated for a series of catalysts, using a rapid QSSR (quantitative structure–selectivity relationship); based on quantum molecular interaction fields, the predictions have since been tested by independent experiments.[215,216] Sterically congested ferrocenylaziridinoalcohol auxiliaries give up to 99.8% *ee*; evidence for a strong direct steric interaction with the substrate – which can even lead to inversion of configuration – is presented.[217]

γ-Amino alcohols derived from (+)- and (−)-α-pinene act as catalysts for enantioselective addition of diethylzinc to aromatic aldehydes.[218] The *ee* is highly dependent on the *N*-substituent, and *ab initio* molecular modelling has been used to interpret this finding.

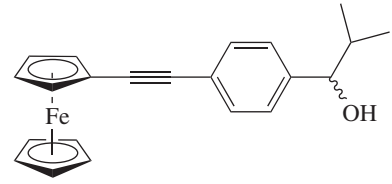
A chiral Schiff base with pendant phenol and alcohol functions (**76**) catalyses addition to aldehydes in cold hexane with up to 96% *ee*.[219] Non-linear effects on the *ee* suggest that zinc aggregation occurs, and NMR evidence indicates that both ethyl groups react with both hydroxyls in the catalyst.



(**76**)



(**77**)



(**78**)

A chiral [2.2]paracyclophane bearing a β-hydroxyamino side-chain catalyses enantioselective reaction with aromatic and α,β-unsaturated aldehydes.[220] Comparison with simpler catalysts suggests that the new one exhibits cooperative effects between planar and central chiralities.

Unsymmetrical substitution of BINOL with a bulky group gives enhanced activity: 95% *ee* was achieved with <1 mol% loading of catalyst, compared with comparable conditions employing 20 mol% BINOL.[221]

In other diethylzinc studies, a neural network modelling approach has been used to predict the utility of new enantioselective catalysts,[222] norephedrine-derived ligands with three stereogenic centres catalyse enantioselective addition to aldehydes and to chalcones,[223] and a chiral sulfonamide ligand based on tartaric acid gives good *ee*s in addition to both aldehydes and ketones.[224]

A new enantiopure constrained 1,4-amino alcohol (**77**) allows alkynylation and also ethylation by zinc reagents with best *ee*s of 70 and 98%, respectively.[225]

A commercially available chlorochromium–salen complex has been shown to be a good enantioselective catalyst for the addition of di*methyl*zinc to aromatic aldehydes, with yields up to 95% and *ee*s up to 99%, using 2–4 mol% catalyst.[226] (*ee*)

(*R*)- and (*S*)-pyrimidyl alcohols (**78**), prepared from reaction of the corresponding pyrimidylaldehyde with diisopropylzinc, are also autocatalysts: starting from a near racemic 'seed', a large positive non-linear effect gives >99% *ee*.[227] (*ee*)

A mandelamide diastereomer catalyses addition of both aryl- and alkyl-zincs to heteroaromatic aldehydes in high yield and *ee*, giving heterocyclic propargyl alcohols, under otherwise metal-free conditions.[228] (*ee*)

A chiral H_8-BINOL derivative catalyses an efficient direct enantioselective addition of diphenylzinc to both aromatic and aliphatic aldehydes, with particularly good results for straight-chain cases.[229] Aggregation phenomena in solution have been studied by NMR spectroscopy. (*ee*)

Chiral amino alcohols derived from BINAP have been employed as catalysts in a highly enantioselective addition of arylzincs (prepared *in situ*) to aldehydes.[230] (*ee*)

Recent progress in enantioselective addition of organozincs has been reviewed.[231] (*ee*)

Addition of Other Organometallics, Including Grignards

1,2-Additions of a range of organolithium reagents, RLi, ArLi, NC–CH_2Li, RC≡CLi, and ArC≡CLi, show *ee*s of 65–98%, using a chiral lithium aminosulfide auxiliary, superior to similar lithium amides with an ether instead of a sulfide, or without either chelator.[232] (*ee*)

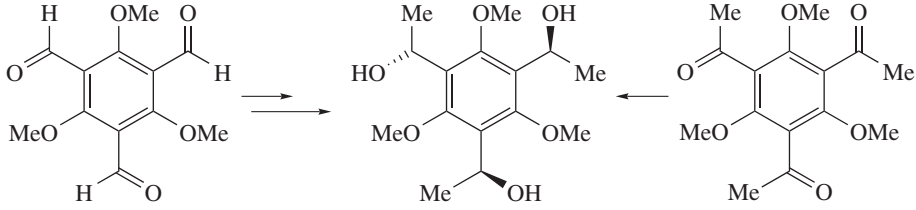
Lithium carbazolates have been added enantioselectively to aldehydes, giving heterocyclic carbinols.[233] (*ee*)

The preparation and synthetic applications of α-lithio aldehydes and ketones and related compounds have been reviewed.[234]

Mixed lanthanide–alkali chlorides, $LnCl_3.2LiCl$ (Ln = La, Ce, Nd) can be readily prepared as 0.5 mol dm^{-3} solutions in THF.[235] They act as improved promoters of addition of organomagnesium reagents to ketones, and also to aldimines, and in addition have been found to promote organolithium addition.

2,4,6-Trimethoxybenzene-1,3,5-tricarbaldehyde (**79**) and its keto homologue (**80**) involve three symmetry-equivalent carbonyl centres, each in a 1,5-relationship to their neighbours.[236] Two diastereoselective reactions have been performed: (i) the trial can be trimethylated to give triol (**81**) with methyllithium in THF, and (ii) the triketone can be reduced (to the same product), in both cases with >95% *de* (*anti*, *syn*). Chelation and steric (gearing) effects about the crowded aromatic core are discussed to explain the observed diastereoselectivity. (*de*)

A range of di- and tri-methoxybenzaldehydes, expected to give alkyl carbinols on treatment with alkylmagnesium bromides (RMgBr), instead gave the *di*alkyl carbinol, $(MeO)_{2/3}$–$C_6H_{3/2}$–$C(OH)R_2$.[237] It is proposed that the intended product is subject to an internal Cannizaro-type oxidation process to give the ketone, allowing the Grignard to re-alkylate.



(**79**) (**81**) (**80**)

The Wittig and Aza-Wittig Reactions

A detailed DFT study of the mechanism of the Wittig reaction has been carried out on a range of non-stabilized, semi-stabilized, and stabilized ylides: experimentally realistic results required explicit consideration of solvent effects, and practical large-scale systems which allow steric, electronic, and stereochemical effects to be captured.[238] Significant results for the non- and semi-stabilized systems include the necessity of considering the energy of the elimination TS in order to identify *E/Z* selectivity. Also, puckering of the addition TS depends not on ylide stabilization, but on 1,2-, 1,3-, and C−H· · ·O interactions. For stabilized substrates, puckering depends on dipole–dipole interactions: these determine the high *E* selectivity seen in such cases.

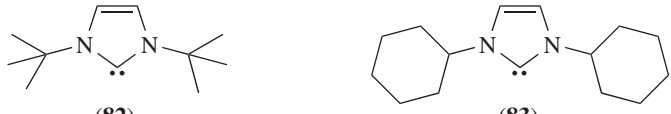
A QSAR (quantitative structure–activity relationship) approach has been taken to predicting stereoselectivity in the Wittig reaction.[239]

Pyrazolo[1,5-*a*]pyrimidines and imidazo[1,2-*b*]pyrazoles have been prepared from phosphine derivatives of 5-amino-3-phenylpyrazole in aza-Wittig reactions with selected α-chloroketones.[240]

An enantioselective aza-Wittig strategy has been employed in the desymmetrization of prochiral 1,3-diketoazides, to produce β-quaternary azacycles.[241] (*ee*)

Hydrocyanation, Cyanosilylation, and Related Additions

A range of *N*-heterocyclic carbenes catalyse TMSCN addition to aldehydes (RCHO) to yield cyanohydrin TMS ethers, R–*CH(OTMS)CN; acid treatment gives the cyanohydrins.[242] Mechanistic possibilities are discussed, and use of a chiral carbene gives a modest *ee*. Several other studies used such carbenes;[243] for example, a low loading of 0.01−0.5 mol% of 1,3-di-*t*-butylimidazol-2-ylidene (**82**) catalyses TMSCN addition to a wide range of aliphatic and aromatic aldehydes and ketones under mild, metal-free conditions, with a wide functional group tolerance.[244] Also, (**83**) gives comparable results, and has also been used to convert imines to aminonitriles.[245] (*de*)



(**82**) (**83**)

Diastereoselectivities in the tetrabutylammonium cyanide-catalysed cyanosilylation of cyclic α,β-epoxyketones are dependent on ring size, with a switchover in selectivity between five-membered and larger rings being explained through computation of TSs.[246]

A range of Lewis bases catalyse the addition of TMSCN to aldehydes, with phosphines and amines the most efficient.[247] Kinetic studies indicate that the orders of (*ee*) aldehyde, Lewis base (LB), and TMSCN are 1, 1, and 0, suggesting an $Me_3Si–LB^+$ CN^- ion pair as an intermediate. However, chiral phosphines and amines gave very low *ee*s.

A chiral aluminium-salen–Ph_3PO combination catalyses addition to ketones in up to 92% *ee*; the catalyst system essentially acts as a Lewis acid–Lewis base bifunctional (*ee*) system.[248] A similar chiral manganese(III)-salen–Ph_3PO method is comparable.[249] (*ee*)

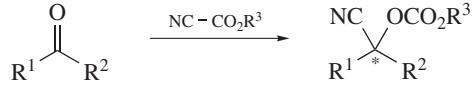
Another effective catalyst is 1,1,3,3-tetramethylguanidine, which works well at 0.1 mol% loading in solvent-free conditions at ambient temperature.[250]

Aliphatic aldehydes have been converted to their (*R*)-cyanohydrins using a biphasic system to accommodate hydroxynitrile lyase enzyme (from the Japanese apricot, (*ee*) *Prunus mume*) as the enantioselective catalyst.[251]

An alternative TS for asymmetric addition of cyanide to aldehydes catalysed by titanium–salen complexes has been proposed, based on a comparison with a related (*ee*) iron–salen complex for which a crystal structure is reported.[252]

High-yielding, high-*ee* cyanation has been achieved using a multi-component bifunctional catalyst system.[253] Aldehyde (RCHO) and nitrile (NC–CO_2Et) react at (*ee*) −45 °C in DCM to give the corresponding cyanohydrin ethyl carbonate, R–*CH(CN)–O–CO_2Et. The catalyst used has *four* components: a chiral BINAP, (1*R*,2*S*)-(−)-*N*-methylephedrine, cinchonine, and titanium isopropanoxide. Evidence for all four being essential is presented.

Ketones have been enantioselectively cyanocarbonated to give tetrasubstituted carbon stereocentres (**84**), using cinchona alkaloid catalysts and cyano esters, with *ee*s (*ee*) up to 97%.[254] A fall-off in *ee* at high conversions has been explained by a mechanism involving competing asymmetric processes, and significant retro-cyanation.



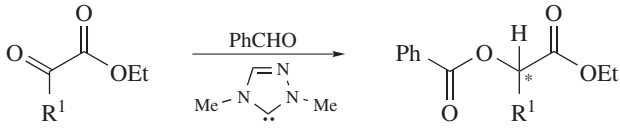
(**84**)

Aldehydes, RCHO, have been cyanophosphorylated with diethyl cyanophosphonate [NC–P(=O)$(OEt)_2$] to give cyanohydrin *O*-phosphonates, R–*CH(CN)–OP(=O)-$(OEt)_2$, in up to 98% yield and 97% *ee*, using a $YLi_3(BINAP)_3$ catalyst.[255] (*ee*)

DBU catalyses cyanoacylation of ketones, R^1COR^2, with aromatic acyl cyanides giving *O*-acyl cyanohydrin adducts, ArOCO–C(CN)R^1R^2, in fair to good yields in 2 h at ambient temperature.[256]

Hydroacylation of carbonyls or alkenes by aldehydes is well known. Hydroacylation of an activated ketone (**85**) by benzaldehyde has now been reported, giving a new asymmetric centre at the ketone carbon (**86**).[257] In a metal-free procedure, the reaction

is catalysed by *N*-heterocyclic carbenes, such as the triazole catalyst (**87**) shown. The reaction involves separate reduction and acylation steps, with the organocatalyst carrying out two key bond-forming processes. Whereas (**86**) is the major product in DCM, methanol solvent decouples reduction and acylation, giving the alcohol 'intermediate', Ph–*CH(OH)CO_2Me, as sole product.



(**85**) (**87**) (**86**)

The use of homogeneous carbonylation reactions for the synthesis of biologically important compounds has been reviewed, covering many methodologies, including direct use of carbon monoxide, and also hydroformylation and alkoxy- and aminocarbonylation, both inter- and intra-molecular.[258]

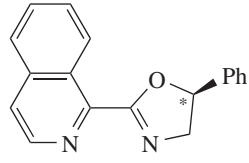
α-Amino-β-keto esters have been prepared in high *ee* via catalytic electrophilic α-amination of β-keto esters, using azodicarboxylate reagents and a chiral palladium complex as catalyst.[259] By immobilizing the catalyst in an ionic liquid, the system can easily be recycled. (*ee*)

The introduction of α-heteroatom functionalization into an aldehyde or ketone is a very useful class of transformation. Performing it directly and asymmetrically, using organocatalysts, has been reviewed for reactions such as amination, oxygenation, halogenation, and sulfenylation (44 references).[260] (*de*) (*ee*)

Propanal has been enantioselectively hydroxyaminated with nitrosobenzene (Ph–N=O) to give a hydroxylamino alcohol, Ph–N(OH)–*CH(Me)CH_2OH, using an axially chiral BINAP secondary amine catalyst in THF at 0 °C, followed by methanolic treatment with sodium borohydride.[261] Yields up to 90% and *ee*s up to 99% were recorded, and one-pot conversions to the corresponding β-amino alcohol or β-diamine are described. (*ee*)

Hydrosilylation and Related Reactions

An enantioselective metal-free hydrosilylation of aromatic ketones (and also of their imines) employs a quinolyloxazoline (**88**), which brings about a relatively long-range induction.[262] (*ee*)



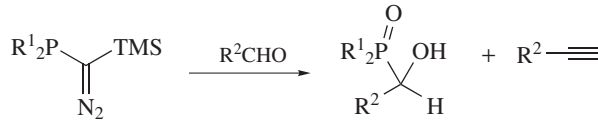
(**88**)

A rhodium(I)–diphosphine complex which is *P*-chiral catalyses enantioselective hydrosilylation of a range of simple ketones.[263] After acidic workup, the corresponding alcohols are obtained in high yields and *ee*s up to 99%. (*ee*)

High-valent rhenium dioxo complexes, $ReO_2I(PR_3)_2$, catalyse the hydrosilylation of carbonyl compounds.[264] DFT calculations suggest rate-determining dissociative addition of the Si–H bond (of H–Si–alkyl$_3$) across the Re=O bond, with subsequent carbonyl coordination and reduction.

Metal complexes of a C_2-symmetric bisproline catalyse the asymmetric hydrosilylation of ketones: ^{29}Si NMR spectra provide evidence of the mechanism.[265] (*ee*)

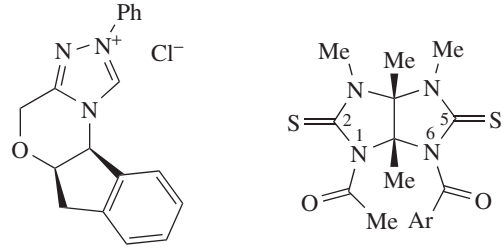
C-Silylated α-diazophosphines (**89**, $R^1 = Me_2N$ or ^{i}Pr–N–CH_2CH_2–N–^{i}Pr) react with 2 mol of aldehyde under mild neutral conditions to give α-hydroxyphosphonamides (**90**) and alkynes.[266] Chiral aldehydes can give (**90**) as single isomers. Isolation of some intermediates, and labelling studies which show that an aldehydic hydrogen ends up in the alkyne, indicate that the aldehyde is nucleophilically attacked by (**89**) to give a betaine, which rearranges to a diazomethylenephosphorane, which in turn undergoes a Wittig-type reaction with another molecule of aldehyde. (*de*)



(**89**) (**90**)

Miscellaneous Additions

Imidazolium salt (**91**) is an enantioselective catalyst for crossed aldehyde–ketone benzoin cyclization.[267] Most examples involve 6-oxoaldehydes giving α-hydroxycyclohexanones, although a 5-oxo- to -cyclopentanone case is also illustrated. Considerable variation in functional group type – aromatic, aliphatic, alicyclic – is tolerated. (*ee*)



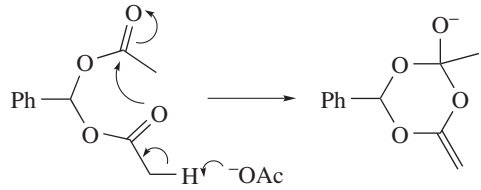
(**91**) (**92**)

(*N*1)-Acetyl-(*N*6)-aroyl-2,5-dithio-3,4,7,8-tetramethylglycolurils (**92**) and related compounds undergo a *t*-butoxide-catalysed Claisen-type condensation.[268] Rate constants have been measured for the template-directed process, Hammett plots have been constructed, and deuterium isotope effects measured at the acetyl group. The

mechanism is discussed with an emphasis on the role of sulfur via comparison with the 2,5-dioxo compounds.

The TEMPO moiety (2,2,6,6-tetramethylpiperidine-1-oxyl) has been incorporated into acetoacetic derivatives to achieve *E*-selective Knoevenagel condensations, exploiting the steric hindrance that it causes.[269] In contrast, acylacetoamides (including Weinreb amides) produce *Z*-adducts. Downstream reductions of carbonyl groups in the products allow access to a variety of useful materials.

In a revisitation of the mechanism of the Perkin condensation, a strong argument is advanced against the common belief that acetate deprotonates acetic anhydride to give its enolate, AcO–C(=CH_2)–O^-.[270] The pK_a of acetic anhydride (estimated 20) is too high, acetate is too weak a base, and the enolate would probably decompose (to ketene and acetate) at the typical reaction temperature of 180 °C. This leaves a problem: what likely two-carbon nucleophile – a formal acetic acid dianion equivalent – is available? The *gem*-diacetate (**93**) is suggested; its simple enolate might be difficult to form, but a type of neighbouring group participation could generate anion (**94**) as nucleophile (for reaction with the second benzaldehyde). The finding that (**93**) can give cinnamic acid product at room temperature (in *t*-BuOK–THF) supports the hypothesis, in addition to pointing the way towards milder conditions.



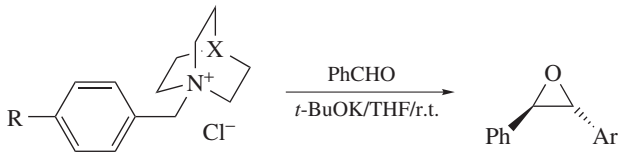
(**93**) (**94**)

An isoborneol with a *cis*-α-amino group gives *ee*s of up to 93% in addition of Reformatsky reagents to aldehydes.[271] (*ee*)

A wide range of benzocyclic ketones have been accessed by intramolecular arylation using aldehyde groups.[272] This intramolecular Friedel–Crafts-type acylation is promoted by iodinium species, using the reagent combination IPy_2BF_4–HBF_4.

Chiral benzoylformate esters, $PhCOCO_2R^*$, react with diazomethane to give α-oxiranyl esters, but *de* is typically negligible.[273] (*de*)

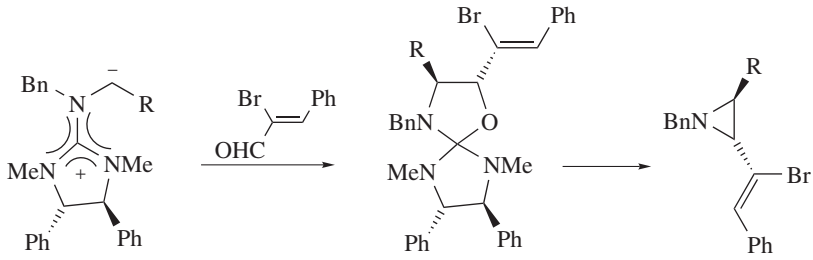
Aryl-stabilized ammonium ylides from deprotonation of (**95**; X = CH, N) react with benzaldehyde to give epoxides (**96**).[274] The diastereoselectivity is highly sensitive to the nature of the amine and the ylide substituent, e.g. it reaches 99:1 *trans*:*cis* (*de*)



(**95**) (**96**)

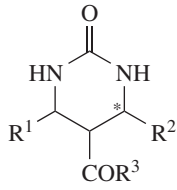
for R = CF_3. DFT calculations suggest that – although the ylide is a high-energy species – betaine formation is reversible, as the next step of ring closure also has a high barrier. Thus groups that stabilize the ylide and/or increase the barrier to ring closure (electron-deficient aryls) favour *trans* selectivity.

A spiro imidazolidine–oxazolidine intermediate (**97**) has been isolated in an aziridination of α-bromocinnamaldehyde mediated by a guanidinium ylide (**98**).[275]

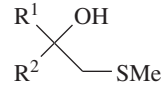


(**98**) (**97**)

Biginelli synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (**99**) from an aldehyde, a β-diketone, and urea is catalysed by L-proline methyl ester hydrochloride.[276] Although evidence strongly supports an enamine mechanism, the products were essentially racemic. (*ee*)



(**99**)



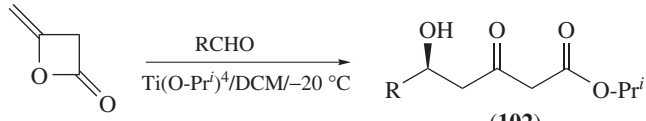
(**100**)

Corey–Chaykovsky reaction of a ketone R^1COR^2 with Me_3S^+ I^-–NaH in DMSO is a useful synthesis of epoxides, but a re-investigation in THF using *n*-BuLi as base gave significant amounts of β-hydroxymethyl thioether (**100**), in addition to epoxide.[277] This represents formal addition of Me_2S.

Di- and tri-substituted enamines of aldehydes have been generated under mild conditions (1 h, 0 °C, 1.2 equiv. of amine).[278] Although easily isolable, they can be conveniently employed *in situ*. The reaction is chemoselective (ketones present are not affected), it tolerates sensitive groups such as acetals and silyl ethers, and it works for both aliphatic and aromatic aldehydes.

Chiral Schiff bases derived from salicylaldehyde, when complexed to titanium(IV), catalyse enantioselective addition of diketene (**101**) to aldehydes (RCHO; R = Ph, alkyl, alkenyl) to yield δ-hydroxy-β-keto esters (**102**), with up to 84% *ee*.[279] (*ee*)

2-Aryl aldehydes and ketones with an α-substituent, Ar–CHMe–COR (R = H, Me), are sulfamidated to give α,α-disubstituted product, Ar–C(NHTs)Me–COR, by



(**101**) (**102**)

chloramine-T.[280] In the case of the aldehydes, oxidation and removal of the tosyl group give access to α,α-disubstituted amino acids.

The Willgerodt reaction allows amide synthesis from aromatic aldehydes or ketones, using a secondary amine and a thiating agent. The mechanism of the more convenient Kindler modification, employing sulfur and morpholine, has been reviewed.[281]

Tetrakis(dimethylamino)ethylene (TDAE) has been used as a reagent for the nucleophilic perfluoroalkylation of aldehydes, ketones, imines, disulfides, and diselenides.[282] Analogous to triflouromethylation with CF_3I, the reagents C_2F_5I and n-C_4F_9I ('R_F-I') give perfluoroalkylation in DMF solution. The aldehyde and ketone reactions give enhanced yields upon irradiation. TDAE is presumed to reductively cleave R_F-I to give RF^- and I^- (and $TDAE^{2+}$).

The conjugate bases of amides, imides, and carboxylic acids have been used as Lewis acids for perfluoroalkylation of carbonyl compounds and aldimines, using TMS-R_F reagents ($R_F = CF_3$, C_2F_5, and n-C_3F_7).[283]

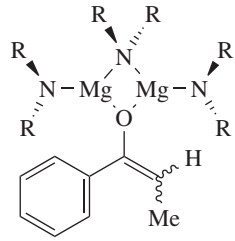
Catalytic asymmetric synthesis of enantiopure diaryl-methanols and -methylamines (important pharmaceutical intermediates) has been reviewed (76 references), focusing on (i) aryl transfers on to aryl-aldehydes and -imines and (ii) asymmetric reductions (*ee*) of diaryl-ketones and -ketoimines.[284]

Asymmetric synthesis of diarylmethanols can be achieved via rhodium-catalysed addition of arylboronic acids to benzaldehydes, using chiral mono- or bi-dentate phos- (*ee*) phoramidites based on BINOL.[285]

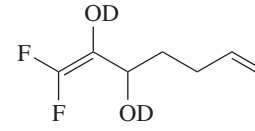
Benzaldehyde undergoes nucleophilic arylation with phenyltrimethoxysilane, PhSi-$(OMe)_3$, to give diphenylmethanol in good yields under moderately vigorous conditions: $Bu_4N^+F^-$ catalysis in refluxing acetonitrile.[286] However, this 1,2-addition process is completely switched to give methyl benzoate, the oxidative esterification product (at 25 °C), by addition of a palladium–phosphinous acid catalyst. NMR evidence suggests that the siloxane may perform three functions: generating a Lewis acidic silicate to activate the aldehyde, while acting as methoxy donor and hydride acceptor.

Enolization and Related Reactions

Magnesium bis(hexamethyldisilazide), $Mg(HMDS)_2$, catalyses the enolization of ketones.[287] On addition to propiophenone in toluene at ambient temperature, a ca 3:1 *E:Z* mixture of enolates (**103**, R=$SiMe_3$) is formed. These enolates, and an initial ketone complex, have been characterized by NMR, X-ray, IR, and UV–visible spectroscopy and computational studies. Kinetics of tautomerization have been measured, with proton transfer confirmed as rate determining ($k_H/k_D = 18.9$ at 295 K). The significant temperature dependence of the primary isotope effect is indicative of tunnelling.



(**103**)



(**104**)

Enol (**104**), generated rapidly in acidic solution from a precursor acetal, shows remarkable stability: $t_{1/2} > 3$ h in 0.1 mol dm^{-3} DCl in CD_3OD at 300 K, allowing its characterization by 2D NMR spectroscopy. A DFT study of a simple model, 2,2-difluoroethenol, indicates that there are significant differences in timing of the protonation TS compared with the non-fluorinated enol.[288]

Keto–enol tautomerization of 3-hydropyridazine derivatives has been investigated using DFT: the 2-hydropyridazin-3-one tautomer is typically found to be the most stable.[289]

Triethylgallium has been used as a non-nucleophilic base to generate enolates from ketones, both cyclic and acyclic, without forming carbonyl addition products.[290] The gallium enolates can then be *C*-benzoylated, and can participate in aldol reactions. Unsymmetrical ketones preferentially enolized at the methylene, under kinetic control.

Silyl enol ethers of decalones have been synthesized which allow stereoselective protonation of the corresponding enol to be initiated and followed kinetically.[291] Pendant groups have been placed so that the relative rates of intermolecular protonation and intramolecular protonation (by the proximate group) can be measured. Examples of groups which give one or other mechanism are detailed: CO_2^- and CO_2H typify the latter.

Commercially available amino acid derivatives have been tested as chiral proton sources for protonation of lithium enolates: catalytic N^{β}-L-aspartyl-L-phenylalanine methyl ester gave an *ee* of 88%.[292] (*ee*)

A stereoselective enolate protonation has been achieved by changing the counterion of the chiral alkoxide base employed: the lithium alkoxide-generated enolate gives close to 90% of the β-epimeric ketone product, whereas the use of the potassium cation gives 99% α-epimer.[293] (*ee*)

A chiral BINAP-diphosphine complexed to silver(I), with fluoride as counterion, catalyses the enantioselective protonation of TMS-enolates, giving ketones with a tertiary asymmetric α-carbon in up to 99% *ee*.[294] (*ee*)

α-Halogenation, α-Alkylation, and Related Reactions

Key advances in α-fluorination which occurred in 2005, using both organo- and metallo-catalytic approaches, have been reviewed (21 references).[295] (*ee*)

A mild metal-free α-iodination of ketones uses molecular iodine in a neutral reaction medium.[296] Aliphatic ketones react predominantly on the more substituted side, with

about 1 day at room temperature being sufficient. Aryl alkyl ketones require the solvent, dimethoxyethane, to be heated to reflux for a few hours. Iodine is proposed to act as a Lewis acid promoter of initial enolization of the ketone, while HI formation should give autocatalysis; pyridine stops the reaction.

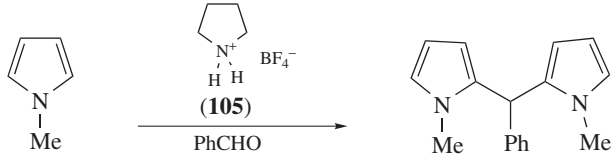
A new synthesis of pyrroles generates a 1,3-diketone by reacting a lithium enolate of a ketone with an acid chloride; *in situ* addition of a hydrazine yields, potentially, a tetrasubstituted pyrazole.[297] Tolerant of a wide range of functional groups, it is also easily adapted to rapid preparation of fused bicyclic pyrazole systems.

The utility of global and local reactivity descriptors to predict chemical reactivity and *C*- versus *O*-alkylation has been investigated for the case of lithium enolates.[298]

The origin of the dramatically increased enantioselectivity of α-alkylation of aldehydes when 2-methylproline is substituted for proline as organocatalyst has been investigated using DFT.[299] (*ee*)

Direct catalytic intermolecular α-allylic alkylation of aldehydes and cyclic ketones has been achieved using a one-pot combination of a transition metal catalyst, $Pd(PPh_3)_4$, and an organocatalyst: a secondary amine which facilitates enamine catalysis.[300]

Pyrrolidinium tetrafluoroborate (**105**) serves as an organocatalyst for the reaction of benzaldehyde with *N*-methylpyrrole, to give the corresponding dipyrromethanes (**106**) under mild conditions.[301] Initial formation of an iminium ion by condensation of the aldehyde with the catalyst is proposed.



(**106**)

2-, 3-, and 4-pyridinecarboxaldehyde condense with benzene in $F_3C–SO_3H$ (triflic acid), to give the *gem*-diphenyl product, $PyCHPh_2$.[302] Substituted pyridine aldehydes also gave the reaction, and deactivated arenes (e.g. *o*-dichlorobenzene, nitrobenzene) also work. Even hydrocarbons such as adamantine work, in the presence of high-pressure CO, giving adamantanyl–CO–CH_2Py derivatives. Evidence for the formation of dicationic intermediates (diprotonated pyridinecarboxaldehydes) is seen at low temperatures in superacid ($FSO_3H–SbF_5$) using ^{13}C NMR spectroscopy.

Oxidation and Reduction of Carbonyl Compounds

Regio-, Enantio-, and Diastereo-selective Reduction Reactions

An integration of readily available computational methods and visualization techniques has rendered a simple method to predict nucleophilic asymmetric induction of prochiral electrophiles.[303] Taking the examples of ketone and aldehyde reductions, electrostatic potential has been mapped on to the frontier orbital involved. A distinct difference in (*de*)

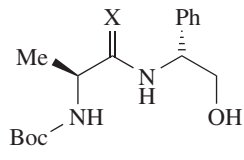
potential between the faces of the carbonyl has been used to predict the direction of nucleophilic attack.

In a probe for the presence of stereoelectronic effects in nucleophilic addition to 12 sterically unbiased ketones, calculations have identified subtle bond length differences in the C–Nu bond of the diastereomeric alcohol products, where $Nu^- = H^-$ or Me^-.[304] The calculated differences are weak (<1%) but consistent: the bond is longer in the major product, acting as a 'fossil record' of the TS. Using microscopic reversibility, the easier bond to cleave (the longer one) is the easier to form. The effect bears comparison with the kinetic anomeric effect in sugars, where such bond length differences in calculation are borne out in X-ray crystal structures.

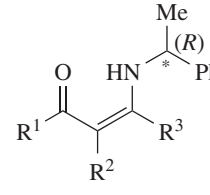
Asymmetric hydrogenation of ketones is one of the more common reduction methods, with ruthenium complexes often used as catalysts, a topic which has been reviewed.[305] (*ee*)

Noted results in this area include the following: [$RuCl_2$(*p*-cymene)]-pseudo-dipeptide catalysts are markedly affected by alkali metal cations (calculations show that the higher *ee* associated with addition of lithium cation is due to a tighter TS);[306] a kinetic study of continuous homogeneous hydrogenation uses a chemical membrane reactor with a 'polymer-enlarged' chiral ruthenium catalyst while retaining *ee* and conversion from the batch process;[307] and Noyori's catalyst system of *trans*-Ru(diphosphine)Cl_2(diamine) plus base in propan-2-ol has been investigated in its chiral form (both ligands chiral): several inaccessible intermediates have been identified which shed light on the role of added base.[308] Ruthenium(II) catalysis with ferrocenylamino auxiliaries shows asymmetric contributions from both planar and carbon-centred chirality,[309] and terpene-derived β-amino alcohols complexed to the same metal centre give moderate *ee*s for reduction of aryl alkyl ketones.[310] High *ee*s are obtained when the ruthenium is complexed with two common chiral chelators: *trans*-1,2-diaminocyclohexane and BINOL-derived phosphines.[311] (*ee*) (*ee*) (*ee*) (*ee*) (*ee*) (*ee*)

A range of α,β-unsaturated, α-tosyloxy, and α-substituted ketones have been reduced via asymmetric transfer hydrogenation using chiral ruthenium(II) and rhodium(III) complexes.[312] A chiral amide (**107**, X = O) promotes enantioselective transfer hydrogenation of aryl alkyl ketones, giving the (*S*)-secondary alcohols with modest *ee*, using the same two metal cations.[313] Switching from the simple α-amino acid amide to its thioamide analogue (**107**, X = S) raises *and* reverses the selectivity, giving *R*-product with up to 97% *ee*. This dramatic switch may arise from a different coordination mode: simple thioamides have an N–H pK_a about 7 units below amides, so that the NH of the thioamide auxiliary is likely to be an acidic site, with the BocNH as a basic site. (*ee*) (*ee*)



(**107**)



(**108**)

2,2,2-Trifluoroacetophenones, Ar^1COCF_3, react with arylboronic acids, $Ar^2B(OH)_2$, to give tertiary alcohols, Ar^1Ar^2–*CHOH:[314] the auxiliary is a phosphoramidite derived from BINAP, complexed to rhodium(I). A rhodium(III) chloride catalyst bearing a cyclopentadienyl ligand with a chiral cyclohexadiamine–monotosylate tether gives near quantitative conversion, with *ee*s up to 99.5%.[315] Employing transfer hydrogenation methods – ammonium formate in water or formic acid–triethylamine – loadings of 0.5% catalyst give completion in typically a few hours at 28 °C. Trials with loadings as low as 0.01% took longer, naturally, but gave the same *ee*, indicating negligible background rates. (*ee*) (*ee*)

Perfluoroalkyl ketones have been reduced in high *ee* using a simple alkoxide; lithium (*S*)-1-phenylethoxide, for example, reduces 2,2,2-trifluoroacetophenone to its (*S*)-carbinol in 80% *ee* and 61% yield at 0 °C, with acetophenone produced as by-product.[316] (*ee*)

The asymmetric reduction of achiral ketones using borohydrides has been reviewed, particularly the use of sodium borohydride in combination with chiral Lewis acids.[317] Such a reduction of unsymmetrical benzophenones gives poor *ee* (0–46%), unless an *o*-fluoro substituent is present, where *ee* values range from 80 to 96%.[318] Aliphatic ketones have been reduced in high *ee*, using a tartrate-derived boronic ester and borohydride.[319] Enantiopure *syn*-γ-amino alcohols have been prepared by reduction of chiral β-enaminoketones (**108**; R^1 = Me, Ph; R^2 = H, Cl; R^3 = Me, CF_3) using sodium borohydride in acetic acid at 10 °C.[320] Molecular modelling, X-ray, and ^{1}H NMR data afforded absolute configurations. The acidic conditions convert the reactant to its protonated enolimine form, setting up boron attachment to oxygen, so that C=N reduction occurs first. (*ee*) (*ee*) (*ee*) (*de*)

Chiral C_2-symmetric boron bis(oxazolines) act as enantioselective catalysts in the reduction of ketones promoted by catecholborane.[321] DFT calculations indicate that the stereochemical outcome is determined by such catalysts being able to bind both the ketone and borane reducing agent, activating the latter as a hydride donor, while also enhancing the electrophilicity of the carbonyl. X-ray structures of catalyst–catechol complexes are also reported. (*ee*)

(*S*)-Methyl lactate gives a poor *ee* in hydroboration of acetophenone, but $ZnCl_2$ raises it.[322] A molecular orbital method has looked at the enantioselectivities associated with four oxazaborolidine catalysts acting on phenyl methyl ketone.[323] (*ee*) (*ee*)

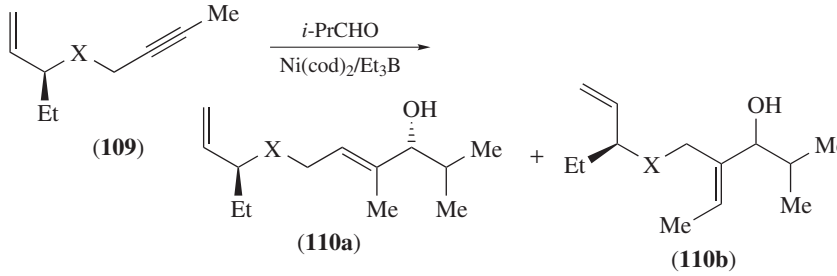
1-Ethylpyridinium tetrafluoroborate, a readily accessible ionic liquid, is an effective solvent for BINOL-promoted enantioselective reduction of aryl alkyl ketones by LAH.[324] A chiral diol modifies LAH reagents to give up to 98% *ee*.[325] (*ee*)

A new active-iron reducing system – iron(II) chloride tetrahydrate–excess lithium powder–5 mol% 4,4′-di-*t*-butylbiphenyl in THF – reduces ketones and imines.[326] Mono- and poly-cyclic ketones in particular are reduced with good to excellent *ee*. (*de*)

Camphor-derived α-ketoamides undergo two reactions with 98% yield and *de*: (i) allylation with allyltributylstannane and a Lewis acid catalyst and (ii) reduction with K-Selectride.[327] The stereoselectivity of the allylation can be reversed by appropriate change of Lewis acid. (*de*)

Chiral 1,6-enynes (**109**, X = O or CH_2) undergo nickel-catalysed reductive coupling with aldehydes to give regioisomers, **110a** and **110b**; regioselectivity is 95:5, with a

de of 90%.[328] However, addition of catalytic amounts of tri(cyclopentyl)phosphine completely reverses the regioselectivity to give >95% of **110b**, this time with no *de*. Three distinct mechanistic possibilities are discussed, with the authors favouring coordination of alkyne and alkene to the metal centre during the C−C bond-forming step (favouring **110a** with high *de*). The phosphine, however, can directly coordinate to the metal, disrupting this effect.



Developments in the enantioselective formation of tertiary alcohols via asymmetric addition to ketones have been reviewed.[329]

Other Reduction Reactions

The kinetics and mechanism of hydride transfer between Michler's hydride and 2,3,5,6-tetrabromo-*p*-benzoquinone have been investigated spectrophotometrically, examining both solvent and pressure effects.[330]

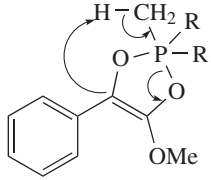
A remarkable reduction protocol reduces a wide range of oxygen functionality to hydrocarbon, including carboxylic acids, aldehydes, ketones, and all alcohols: (primary, secondary and tertiary). Using a simple silane (*n*-butyl or diethyl) and a Lewis acid catalyst, tris(pentafluorophenyl)borane, the reaction takes a few hours in DCM under argon.[331] Alkene functionality, nitro groups, and ethers are all unaffected, while phenols are merely silylated. Similar mechanisms are proposed for all reductions: hydride abstraction by boron with simultaneous oxygen attack on silicon, giving a silyloxy cation, followed by hydride return to carbon.

A dynamic kinetic resolution has been employed to achieve a catalytic asymmetric reductive amination of aldehydes.[332] Reductive amination of ketones and aldehydes by sodium triacetoxyborohydride has been reviewed, highlighting its advantage over other reagents.[333]

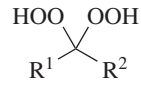
Reductive amination of ketones using *p*-anisidine and the Hantzsch ester for transfer hydrogenation is a low-yielding reaction in toluene at room temperature, but thiourea is an efficient catalyst, and yields of up to 94% are reported at 50 °C.[334] A mechanism involving thiourea hydrogen bonding to the intermediate imine is supported by *ab initio* calculations.

A variety of activated carbonyls such as α-keto esters, benzils, cyclohexane-1,2-dione, and α-ketophosphonates have been reduced to the corresponding α-hydroxy compounds in THF at room temperature, using alkylphosphines (PMe_3 or $PPhMe_2$).[335]

^{2}H- and ^{18}O-labelling experiments suggest that proton transfer from alkylphosphine occurs (via e.g. **111**?), with aqueous workup releasing the product plus $R_2P(=O)Me$.



(**111**)



(**112**)

A rhodium(I)–*N*-heterocyclic carbene complex has brought about a chemoselective decarbonylation, converting a cyclobutanone to the corresponding cyclopropane, while leaving an aldehydic substituent untouched.[336]

Oxidation Reactions

Ketones, R^1COR^2, have been converted to their *gem*-dihydroperoxides (**112**) using a 'green' oxidant, aqueous 30% hydrogen peroxide, with iodine as catalyst.[337] The iodine may enhance the electrophilic character of the carbonyl carbon and/or the nucleophilicity of the hydrogen peroxide. The reaction has also been extended to acetals and aldehydes.

A new ionic liquid, 1-butyl-3-methylimidazolium tribromide can act as an oxidizing agent to convert alcohols to aldehydes and ketones.[338] In the case of benzyl alcohols and diols, [Bmim][Br_3] combines oxidizing and brominating properties in a one-pot synthesis of β-bromoethyl esters.

The kinetics of the oxidation of aromatic aldehydes by *N*-chloronicotinamide in aqueous acetic acid are first order in both reactants and in proton.[339] The effect of substituents has been studied, and data at different temperatures yield activation parameters.

Several reports deal with the action of heterocycle–chromate agents such as: quinolinium dichromate on five-membered heteroaldehydes[340] and quinolinium bromochromate on benzaldehydes,[341,342] all in acetic acid solution. The latter studies show a second-order dependence on proton concentration, acceleration by electron-withdrawing *para*-substituents, and a substantial kinetic isotope effect for the deuterated aldehyde.

Oxidative amidation of aldehydes can be achieved with primary amine hydrochlorides, CuI as catalyst, and *t*-BuOOH as oxidant, probably via a carbinolamine intermediate.[343]

An experimental and theoretical study of the Baeyer–Villiger (BV) oxidation of ketones has examined its uncatalysed and acid-catalysed forms, and fluoro- and chloro-substituted substrates.[344] In assessing migratory aptitudes, fluoroalkyl groups are only slightly less favourable than alkyl (by 0.3/0.5 kcal mol^{-1}, calculated/observed), whereas migration of a chlorinated substituent is significantly more difficult (ca 2.6 kcal mol^{-1}).

Cyclohexanone and cyclopentanone monooxygenases have been used in the microbial BV oxidation of prochiral bicycloketones. A significant difference in behaviour of [3.3.0] and [4.3.0] substrates has been analysed by high-level DFT calculations.[345] Al–BINOL complexes catalyse the enantioselective BV oxidation of cyclobutanones to give the corresponding γ-butyrolactones in up to 84% *ee*.[346] Advances in the enantioselective metal-catalysed reaction have been reviewed, especially for lactone preparation.[347]

Other Reactions

Terminal alkynals (**113**) of appropriate length ($n = 1, 2$) and substitution [X = $C(CO_2Me)_2$, $C(CH_2OR)_2$, NTs, and others] have been cyclized with decarbonylation to cycloalkenes (**114**), using a ruthenium(I) catalyst.[348] In some cases, cycloisomerization to give conjugated aldehyde occurred. Both processes are believed to involve catalytic ruthenium vinylidenes.

(**113**) (**114**)

Alkynals and alkynones have been alkylatively cyclized in a palladium(0)-catalysed *trans*-addition of organoboronic acids.[349]

3-Silyloxy-2-aldehydes can undergo hetero-Diels–Alder reaction with aldehydes to give useful heterocycles.[350] A model reaction, $H_2C{=}C(OSiH_3){-}N{=}CH_2$ with formaldehyde, has been explored theoretically. Lewis acids such as boron trifluoride catalyse the reaction by coordinating to the aldehyde oxygen, making the aldehyde more electrophilic. Concerted and stepwise mechanisms for this process are considered.

Aromatic aldehydes react with triphenylphosphine and trichloroacetic acid derivatives ($Cl_3C{-}CO_2Et$, $Cl_3C{-}CN$) to give benzylidene dichlorides or α-chlorocinnamates.[351] Substituent and reaction condition effects on chemo- and regio-selectivity are described.

A variety of ketones and aldehydes have been condensed with sulfones, using *t*-BuOK catalysis in *N*,*N*-dimethylacetamide solvent.[352] Typical results – for α-methylcarbonyl compounds – include useful yields of the corresponding butadiene, whereas aromatic ketones give variations on the theme. α-Tetralone, for example, gives naphthalene and its α-methyl derivative (mainly the latter), but acetophenone interestingly gives some *p*-terphenyl.

Rates of alkaline hydrolysis of isatin (indane-2,3-dione) and its *N*-methyl derivative have been measured in a range of DMSO–water mixtures from 30 to 45 °C.[353] Analysis of activation parameters and rate variation with dielectric constant suggest selective solvation by water.

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CHAPTER 2

Reactions of Carboxylic, Phosphoric and Sulfonic Acids and their Derivatives

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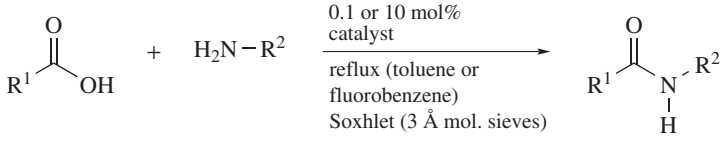
INTERMOLECULAR CATALYSIS AND REACTIONS

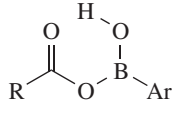
Carboxylic Acids and their Derivatives

(a) Acids

Reactions between a representative range of alkyl- and aryl-amines and of aliphatic and aromatic acids showed that the direct formation of amides from primary amines and carboxylic acids without catalyst occurs under relatively low-temperature conditions (Scheme 1). The best result obtained was a 60% yield of *N*-benzyl-4-phenylbutanamide from benzylamine and 4-phenylbutanoic acid. For all these reactions, an anhydride intermediate was proposed. Boric and boronic acid-based catalysts improved the reaction, especially for the less reactive aromatic acids, and initial results indicated that bifunctional catalysts showed even greater potential. Again, anhydride intermediates were proposed, in these cases mixed anhydrides of carboxylic acids and arylboronic acids, e.g. (**1**).[1]

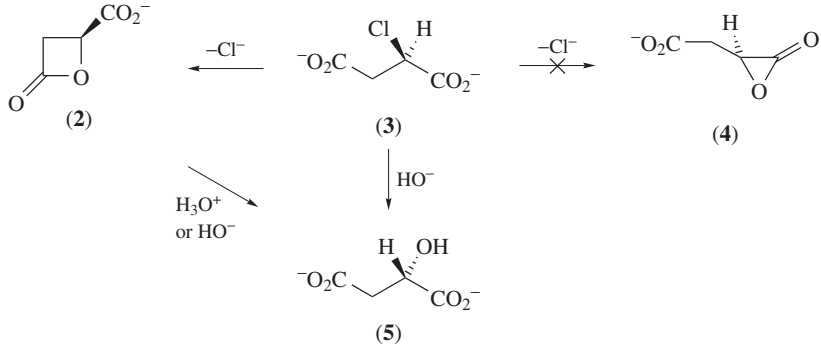


SCHEME 1

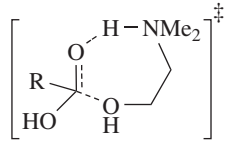


(**1**)

The text-book Walden-style cycle which interconverts the stereochemical configurations of chlorosuccinate (**3**) and malate (**5**) involves a β-lactone intermediate (**2**) in preference to an α-lactone intermediate (**4**) (Scheme 2) because the O_{nuc}–C–Cl angle in the transition structure for the former (174°) is more favourable than that for the latter (139°), as determined by PCM($\varepsilon = 78.4$)/B3LYP/6–31+G* calculations; the smaller ring-strain energy of the β-lactone contributes little to the reactivity difference.[2] *N*,*N*-Dimethylethanolamine esterified hexanoic acid about 10-fold faster than did hexanol as a consequence of intermolecular hydrogen bonding; a seven-membered transition state (**6**) was proposed.[3]



SCHEME 2



(**6**)

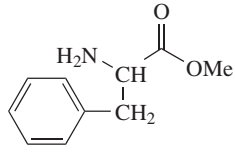
(b) Esters

(i) Transesterification

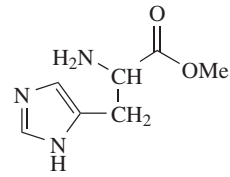
The rates and mechanisms of hydrolysis and transesterification of phenyl benzoate in aqueous ethanolic KOH solution were determined by non-linear least-squares regression.[4] Kinetic studies of the transesterification of a series of 4-nitrophenyl 3- and 4-substituted benzoates by 4-chlorophenol in DMF in the presence of potassium carbonate at various temperatures were reported.[5]

(ii) Solvolysis reactions

Solvolysis of esters was discussed in a review of secondary isotope effects.[6] Statistical analysis of various combinations of eight descriptors (e.g. bond lengths, atomic charges, LUMO, HOMO) that might allow the prediction of alkaline hydrolysis rates of esters showed that two of them, charge distribution of the C=O group and LUMO energy, are the best indicators.[7] An introduction to the concept of 'instantaneous rate constants' was made together with a description of its application to the alkaline hydrolysis of *p*-nitrophenyl acetate in water and in aqueous MeCN.[8] Hydroxide-catalysed ester hydrolysis for molecules of coexisting species has been quantitated in terms of microscopic rate constants, a new species-specific physicochemical parameter. Such rate constants take account of the various protonation states of the basic site(s) adjacent to the ester group, and they have been determined for the hydroxide-catalysed ester hydrolysis of phenylalanine methyl ester (**7**) and histidine methyl ester (**8**), which possess one and two adjoining basic groups, respectively, and yield two and four, respectively, microscopic rate constants.[9]



(**7**)

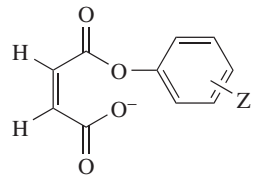


(**8**)

In a review of nucleophile isotope effects in chemistry, the hydrolysis of formates was discussed.[10] The effect of dioxane on the acid-catalysed hydrolysis of ethyl formate was studied by carrying out the reaction in 0–80% (v/v) dioxane at different temperatures ranging from 20 to 40 °C. It was proposed that up to 1.5 mol of water are associated with the activated complex.[11] Kinetic studies of the alkaline hydrolysis of ethyl decanoate[12] in DMF–H_2O solutions and of ethyl isovalerate[13] in aqueous acetone were reported.

Hydrolysis of *p*-tolyl trichloroacetate in MeCN–H_2O mixtures was studied as a function of water concentration in the range 5.5–55.5 M. The proton inventory technique, in H_2O–D_2O mixtures, showed, for a value of D atom fraction in the solvent $n = 0.5$, deviations from the expected value (for a reaction with one proton being transferred) of 7.5 and 12.3%, for experiments in the presence of 16.6 and 33.3 M L_2O (L = H or D), respectively. Theoretical treatment of the data obtained at $[L_2O] = 16.6$ and 33.3 M using the Gross–Butler equation were consistent with, respectively, a cyclic transition-state structure with three protons involved and a transition state in which multiple water molecules are involved.[14] The pH-independent hydrolysis of 4-nitrophenyl heptafluorobutyrate in MeCN–H_2O proceeded via a cyclic transition state containing the ester and three water molecules.[15] Kinetic studies of the alkaline hydrolysis of a wide range of alkyl benzoates, $PhCO_2R$ (R = Me, CH_2Cl, CH_2CN, $CH_2C{\equiv}CH$, CH_2Ph, CH_2CH_2Cl, CH_2CH_2OMe, Et) in various solvents concluded that the solvent electrophilicity, E, was the main factor responsible for changes in alkyl substituent effects with medium.[16]

Kinetic and theoretical studies of the hydrolysis reaction of Z-phenyl hydrogenmaleates (**9**; Z = H, *m*-CH_3, *p*-CH_3, *m*-Cl, *p*-Cl and *m*-CN) in aqueous solution showed that the Brønsted-type plot was linear with slope $\beta_{lg} = -1$, the results being consistent with a mechanism that involves significant bond breaking in the rate-limiting transition state ($\alpha_{lg} = 0.64$). Theoretical results for the reaction in the gas phase showed an excellent Brønsted-type dependence with a β_{lg} of −1.03, but a tetrahedral intermediate could not be found through DFT gas-phase studies (B3LYP/6–311+G*). It was suggested that an enforced concerted mechanism best describes these reactions.[17]

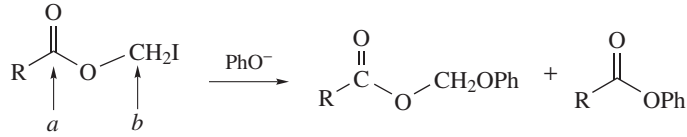


(**9**)

In a study of the influence of DMSO on the α-effect, second-order rate constants (k_{Nu^-}) were determined for reactions of a series of substituted phenyl acetates with butane-2,3-dione monooximate (Ox^-, α-nucleophile) and *p*-chlorophenoxide (*p*-$ClPhO^-$, reference nucleophile) in DMSO–H_2O mixtures of varying compositions at 25 °C. The magnitude of the α-effect, $k_{Ox^-}/k_{p\text{-}ClPhO^-}$, increased as the DMSO content in the medium increased up to 40–50 mol%, resulting in a bell-shaped α-effect profile regardless of the nature of the substrates. The bell-shaped α-effect profile was attributed to the differential change in the sensitivity of the medium effect on the Ox^- and *p*-$ClPhO^-$ systems but not due to a change in the reaction mechanism or to a drastic change in the basicity of the two nucleophiles upon addition of DMSO to the medium. Through application of calorimetric measurements of ground-state solvation combined with the diagnostic β_{nuc} values, it was shown that the transition-state effect is more dominant than the ground-state effect as the origin of the α-effect in this system.[18] The same group reported results of similar studies with 4-nitrophenyl benzoate, and made comparisons with their previous results obtained in a study of 4-nitrophenyl acetate. Both esters showed a bell-shaped profile for their reactions of butane-2,3-dione monooximate in DMSO–H_2O mixtures, and this modulation of the α-effect by the solvent medium was attributed to a ground-state effect in the H_2O-rich region and a transition-state effect in the DMSO-rich region.[19]

The *ortho* substituent effect in the alkaline hydrolysis of aryl esters of substituted benzoic acids in water was evaluated.[20] A kinetic study was reported for the reactions of 4-nitrophenyl X-benzoates and Y-phenyl benzoates with two anionic nucleophiles (OH^- and CN^-) and three amines (piperidine, hydrazine, and glycylglycine) in H_2O–DMSO (4:1) at 25 °C. Each Hammett plot exhibited two intersecting straight lines for the reactions of the 4-nitrophenyl benzoates with the anionic nucleophiles and piperidine, whereas the Yukawa–Tsuno plots for the same reactions were linear. The Hammett plot for the reactions of the phenyl benzoates with hydrazine and glycylglycine demonstrated much better linear correlations with σ^- constants than with σ^0 or σ constants, indicating that the leaving group departure occurs at the rate determining step (RDS). By contrast, σ^- constants resulted in poorer Hammett correlation than σ^0 constants for the corresponding reactions with OH^- and CN^-, indicating that the leaving group departure occurs after the RDS for the reactions with the anionic nucleophiles. The large ρ_x value (1.7 ± 0.1) obtained for the reactions of the 4-nitrophenyl benzoates with the anionic nucleophiles supported the proposal that the reactions proceed through an addition intermediate with its formation being the RDS.[21]

When acyloxymethyl iodides (**10**) were treated with PhO^- in acetone, the major products were the phenoxymethyl esters (**11**) resulting from attack at sp^3 carbon (*b*), with lesser amounts of the phenyl esters (**12**), the products of PhO^- attack at the C=O group (*a*) (Scheme 3). However, when the corresponding acyloxymethyl chlorides (**10**; Cl instead of I) were treated similarly, attack at only C=O was observed.[22] Rate and equilibrium constants were reported for reactions between a series of *N*-benzoyloxypyridinium salts and pyridine *N*-oxides and DMAP in MeCN.[23]



(**10**) (**11**) (**12**)

SCHEME 3

(iii) Aminolysis reactions

DFT was employed to study the mechanism of ammonolysis of phenyl formate in the gas phase, and the effect of various solvents on the title reaction was assessed by the polarizable continuum model (PCM). The calculated results show that the neutral concerted pathway is the most favourable one in the gas phase and in solution.[24] The structure and stability of putative zwitterionic complexes in the ammonolysis of phenyl acetate were examined using DFT and *ab initio* methods by applying the explicit, up to $7H_2O$, and implicit PCM solvation models. The stability of the zwitterionic tetrahedral intermediate required an explicit solvation by at least five water molecules with stabilization energy of approximately 35 kcal mol^{-1}.[25]

The rates of the reactions of 2,4-dinitrophenyl X-benzoates and Y-phenyl benzoates with a series of alicyclic secondary amines in MeCN at 25 °C were only slightly larger than those in H_2O, although the amines studied were approximately 8 pK_a units more basic in the aprotic solvent than in H_2O. The electronic nature of the substituent X in the non-leaving group did not affect the rate-determining step for the aminolysis of the 2,4-dinitrophenyl X-benzoates, for which a concerted mechanism was proposed. The medium change from H_2O to MeCN appears to force the reaction to proceed concertedly by decreasing the stability of the zwitterionic tetrahedral intermediate in the aprotic solvent.[26]

The aminolysis of Y-phenyl X-benzoates by piperidine in 20 mol% DMSO–H_2O at 25 °C proceeded, on the basis of a curved Brønsted-type plot, via a zwitterionic tetrahedral intermediate with a change in the RDS; the curvature centre of the plots was at p$K_a = 6.4$ regardless of the electronic nature of the substituent X in the benzoyl moiety.[27] The rates of aminolysis of a series of Y-phenyl benzoates by acylic secondary amines were compared with new results for similar reactions with Y-phenyl diphenylphosphinates (discussed further in the section *Phosphates and Phosphinates*). The results showed that the C=O compounds were more reactive than the P=O compounds.[28]

(c) Acyl Halides and Acid Anhydrides

Solvolysis rates of isopropenyl chloroformate, CH_2=C(Me)OC(O)Cl, were shown to be very similar to those for 4-nitrobenzoyl chloride in mechanism and reactivity.[29] Stepwise mechanisms were observed in the aminolysis of aryl chloroformates by a series of substituted quinuclidines – which were more reactive than isobasic secondary alicyclic amines.[30] The pH-independent hydrolysis of 4-nitrophenyl chloroformate in MeCN–H_2O mixtures proceeded via a cyclic transition state containing the ester and two water molecules.[15] Solvolyses of 2-furancarbonyl chloride in most

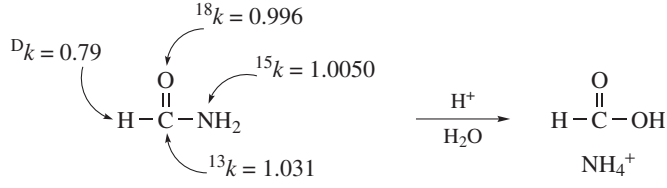
solvents proceeded via an elimination–addition pathway, in contrast to those of 2-thiophenecarbonyl chloride, which progressed via initial ionization.[31]

Steric effects were evaluated by a study of the DMAP-catalysed acylation of 1γ, 2γ and 3γ alcohols by acetic, propionic, isobutyric, isovaleric, and pivalic anhydrides in CH_2Cl_2 at 20 °C. In all cases the reaction kinetics could be described by rate laws containing a DMAP-catalysed term and an uncatalysed (background) term. Steric effects were evident in both reactions, but were generally greater for the DMAP-catalysed reaction. For example, the uncatalysed reactions between cyclohexanol and acetic and pivalic anhydrides differed about 500-fold, but for the corresponding DMAP-catalysed reactions the factor was 8000-fold. The implications of these findings for the kinetic resolution of alcohols were discussed.[32]

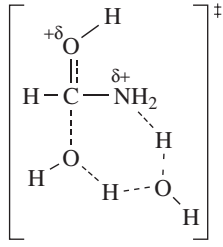
(d) Amides and Lactams

Hydrolysis of amides was discussed in a review of secondary isotope effects.[6]

Results of a multiple KIE study of the acid-catalysed hydrolysis of formamide (Scheme 4) were consistent with a stepwise mechanism, involving at least one tetrahedral intermediate (TI). In this mechanism, rapid protonation of the amide ($pK_a = -2$) is followed by the rate-determining attack of water, as evidenced by a levelling of the rate at high acid concentration and the lack of a sizable leaving-N KIE ($^{15}k = 1.0050$). The carbonyl-O was shown to exchange very little ^{18}O with the solvent, which was further evidence for the rate-determining formation of the TI, followed by the rapid breakdown to products. The formyl-H KIE was large and inverse ($^{D}k_{obs} = 0.79$), indicating that the transition state (**13**) resembled the structure of the TI.[33] The free-energy profile for the first step of formamide hydrolysis in aqueous alkaline solution was computed using Car–Parrinello molecular dynamics simulation combined with umbrella



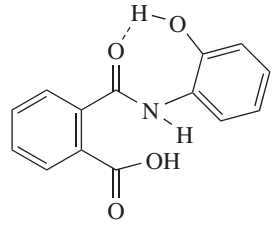
SCHEME 4



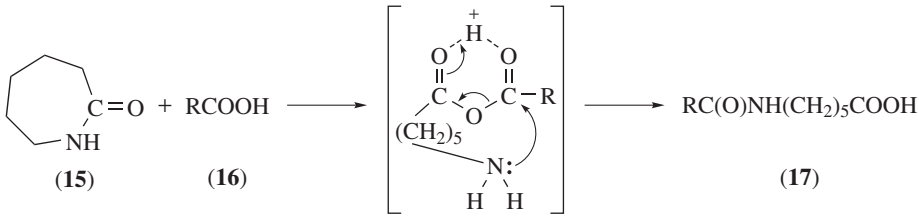
(**13**)

sampling. Activation and reaction free energies were estimated from the potential of mean force and were in unprecedentedly good agreement with the corresponding free enthalpies obtained from experiment.[34] The same group also conducted *ab initio* metadynamics calculations on this reaction, leading to two possible mechanisms.[35] For *N*-methylacetamide, *N*,*N*-dimethylformamide, and *N*,*N*-dimethylacetamide, in which some or all of the H atoms of formamide are replaced by Me groups, theoretical studies showed that the total number of water molecules H-bonding with the attacking HO^- in the transition state decreases from three (in formamide) to two.[36]

Studies of the acid hydrolysis of *N*-(2-hydroxyphenyl)phthalamic acid in MeCN–H_2O revealed that the expected intramolecular general-acid catalysis, as in (**14**), was not observed.[37] An equimolar mixture of *ε*-caprolactam (**15**) and 3-nitrobenzoic acid (**16**; R = 3-$O_2NC_6H_4$) when heated at 180 °C with *p*-toluenesulfonic acid yielded *N*-(3-nitrobenzoyl)-*ε*-aminocaproic acid (**17**; R = 3-$O_2NC_6H_4$), the reaction involving ring opening to an acyclic anhydride in which an N–O acyl migration occurs, as shown in Scheme 5; pentanoic acid (**16**; R = C_4H_9) reacted similarly.[38]



(**14**)



(**15**) (**16**) (**17**)

SCHEME 5

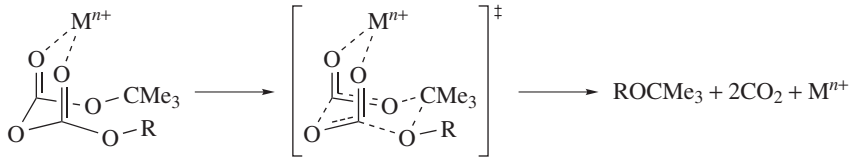
(e) Imides

Studies of the alkaline hydrolysis of *N*-benzylphthalimide in MeCN–H_2O and DMF–H_2O solutions concluded that the reaction mechanism is similar to that of other *N*-alkyl congeners.[39]

(f) Carbonates and Carbamates

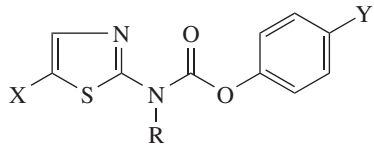
Aminolysis of a series of aryl 2,4-dinitrophenyl carbonates by a series of quinuclidines gave linear Brønsted-type plots, the magnitudes of their slopes confirming their mechanisms as concerted.[40] A comparison[41] of the aminolysis, by primary amines, of 4-nitrophenyl phenyl carbonate (**31**; X = O) with its thiono analogue (**31**; X = S) is discussed in the section *Thioacids, Thioesters, Thiolactones, and Thiocarbonates* below.

A full paper on the conversion of alcohols into *t*-butyl ethers by treatment with *t*-butyl dicarbonate (Boc_2O) and $Mg(ClO_6)_2$ [or, less effectively, $Al(ClO_4)_3$] in CH_2Cl_2 has elaborated upon the proposal made in a 2005 communication (see ORM 2005, p. 58). The process is now seen to involve initial formation of a mixed anhydride (**18**), which, catalysed by the metal, progresses to the product via a synchronous mechanism in a six-membered ring transition state (Scheme 6).[42]



SCHEME 6

Rates of reactivity of HO^- and HO_2^- towards *p*-nitrophenyl *N*,*N*-dimethylcarbamate in ROH–H_2O mixtures increased with increasing concentrations of Pr^iOH and Bu^tOH, but the reverse was true for $(CH_2OH)_2$.[43] Kinetic studies of the alkaline hydrolysis of a series of secondary *N*-thiazolylcarbamates (**19**; R = H) and tertiary *N*-methyl-*N*-thiazolylcarbamates (**19**; R = Me) have shown that they proceed by an *E*1*cB* and a $B_{Ac}2$ mechanism, respectively.[44]



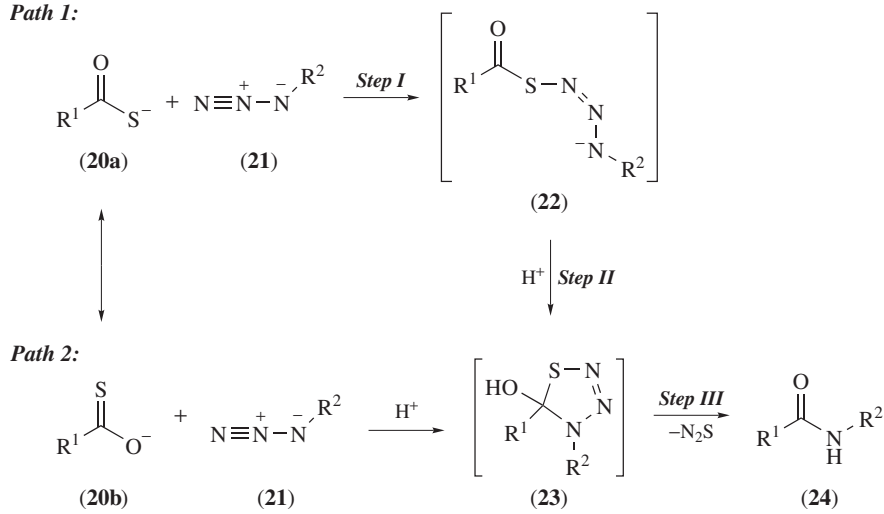
(**19**)

(g) Other Heterocyclic Nitrogen Centres

The acid and base hydrolysis of *N*-propionyl-imidazole and -benzimidazole derivatives proceeded via tetrahedral intermediates in both acidic and basic regions.[45]

(h) Thioacids, Thioesters, Thiolactones, and Thiocarbonates

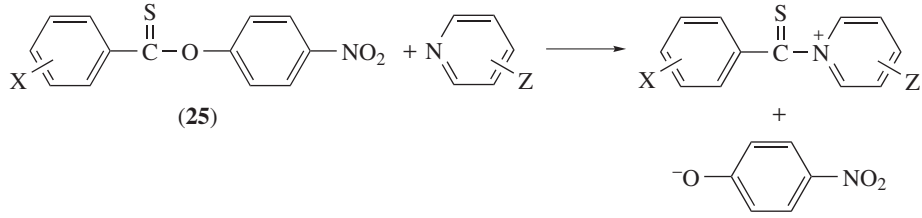
A combined experimental and computational mechanistic study of amide formation from thioacids and azides has shown that there are two distinct mechanistic pathways depending on the electronic character of the azide component (**21**) (Scheme 7). Highly electron-poor azides couple (*Path 1*) via bimolecular union of the terminal nitrogen of the azide with sulfur of the thiocarboxylate (**20a**) to give linear adducts (**22**) (*Step I*). Cyclization of these intermediates (*Step II*) gives thiatriazolines (**23**). Relatively electron-rich azides undergo bimolecular coupling with thiocarboxylates (*Path 2*) via an anion-accelerated 3 + 2-cycloaddition to give directly the same thiatriazolines (**23**). Decomposition to amide (**24**) (*Step III*) proceeds via retro-3 + 2-cycloaddition of the neutral thiatriazoline intermediates (**23**). Computational analysis [DFT, 6–31+G(d)] identified pathways by which both classes of azide undergo cycloaddition with thioacid to give thiatriazoline intermediates, although these paths are higher in energy than the thiocarboxylate amidations.[46]



SCHEME 7

In studies of the reactions of *S*-(4-nitrophenyl) 4-methylthiobenzoate with a series of six secondary alicyclic amines and a series of eight pyridines in 44 wt% ethanol–water at 25 °C, the Brønsted-type plots were non-linear with the curvature centre defined as pK_a^0 located at pK_a 9.7 and 9.4 for the reactions of secondary alicyclic amines and pyridines, respectively. The plots are consistent with a zwitterionic tetrahedral intermediate on the reaction path and, as the basicity of the amine increases, a change in rate-determining step from its breakdown to its formation.[47]

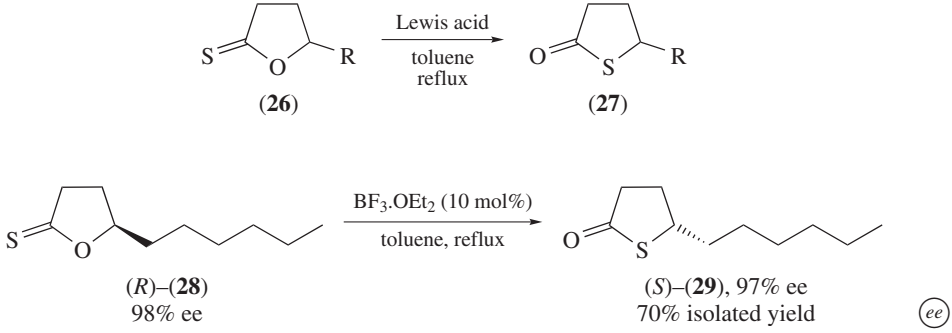
The reactions of 4-nitrophenyl benzoate and *O*-4-nitrophenyl X-thionobenzoates (**25**) with a series of pyridines in 20 mol% DMSO were studied at 25 °C (Scheme 8). *O*-4-Nitrophenyl thionobenzoate (**25**; X = H) was more reactive than its oxygen



SCHEME 8

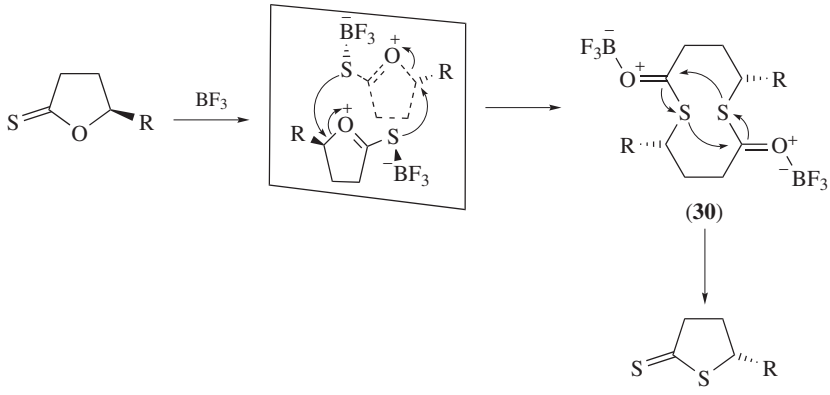
analogue towards all the pyridines studied. The Brønsted-type plot was linear with $\beta_{nuc} = 1.06$ for reactions of the benzoate but curved for the corresponding reactions of the thionobenzoate, with β_{nuc} decreasing from 1.38 to 0.38 as the pyridine basicity increases, indicating that the reaction mechanism is also influenced on changing the electrophilic centre from C=O to C=S. The curvature centre (pK_a^0) of the curved Brønsted-type plots occurred at $pK_a = 9.3$ regardless of the electronic nature of the substituent X in the non-leaving group.[48]

Boron trifluoride and indium(III) triflate were found to catalyse efficiently the isomerization of thionolactones (**26**) to thiolactones (**27**) in good yields. When applied to an optically active γ-thionolactone [(*R*)-**28**], the isomerization reaction proceeded with complete inversion of configuration to [(*S*)-**29**] by using $BF_3.OEt_2$ (Scheme 9). The proposed mechanism (Scheme 10) implicates a double S_N2-type process involving two molecules of thionolactone, each complexed with BF_3, that progresses to the product via the dimer (**30**).[49]



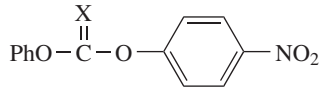
SCHEME 9

In a study of the aminolysis of 4-nitrophenyl phenyl carbonate (**31**; X = O) and thionocarbonate (**31**; X = S) with a series of primary amines, the thiono compound was found to be less reactive than its oxygen analogue toward strongly basic amines but was more reactive towards weakly basic $CF_3CH_2NH_2$. As the Brønsted-type plots obtained from the aminolyses of both compounds were curved downwards, it was proposed that the reactions proceeded via a stepwise mechanism with a change in the rate-determining step.[41]



(**30**)

SCHEME 10



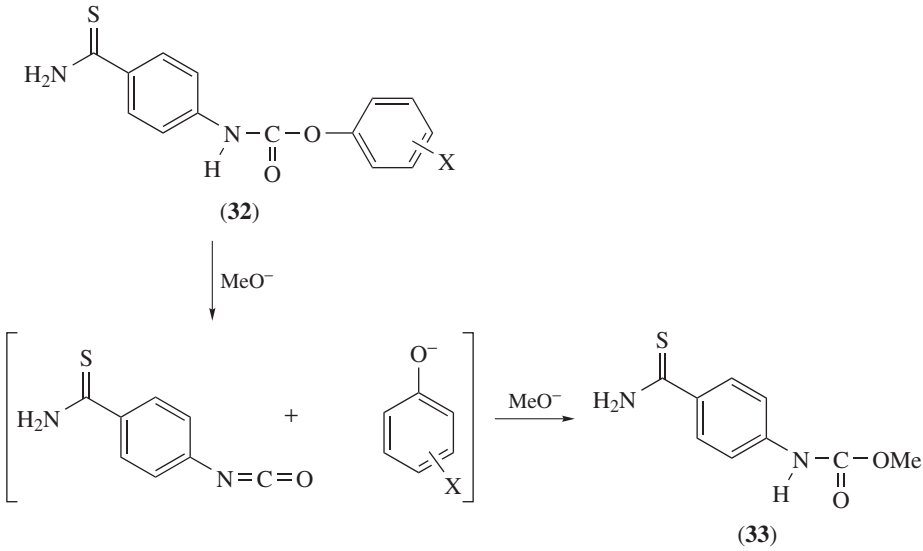
(**31**)

The reliability and usefulness of a new empirical nucleofugality index, which is defined as the group electrophilicity of the leaving group embedded in the substrate that undergoes the nucleophilic attack, were tested against experimental kinetic data recorded for aminolysis reactions of variously substituted phenoxy- and thiophenoxy-carbonyl and the corresponding thiocarbonyl derivatives.[50]

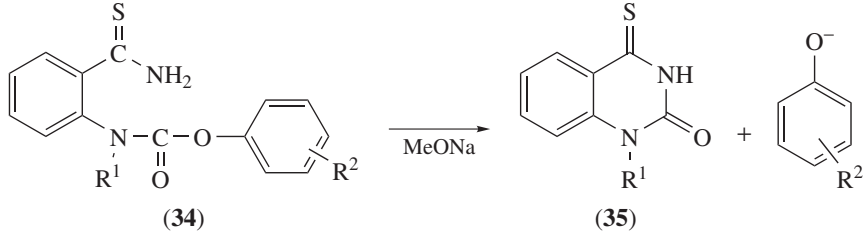
(i) Thiocarbamates and Thioacyl Halides

Two classical tools, the intermolecular stretching force constants of H-bonded complexes and the molecular electrostatic potential, were used to develop a nucleophilicity index, which was validated against kinetic data recorded for the aminolysis of *S*-methyl 2,4-dinitrophenylthiocarbamate.[51] Aminolysis of *N*-phenylthionocarbamates by benzylamines in MeCN proceeded by a stepwise mechanism in which the rate-determining step was the breakdown of the zwitterionic tetrahedral intermediate.[52]

Methoxide converted a series of X-phenyl *N*-(4-thiocarboxamidophenyl)carbamates (**32**; X = 4-MeO, 3-MeO, 4-Cl, 3-Cl, H) into methyl *N*-(4-thiocarboxamidophenyl) carbamate (**33**) and the corresponding phenate via an *E*l*c*B mechanism (Scheme 11). However, when a series of the corresponding aryl *N*-(2-thiocarboxamidophenyl)carbamates (**34**; R^1 = H, R^2 = 4-MeO, 3-MeO, 4-Me, 3-Cl, 4-Cl, 3-NO_2, H) were treated similarly, a rapid intramolecular cyclization occurred to give 4-thioxo-1*H*,3*H*-quinazolin-2-one (**35**; R^1 = H) and the corresponding phenate (Scheme 12). All the



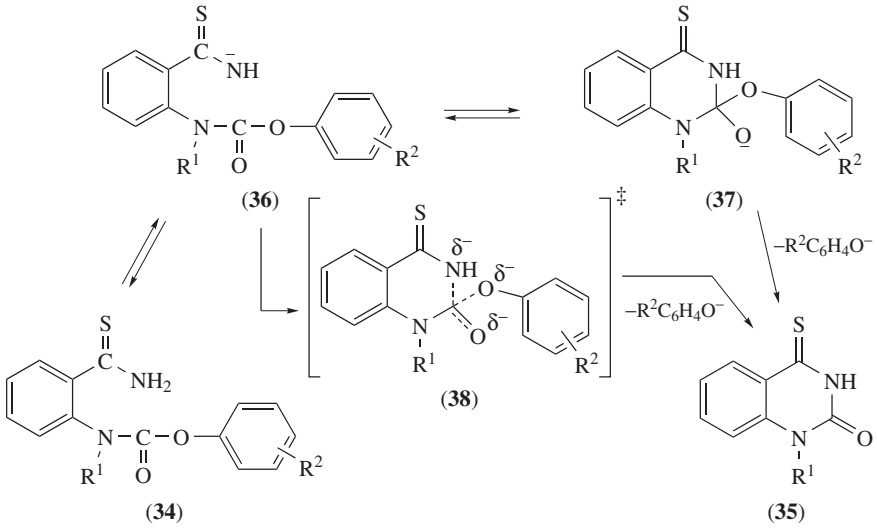
SCHEME 11



SCHEME 12

experimental evidence, in this case, pointed to a $B_{Ac}2$ mechanism (Scheme 13), involving initial formation of anion (**36**), which either progressed stepwise to a tetrahedral intermediate (**37**) and thence, with expulsion of phenate, to the product (**35**) or formed product concertedly via transition state (**38**).[53]

The pyridinolysis of *S*-methyl chlorothioformate, MeSC(O)Cl, showed a biphasic Brønsted-type plot, in agreement with a stepwise mechanism and a change in the rate-limiting step, from formation of a zwitterionic tetrahedral intermediate ($T^{\pm}$) at high pK_a to its breakdown at low pK_a. The reaction of the same substrate with secondary alicyclic amines showed a linear Brønsted-type plot of slope 0.23, which is in accordance with a stepwise mechanism where formation of $T^{\pm}$ is the rate-determining step for the whole pK_a range examined.[54]



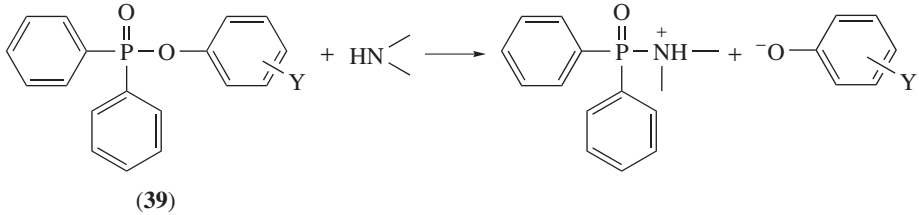
SCHEME 13

Phosphoric Acids and their Derivatives

(a) Phosphates and Phosphinates

The hydrolysis of phosphates is discussed in reviews of nucleophile[10] and secondary[6] isotope effects. The kinetics and mechanism of the acid hydrolysis of 3-aminophenyl phosphate were studied in 0.1–0.6 M HCl at 90 °C.[55]

The rates of aminolysis of Y-phenyl diphenylphosphinates (**39**) (Scheme 14) by a series of alicyclic secondary amines were determined in 20 mol% DMSO–H_2O at 25 °C. The phosphinates were less reactive than the corresponding Y-phenyl benzoates (the rates of which had been reported earlier). The reactions of 2,4-dinitrophenyl diphenylphosphinate [**39**; Y = 2,4-$(NO_2)_2$] with alicyclic secondary amines resulted in a linear Brønsted-type plot, whereas the corresponding reactions of 2,4-dinitrophenyl



SCHEME 14

benzoate had yielded a curved Brønsted-type plot, indicating, respectively, a concerted mechanism and a change in the rate-determining step of a stepwise mechanism.[28]

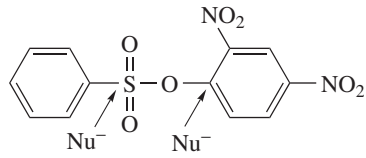
(b) Phosphoramidates and Phosphonamidates

When the mixed anhydride, $R_2CHP(O)(NEt_2)OS^{18}O_2Ar$ (R_2CH = 9-fluorenyl, Ar = *p*-tolyl) underwent nucleophilic substitution (elimination–addition) with Et_2NH (0.4 M in $CHCl_3$), the phosphene intermediate, $R_2C{=}P(O)NEt_2$, recombined with the sulfonate leaving group (internal return), causing scrambling of the ^{18}O label, more quickly than it diffused away; efficient conversion into $R_2CHP(O)(NEt_2)_2$ therefore depends on preassociation between the substrate and the nucleophile.[56] Kinetic studies were reported of the acid hydrolysis in 0.1–7.0 M HCl at 80 °C of *N*-(2,5-dichlorophenyl)phosphoramidic acid.[57]

Sulfonic Acids and their Derivatives

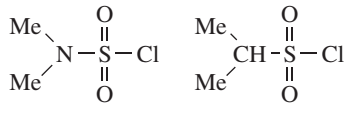
(a) Sulfonates and Sulfonyl Halides

Studies of the reaction between 2,4-dinitrophenyl benzenesulfonate and OH^-, CN^-, and N_3^- in 20 mol% DMSO–H_2O at 25 °C have shown that OH^- attacks exclusively at the sulfonyl group, but the softer nucleophiles react – as shown in (**40**) – to give mixtures of products of S–O and C–O bond fission, the fraction of the latter being 0.10 for CN^- and 0.66 for N_3^-. [58] The rate of reaction of hydroperoxide ion with 4-nitrophenyl 4-toluenesulfonate was reported.[43]



(**40**)

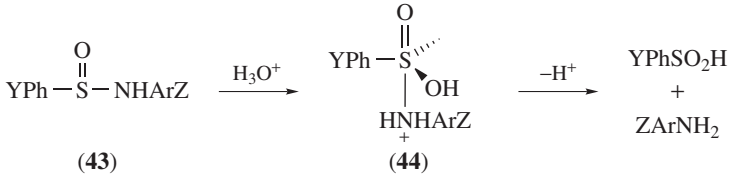
Contrary to earlier suggestions of an S_N1 pathway for solvolyses of *N*,*N*-dimethylsulfamoyl chloride (**41**), the results of an extended Grunwald–Winstein equation treatment of the specific rates of solvolysis of (**41**) in 32 solvents pointed to an S_N2 pathway. Results of a similar treatment of its rates of solvolysis in a range of solvents supported an S_N2 pathway for 2-propanesulfonyl chloride (**42**).[59]



(**41**) (**42**)

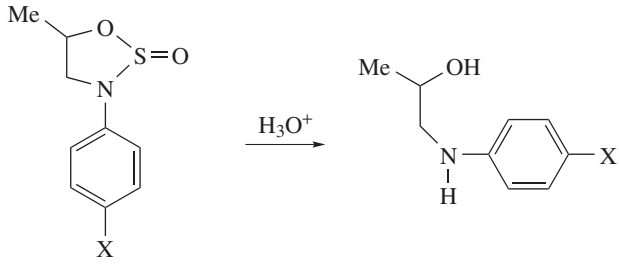
(b) Sultams, Sulfinamides, and Amidosulfites

The ring opening of β-sultam via an H_2O-assisted ammonolysis process was studied by using a DFT method at the B3LYP/6–31G* level as a further step in the theoretical investigation of the ammonolysis reaction of β-sultams. The calculated pathways were analogous to those previously described for the non-assisted ammonolysis reaction.[60] Acid hydrolysis of *N*-(Z-aryl)-Y-benzenesulfinamides (**43**) to Y-benzenesulfonic acids and Z-arylamines (Scheme 15) proceeded via a hypervalent intermediate (**44**).[61] Studies of the acid hydrolysis of three *N*-(X-phenyl)amidosulfites (**45**; X = H, Me, Cl) showed that the ring-opened products (**46**) were formed via water attack at the S=O group of an *N*-protonated intermediate.[62]



(**43**) (**44**)

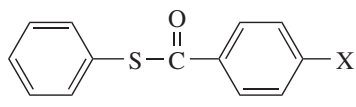
SCHEME 15



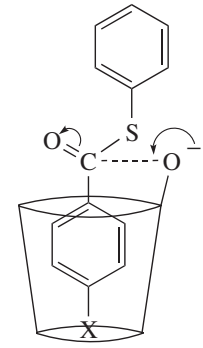
(**45**) (**46**)

ASSOCIATION-PREFACED CATALYSIS

Alkaline hydrolysis rates of a series of thiophenyl 4-X-benzoates (**47**; X = H, Me, NO_2) was significantly enhanced in the presence of cyclodextrins (CDs), and this was attributed to strong binding of the benzoyl moiety within the CD cavity and covalent catalysis by secondary hydroxy groups of the CDs (**48**).[63] The effect of MeCN and MeOH on the alkaline hydrolysis of acetylsalicylic acid in aqueous micellar solutions was reported.[64] Butylaminolysis of *p*-nitrophenyl acetate in chlorobenzene in the presence of different kinds of phase-transfer catalysts (crown ethers and glymes) supported the existence of a novel reaction pathway exhibiting a first-order dependence on the concentration of the phase-transfer catalyst and a second-order



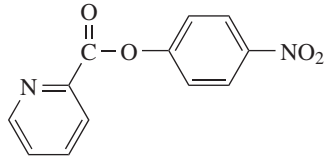
(**47**)



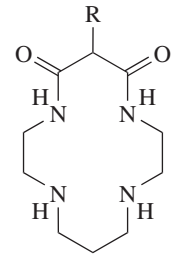
(**48**)

dependence on the concentration of butylamine.[65] Three double-headed hydroxamates, $^{-}ONHC(O)(CH_2)_nC(O)NHO^{-}$ ($n = 1, 2, 3$) exhibited α-nucleophile reactivities towards *p*-nitrophenyl acetate at pH 7.9 that were enhanced by cetyltrimethylammonium bromide (CTAB); the order of reactivity was (n) $1 > 2 > 3$.[66] In a wider study, the effect of cationic, anionic, and non-ionic surfactants on the reactivity towards *p*-nitrophenyl acetate of the α-nucleophile *N*-phenylbenzohydroxamate, PhC(O)N(Ph)O^{-}, at pH 7.7 was reported.[67]

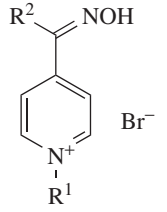
p-Nitrophenyl picolinate (**49**) has been studied in three reports. In the first, complexes of Ni(II) with dioxocyclam (**50**) increased the rate of hydrolysis of (**49**) some 3000-fold in the presence of a variety of surfactants, *n*-lauroylsarcosine sodium proving the most potent.[68] In the second, studies of the hydrolysis of (**49**) mediated by the micellar catalytic systems of two gemini cationic surfactants with different hydrophobic tail groups [ethanediyl-1,2-bis(dodecyldimethylammonium bromide) (12-2-12, $2Br^{-}$), and dimethylene-1,2-bis(cetyltrimethylammonium bromide) (16-2-16, $2Br^{-}$)] in the pH range 7.0–9.0 and at 25 °C showed that (16-2-16, $2Br^{-}$) enhanced the hydrolytic reaction notably more than gemini surfactant (12-2-12, $2Br^{-}$) under the same reaction conditions, which may be ascribed to the micelle effect.[69] In the third, the effect of Brij 35 surfactant on the hydrolysis of (**49**) catalysed by Ni^{2+}, Zn^{2+}, and Co^{2+} complexes of *N*-methyldiethanolamine, $MeN(CH_2CH_2OH)_2$, was studied kinetically at pH 7.00 and 30 °C.[70]



(**49**)



(**50**)



	R^1	R^2
51a	Me	n-C_8H_{17}
51b	Me	n-$C_{10}H_{21}$
51c	Me	n-$C_{12}H_{25}$
51d	Me	n-$C_{16}H_{33}$
52a	n-C_8H_{17}	Me
52b	n-$C_{10}H_{21}$	Me
52c	n-$C_{12}H_{25}$	Me
52d	n-$C_{16}H_{33}$	Me

The amphiphilic pyridinium ketoximes 4-[1-(hydroxyimino)alkyl]-1-methylpyridinium bromides (**51a–d**) and 1-alkyl-4-[1-(hydroxyimino)ethyl]pyridinium bromides (**52a–d**) are isomeric cationic surfactants bearing the nucleophilic hydroxyimino group but differing in the position of the nucleophilic function relative to the polar head group and the hydrophobic alkyl chain. 4-Nitrophenyl diphenyl phosphate cleavage by the oximate anions generated from (**51a–d**) and (**52a–d**) was used as a model reaction for the investigation of the influence of the structure and lipophilicity of functional surfactants on their reactivity in micelles and microemulsions. Investigation of the model reaction in cationic micelles of CTAB, in non-ionic micelles (Triton X-11 and Brij 35) and in oil–water microemulsion (isooctane–phosphate buffer–CTAB and butanol) revealed that lipophilicity is the most important factor influencing the localization and reactivity of functional surfactants in nanoaggregates.[71] The rate of alkaline hydrolysis of 2,4-dichloro- and 2,4-dibromo-phenyl phosphate increased in the presence of CTAB, an observation attributed to bromide ions in the micellar pseudophase.[72]

BIOLOGICALLY SIGNIFICANT REACTIONS

Enzymic Catalysis

(a) Peptidases

In a review of nucleophile isotope effects, results of studies of the hydrolysis of esters and amides by carboxypeptidase were discussed.[10]

(b) Phosphatases and Phosphotransferases

Although alkaline phosphatase evolved to hydrolyse phosphate monoesters, it also has significant diesterase activity. Now studies using a series of substituted methyl phenyl phosphate diesters have shown that phosphodiester hydrolysis within the enzyme proceeds by a similar transition state to that found in solution, validating the rational design of synthetic enzymes that operate in solution. Furthermore, those studies suggest that stabilizing the solution-phase transition state affords enzymes a degree of promiscuity that allows them to evolve alternative catalytic specificities.[73] Results of studies of secondary isotope effects of enzymes that effect phosphoryl transfer were reviewed.[6]

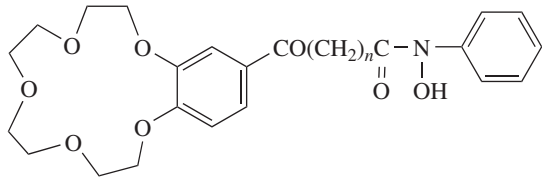
Intermolecular, Biomimetic, and Model Reactions

(a) Carboxylic Acids and their Derivatives

(i) Esters, lactones and carbonates

Acetylcholine, $Me_3N^+CH_2CH_2OCOMe$, is a neurotransmitter generated from choline, $Me_3N^+CH_2CH_2OH$, and acetyl coenzyme A. As a model of this process, a cavitand derived from resorcinarenes that specifically guests a trimethylammonium group has been derivatized at its periphery with a Zn-salen known to catalyse the acetylation of alcohols with acetic anhydride (Ac_2O). The salen-catalysed rate of acetylation of choline with Ac_2O was thereby enhanced 23-fold.[74] The rate of alkaline hydrolysis of the local anaesthetic novocaine (diethylaminomethyl 4-aminobenzoate) was reported.[75] Kinetic studies of the reactions of polyalkylamines with aryl acetates and aryl methyl carbonates at pH 7–11.5 showed that concerted mechanisms operate.[76] The hydrolysis of glycine methyl ester, $CH_2(NH_2)CO_2Me$, and methionine methyl ester, $MeSCH_2CH_2CH(NH_2)CO_2Me$, was catalysed with high effectiveness by the Cu(II) complex of *N*,*N*,*N*,*N*-tetramethylethylenediamine, the observed catalytic enhancement being 10^4-fold.[77]

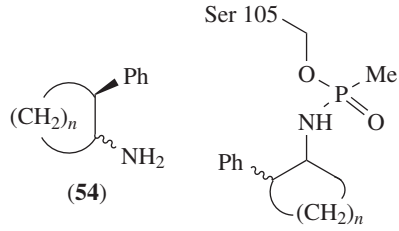
Binuclear Mn(II) and Zn(II) complexes of a polyether-bridged dihydroxamic acid, $[CH_2OCH_2CH_2OC_6H_4C(O)NHOH]_2$, as models of metallohydrolases exhibited high catalytic activity in the hydrolysis of *p*-nitropicolinate (**49**).[78] In a further development by the same group, bis complexes of two hydroxamic acids (**53**; $n = 4, 6$) containing benzo-crown-5 with Cu(II), Co(II), Zn(II), or Mn(II) were also highly effective catalysts for the hydrolysis of (**49**), the rate enhancements observed being more than 1000-fold.[79]



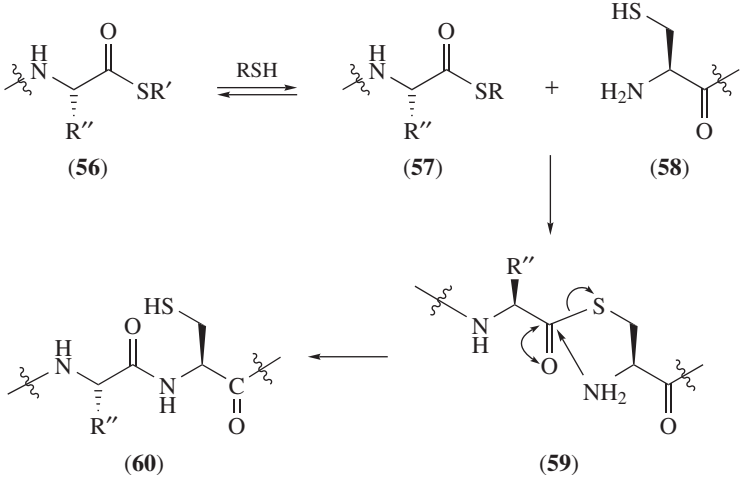
(**53**)

Studies of the ability of the lipase B from *Candida antarctica* (CAL-B) to catalyse the enantioselective aminolysis of esters by *cis*- and *trans*-2-phenylcycloalkanamines (**54**; $n = 1, 3, 4$) have been followed up by molecular modelling approaches in order to probe the lipase-catalysed aminolysis mechanism. CAL-B possesses a typical serine-dependent triad, so it was possible, with access to an X-ray crystal structure of CAL-B, to model a series of phosphonamidates (**55**; $n = 1, 3, 4$) as analogues of the tetrahedral intermediate (TI) resulting from attack of the amine on the carbonyl of the acyl-enzyme. The results suggested as the most plausible intermediate for the CAL-B-catalysed aminolysis a zwitterionic TI resulting from the direct His-assisted attack of the amine on to a C=O group of the acyl-enzyme.[80]

Native chemical ligation of unprotected peptide segments involves reaction between a peptide-α-thioester and an N-terminal cysteine-peptide to yield a product with a



native amide bond at the ligation site. Peptide-α-thioalkyl esters, used because of their ease of preparation, are rather unreactive so the ligation reaction is catalysed by *in situ* transthioesterification with thiol additives. Although full details of the mechanism of native chemical ligation have not yet been elucidated, reaction is envisioned to occur in the following way (Scheme 16).[81] A peptide-α-thioalkyl ester (**56**) is activated *in situ* by a thiol additive RSH to (**57**), which is reacted at pH 7 with a peptide containing an N-terminal cysteine (Cys) residue (**58**). Transthioesterification of (**57**) via the side-chain thiol of the N-terminal Cys results in a thioester-linked intermediate (**59**), which spontaneously rearranges through a favourable five-membered ring intramolecular nucleophilic attack by the Cys α-amino group to form a peptide (**60**) with a native amide bond. The most common thiol catalyst, RSH, used to date has been a mixture of thiophenol and benzenethiol, when ligation reactions typically take 24–48 h. In order to find a better catalyst, 14 thiol compounds were evaluated. A highly effective and practical catalyst was found to be (4-carboxylmethyl)thiophenol (MPAA), a non-malodorous, water-soluble thiol. Use of MPAA gave an order of

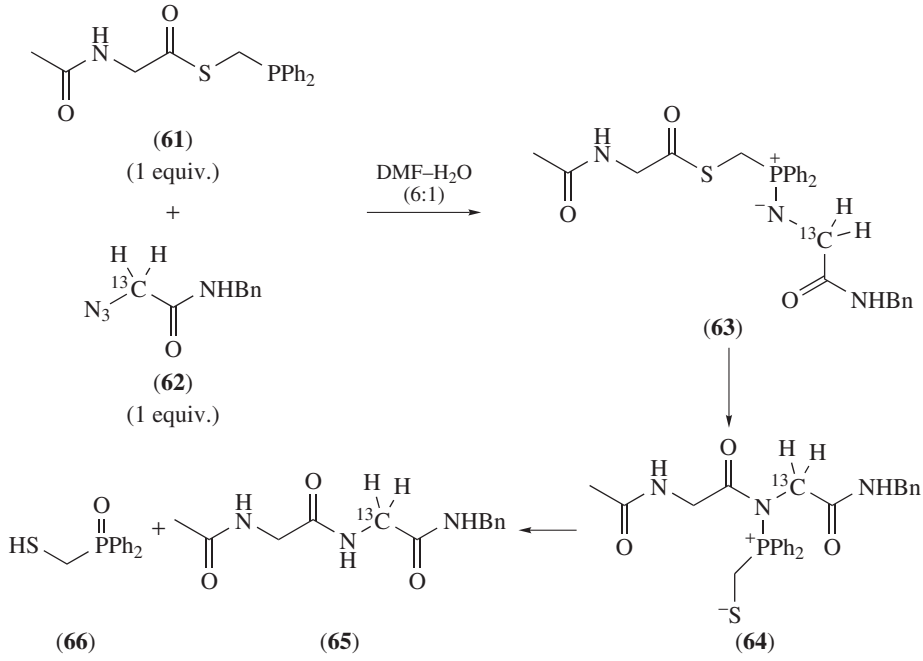


Scheme 16

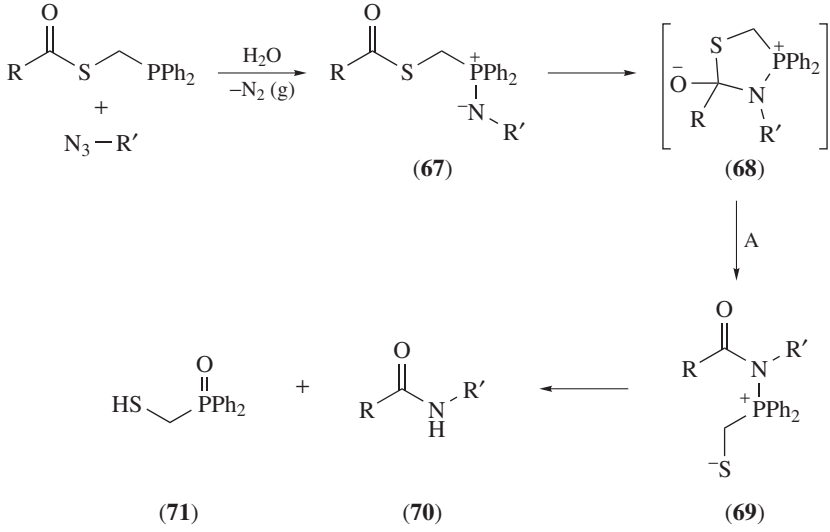
magnitude faster reaction in model studies of native chemical ligation and in the synthesis of a small protein.[81]

The Staudinger ligation is another method for the chemoselective ligation of peptide fragments. A highly efficient variant of it couples a peptide with a C-terminal phosphinothioester with a second peptide having an N-terminal azido acid. Now, detailed ^{13}C NMR studies of a model reaction in DMF–H_2O between two glycine derivatives, (**61**) and the [^{13}C]azide (**62**), have delineated the mechanism.[82] Fugitive amounts of two ^{13}C-labelled intermediates, (**63**) and (**64**), were detected in addition to the ^{13}C-labelled product of the reaction, the desired coupled 'peptide' (**65**) and (unlabelled) (diphenylphosphono)methanethiol (**66**) (Scheme 17). The proposed mechanism (Scheme 18) involves initial formation of an iminophosphorane (**67**) with evolution of N_2, which undergoes rapid cyclization to a tetrahedral intermediate (**68**), collapse of which generates an amidophosphonium salt (**69**) that rapidly hydrolyses to an amide (**70**) and the phosphine oxide (**71**). An experiment with $H_2{}^{18}O$ confirmed the final step, the label being found only in the phosphine oxide (**71**).[82]

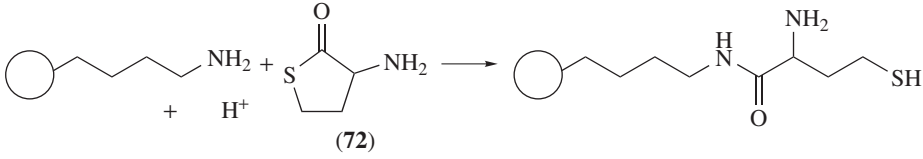
Homocysteine, $HSCH_2CH_2CH(NH_2)CO_2H$, is a toxic amino acid that is thought to acylate lysine residues on proteins via its corresponding thiolactone (**72**) (Scheme 19). Now, for the first time, the kinetics have been studied of the aminolysis of (**72**) and of two model compounds, γ-thiobutyrolactone (**72**; H instead of NH_2) and *N*-trimethylamino homocysteine thiolactone (**72**; Me_3N^+ instead of NH_2). A Brønsted plot for homocysteine thiolactone (**72**) gave $\beta = 0.66$. This and other data supported



SCHEME 17



SCHEME 18

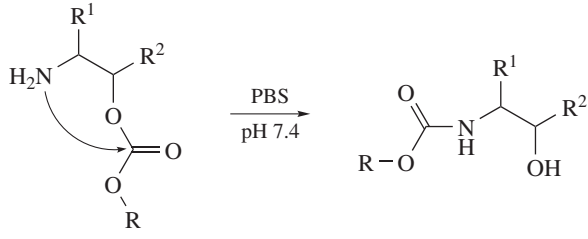


SCHEME 19

the formation of a zwitterionic tetrahedral intermediate as the rate-determining step in the aminolysis of all three thiolactones.[83] Intramolecular O–N alkoxycarbonyl (carbonate → carbamate) migration is potentially a useful reaction in peptide synthesis. Now, in model studies carbonates of 2-amino alcohols (**73**) have been shown to undergo facile intramolecular rearrangement under mildly basic conditions to yield *N*-(2-hydroxyethyl)carbamates (**74**) (Scheme 20).[84]

(ii) Amides and polypeptides

α,α-Dimethylglycines are among the simplest and most widely used structural units in the construction of peptides with a predetermined secondary structure. However, steric crowding prevents their easy incorporation into a peptide chain. A promising way round this difficulty is to synthesize the α,α-dimethylglycine unit already incorporated into the peptide chain. The four-component Ugi–Passerini reaction can yield compounds of the desired type, e.g. *N*,*N*-disubstituted α,α-dimethylglycine cyclohexylamides (**75**; R = aryl). Now, results of a study of the acidolysis of a series of seven of these compounds (**75**; R = 4-X-phenyl) in 5% TFA in MeCN have been

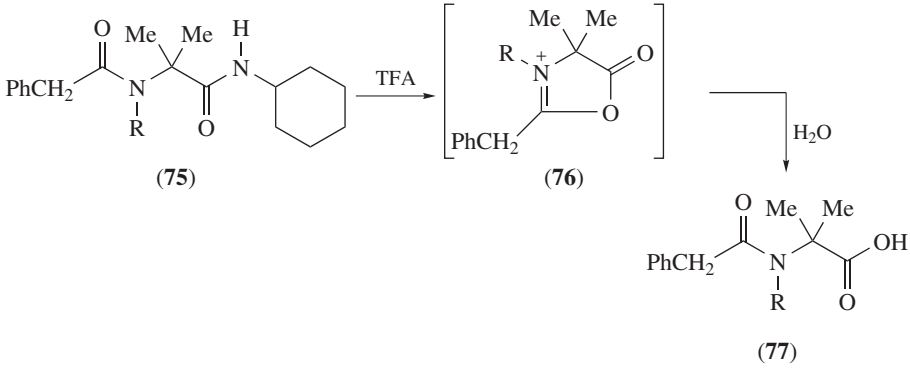


(**73**) (**74**)

PBS = phosphate-buffered saline

SCHEME 20

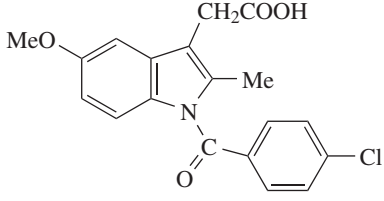
used to assess the influence of the substituents on the lability of the terminal amide (which needs to be removed to generate a free carboxyl group at the C-terminus). The *N*-phenylacetyl group plays a key role in the acidolysis by facilitating the ready formation of an intermediate oxazolone (**76**; R = 4-X-phenyl) (Scheme 21) which ring opens to an *N*-acyl-*N*-4-X-phenyl-α,α-dimethylglycine (**77**; R = 4-X-phenyl).[85]



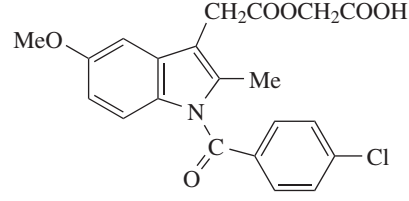
(**75**) (**76**) (**77**)

SCHEME 21

Indomethacin (**78**) and acemethacin (**79**) are both anti-inflammatory drugs, the latter being the glycollic acid ester of the former. As *N*-benzoylindoles, the amide linkage is

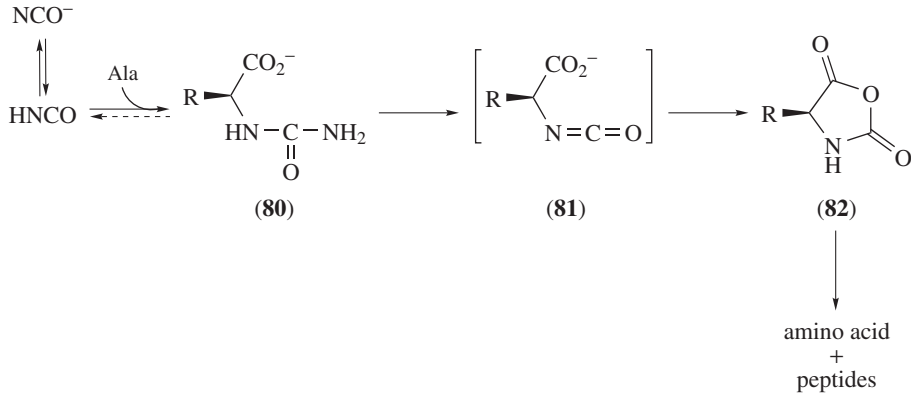


(**78**)



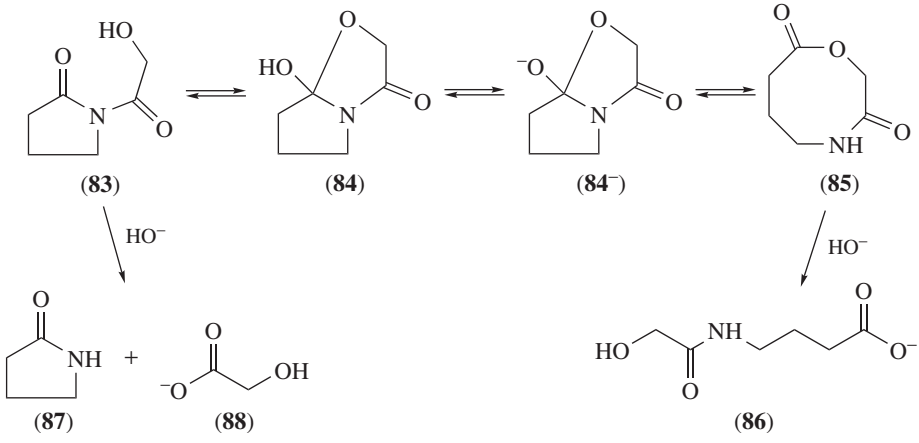
(**79**)

fairly labile; indeed, it was found to be only about 100-fold less reactive than the ester grouping in acemethacin (**79**) in 2–10 M $HClO_4$. At 8 M $HClO_4$, the mechanism of acid hydrolysis of (**78**) and (**79**) changes over from *A*-2 to *A*-1.[86] *N*-Carbamoylalanine (**80**; R = Me) was formed by the action of cyanate – as cyanic acid (HNCO) – upon alanine (Ala) in bicarbonate buffer at pH 7.1, and upon heating at 80 °C for several days a small amount of Ala–Ala was formed. The proposed mechanism (Scheme 22) involves elimination of ammonia from *N*-carbamoylalanine (**80**; R = Me) to form an isocyanate (**81**; R = Me), which cyclizes to an *N*-carboxylanhydride (**82**; R = Me), attack of which by Ala yields Ala–Ala.[87]



SCHEME 22

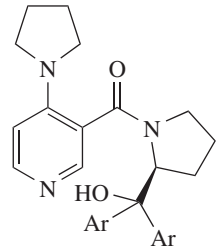
When *N*-(2-hydroxyacetyl)-2-pyrrolidone (**83**) (Scheme 23) was dissolved in water at pH > 8, irreversible cleavage of the exocyclic and endocyclic amide C–N bond occurs. The former led to γ-butyrolactam (**87**) and glycollic acid (**88**). The latter, a



SCHEME 23

lactam scission, and a minor reaction (which, however, occurred to a greater extent at high pH) yielded *N*-(4-hydroxyacetyl)butanoic acid (NBA) (**86**). It was proposed that NBA (**86**) was produced by ester hydrolysis of the ester–amide macrocycle (**85**) that is in equilibrium with the cyclol form (**84**) of (**83**). NMR evidence was obtained for the intermediacy of (**84**) and (**85**), and a rationale was proposed for their formation *vis-à-vis* the alternative direct attack of HO^- upon the C=O group of the 2-pyrrolidone (**83**). Compound (**83**) may be regarded as a candidate drug, since it is a substituted derivative of the lactam form of γ-aminobutyric acid (GABA), an inhibiting neurotransmitter in the brain.[88]

A new class of chiral 4-*N*,*N*-dialkylaminopyridine acyl-transfer catalysts has been developed that are capable of exploiting both van der Waals (π) and H-bonding interactions to allow remote chiral information to control stereochemically the kinetic resolutions of secondary alcohols with moderate to excellent selectivity ($S = 6$–30). Catalysts derived from (*S*)-α,α-diarylprolinol (**89**; Ar = Ph, 2-naphthyl) in combination with isobutyric anhydride were found to possess high activity and selectivity across a broad range of substrates.[89]



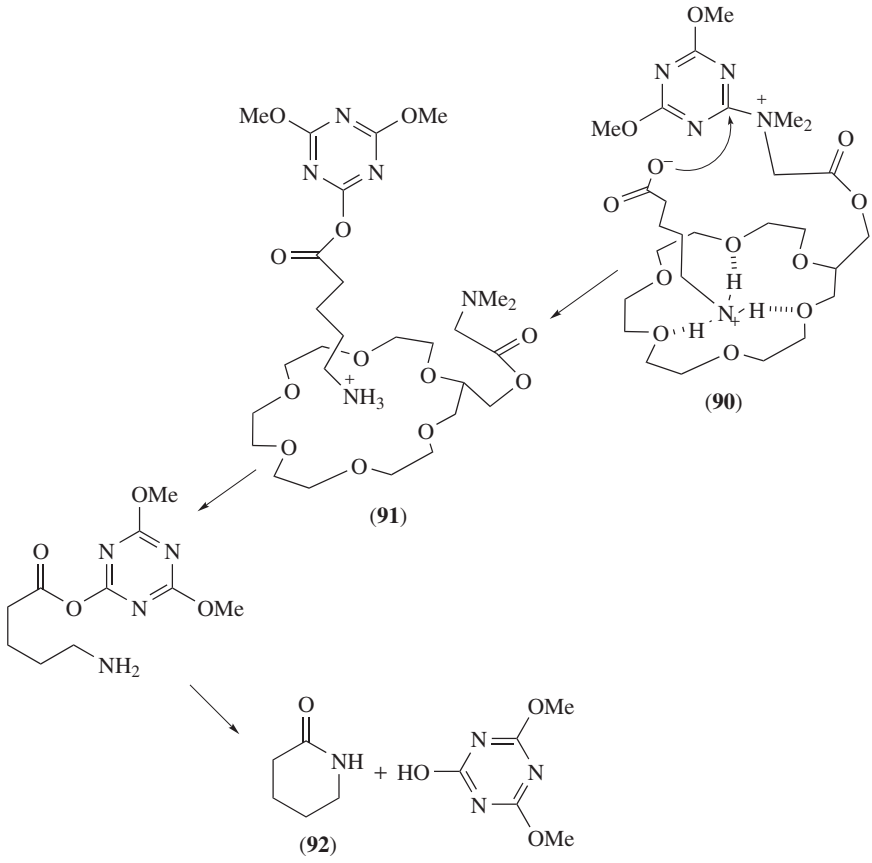
(**89**)

(iii) Lactams

Reviews have appeared of theoretical studies on ring-opening of β-lactams in both solution and in enzymatic media[90] and of a comparison of the mechanisms of reactions of β-lactams and β-sultams, including their reactions with some serine enzymes.[91]

An *ab initio* study of the acid hydrolysis of the lactam 1-azabicyclo[2.2.2]octan-2-one (described as a 'highly twisted amide') and of the model compound 3-methyl-δ-valerolactam showed that both proceed via a stepwise mechanism, but *N*-protonation is preferred to *O*-protonation by the 'twisted amide', whereas the reverse is the case for the model compound.[92]

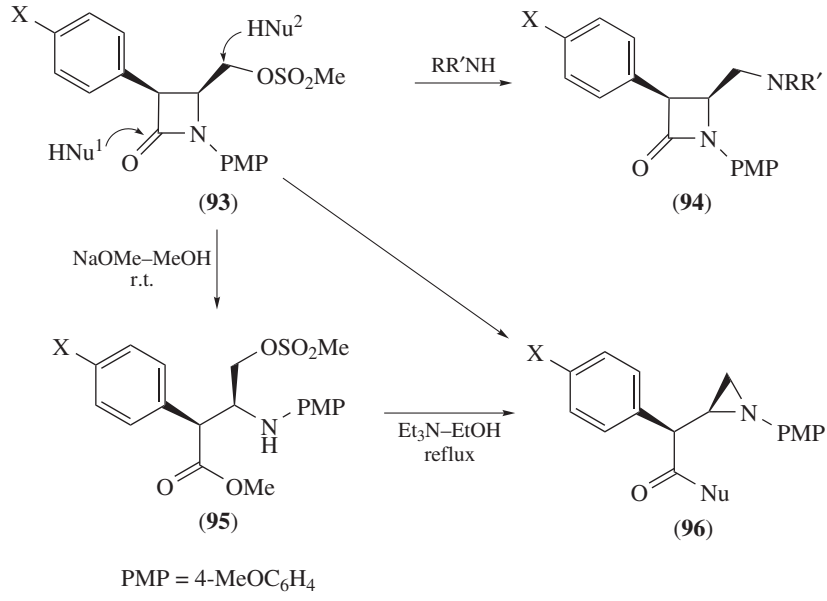
[18]Crown-6 binds alkylammonium ions specifically and this property has been exploited in the development of a model cyclotransferase that converts γ-, δ-, or ε-amino acids into the corresponding lactam. A short side-arm on [18]crown-6 of a $-CH_2OCOCH_2NMe_2$ group provides scope for displacement of the chloro group of activating agent 2-chloro-4,6-dimethoxy-*s*-triazine by the Me_2N group to yield a quaternary ammonium compound that can form a complex with the δ-amino acid (**90**). This complex (**90**) juxtaposes the carboxylate and the triazine ring leading to



SCHEME 24

the formation of a bound triazinyl ester (**91**). Upon release by the polyether, the ester cyclizes with expulsion of 2-hydroxy-4,6-dimethoxy-*s*-triazine to form the lactam (**92**) (Scheme 24).[93]

N-(4-Methoxyphenyl)-3-(4-X-phenyl)-4-(methylsulfonoxymethyl)azetidinones (**93**; X = MeO, Cl, F) were attacked by secondary amines in DMF or MeCN at the sp^3 carbon, but by MeO^- or NH_3 in MeOH by ring-opening attack at the sp^2 carbon (Scheme 25). The former attack led to 4-dialkylaminomethyl derivatives (**94**), but the attack by the harder nucleophiles at the C=O group led to the rearranged aziridin-2-ylacetamides (**96**; Nu = NH_2) by reaction with NH_3–MeOH at room temperature (r.t.) or to the analogous esters (**96**; Nu = OMe) by reaction with MeO^-–MeOH at reflux. The open-chain intermediate (**95**) could be isolated by reaction with MeO^-–MeOH at r.t., which upon heating in Et_3N–EtOH at reflux yielded (**96**; Nu = OMe) by intramolecular displacement of mesylate by the arylamino group. Compounds (**96**; Nu = NH_2) and (**96**; Nu = OMe) are of interest as possible carboxypeptidase A inhibitors.[94]

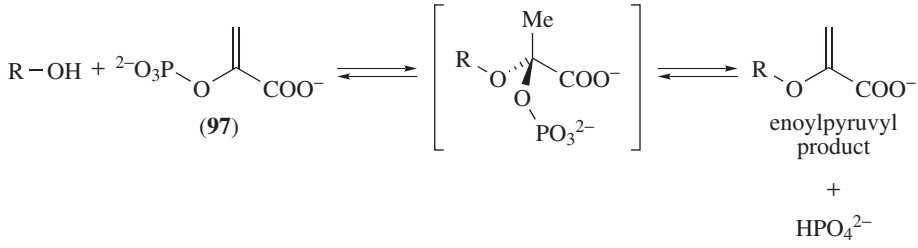


SCHEME 25

(b) Phosphoric Acids and their Derivatives

(i) Phosphate and phosphonate monoesters

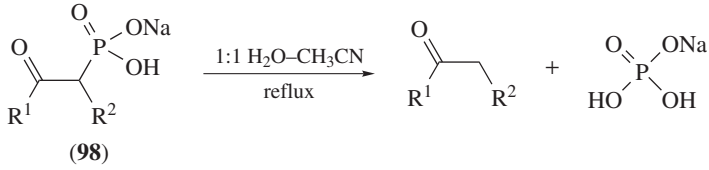
Systematic calculations of the potential surfaces of the reactions of a series of phosphate monoesters with different leaving groups involving *ab initio* calculations with implicit solvent models to *ab initio* QM/MM free energy calculations showed that the character of the transition state changes from associative to dissociative with decrease in the pK_a of the leaving group.[95] Using the B3LYP method of DFT, theoretical studies of the hydrolysis mechanism of 5′-adenosine monophosphate and methyl phosphate (as a model compound) concluded that each reaction is single channel with a two-step process and a pentacoordinated intermediate is formed first.[96]



SCHEME 26

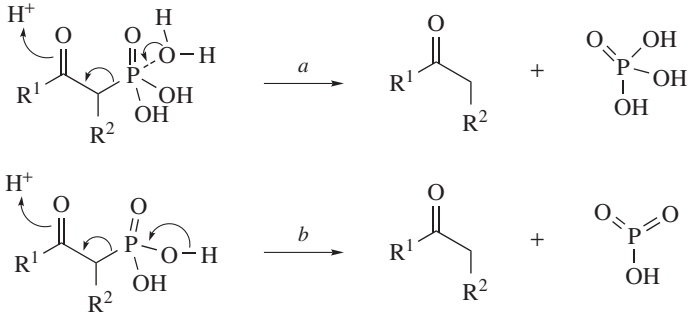
The carboxyvinyltransferases catalyse the addition of hydroxy compounds, ROH, to phosphoenoylpyruvate (**97**) to form, via a tetrahedral intermediate, an enoylpyruvyl product and inorganic phosphate (Scheme 26). The enzyme-catalysed formation of phosphate was found to proceed exclusively via C–O cleavage and, surprisingly, neither protonation of the non-bridging oxygens nor interactions with cationic side-chains had measurable effects on the C–O bond cleavage. This prompted a computational investigation of a series of simple alkyl and aryl phosphate monoesters, $ROP(O)(OH)_2$, in order to elucidate the structural features, especially the extent of protonation or not, that influence whether C–O or P–O bond cleavage occurs. The results showed that protonating the bridging oxygen when the non-bridging oxygens were already protonated favoured C–O cleavage, whereas protonating the bridging oxygen of the dianion form, $(RO)PO_3^{2-}$, favoured O–P cleavage. Alkyl R groups capable of forming stable cations were more prone to C–O bond cleavage with $Bu^t > Pr^i > Me$.[97]

β-Ketophosphonic acids (**98**) were found to undergo facile dephosphonylation under fairly mild conditions (Scheme 27). The rate of dephosphonylation was dependent on the electronic nature of the substituent at the carbon atom α to phosphorus, with electron-withdrawing groups accelerating the process. ^{31}P NMR studies supported a mechanism at low pH that either (Scheme 28) involved water attack in a bimolecular process (path *a*) or transient formation of metaphosphate (path *b*), a process analogous to the decarboxylation of β-keto acids.[98]



(**98**)

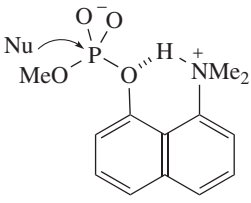
SCHEME 27



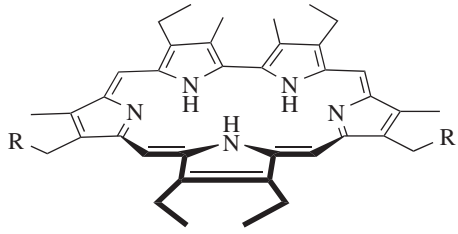
SCHEME 28

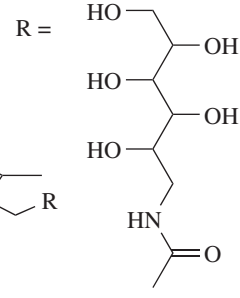
(ii) Phosphate diesters

DFT methods have been used to study the in-line reactivity of H_2O, MeOH, HO^-, and MeO^- towards dianionic, monoanionic, and neutral forms of ethylene phosphate and cyclic-2′,3′-ribose phosphate, the analysis generally supporting an associative mechanism.[99] The hydrolysis of methyl 8-dimethylamino-1-naphthyl phosphate (**99**) and its reactions with a representative range of nucleophiles are catalysed by the dimethylammonium group at acidic pH with rate accelerations of the order of 10^6. The reaction persists up to pH 7 because the strong intramolecular hydrogen bond, which is the key to efficient general acid catalysis, is present also in the reactant. The sensitivity to the basicity of the nucleophile (Brønsted $\beta_{nuc} = 0.29$) lies between values measured previously for mono- and tri-esters. The comparisons suggest that general acid catalysed reactions of phosphate mono- or di-esters with strongly basic oxyanion nucleophiles (such as those derived from a serine oxygen or a bound water molecule in an enzyme active site) will be fastest when their negative charges are neutralized by protonation. It was suggested that the reaction of (**99**) involving NH_2OH as an α-effect nucleophile proceeds through the pre-equilibrium formation of the tautomer $H_3N^+–O^-$ as the active nucleophile; *ab initio* calculations supported that idea.[100]



(**99**)

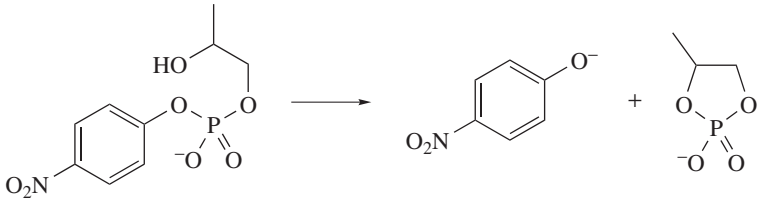




(**100**)

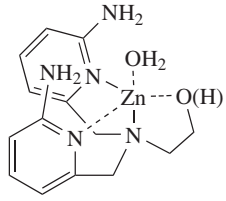
The kinetics of the alkaline hydrolysis of di(*p*-nitrophenyl) phosphate (DNPP) in aqueous DMSO, dioxane, and MeCN were studied. In all solvent mixtures, the reaction rate steadily decreased to half of its value in pure water in the range 0–70 vol.% of organic cosolvent and sharply increased in mixtures with lower water content. Alkali metal ions catalysed the DNPP hydrolysis, the catalytic activity decreasing in the order $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$.[101] Sapphyrins, which are pentapyrrolic porphyrin-like macrocycles, are known to bind phosphate diesters selectively at neutral pH. Now, a doubly substituted sapphyrin (**100**) has been assessed as a metal-free catalyst for phosphodiester hydrolysis using the reactive DNPP as test substrate. The attached side-arms were pentahydroxylated and it was proposed that the two distal HO groups of each side-arm were involved in the modest catalysis observed.[102]

Intramolecular transesterification rates of the RNA model compound 2-hydroxypropyl *p*-nitrophenyl phosphate (HPNPP) (**101**) have been used to compare the reactivity of a mononuclear complex with peripheral hydrogen bonding aminopyridyl groups (**102**) with a dinuclear zinc complex (**103**) that cannot hydrogen bond to the transition state. It was found that hydrogen bonding is more important than having two metal centres in determining the rate of hydrolysis of HPNPP (**101**) to propylene phosphate and *p*-nitrophenate (Scheme 29).[103] When hydrogen-bonding aminopyridyl groups were appended to the periphery of the dizinc complex, the resulting complex (**104**) accelerated the transesterification of (**101**) with a 10^6-fold rate acceleration at pH 7.4 and 25 °C; this is claimed to be the most active artificial zinc complex for catalysing this transesterification. It also displayed turnover, although it was found that the phosphodiester product bound as tightly to the dizinc core as the phosphodiester substrate did to the artificial enzyme, so product inhibition was occurring. HPNPP (**101**) has a better leaving group and a poorer intramolecular nucleophile than RNA, so the observation that complex (**104**) also catalysed the transesterification of the dinucleotide uridyl-3′,5′-uridine (UpU) with a 10^6-fold rate acceleration confirms that the high reactivity of this catalyst is not confined to the activated substrate. The addition of the peripheral aminopyridyl groups accelerated UpU transesterification by two orders of magnitude.[104]

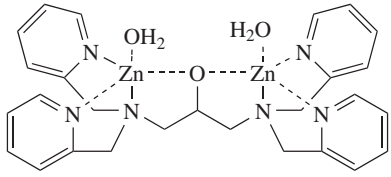


(**101**)

SCHEME 29

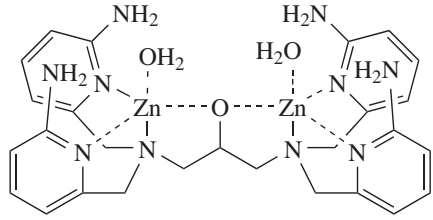


(**102**)



(**103**)

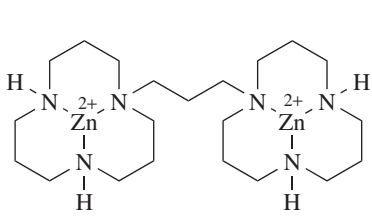
HPNPP (**101**) was also used to probe the catalytic ability of zinc- and copper-containing calix[4]arenes that carried two or three [12]ane-N3 macrocycles on their upper rim. Cooperativity was found between the catalytically active metal complexes during phosphodiester transesterification provided that they were adjacent to each other, i.e. on proximal positions of the calixarene rim, whereas those on opposite



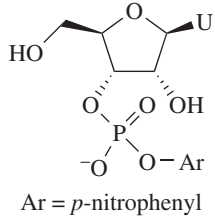
(**104**)

sides did not cooperate during catalysis. The copper complexes cleaved the diribonucleotide monophosphates UpU and UpG with an ability comparable to the best existing synthetic di/tricopper and di/trizinc complexes.[105]

A di(zinc[12]ane-N3) complex (**105**) catalysed the transesterification of the RNA model compound HPNPP (**101**) and of the DNA model compound methyl *p*-nitrophenylphosphate with methoxide in methanol. This dinuclear complex exhibited an enormous 10^{12}-fold rate enhancement for each ester, and a mechanism involving coordination of both Zn(II) ions to the phosphate was suggested.[106] The hydrolysis of HPNPP (**101**) was also used to assess the catalytic ability of cyclen-based lanthanide complexes. Appending amine arms to the cyclen was shown to increase the catalytic ability greatly and shifted maximum activity into the physiological pH range, an effect that was attributed to hydrogen bonding and/or general acid catalysis to the bound phosphate ester. The possibility that the pendant amines deprotonated second-sphere water molecules to make them more nucleophilic was also proposed.[107] The cleavage rates of UpU and the *p*-nitrophenyl analogue UpPNP (**106**) were used to study the catalytic mechanism of a previously studied di(zinc[9]ane-N3) complex (**107**). Greater transition state stabilization during the cleavage of UpU compared with UpPNP was found, which was attributed to stabilizing interactions between the catalyst and the alkoxy leaving group attached to C(5′) of the departing ribonucleoside.[108]

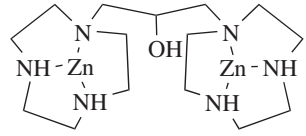


(**105**)



Ar = *p*-nitrophenyl

(**106**)



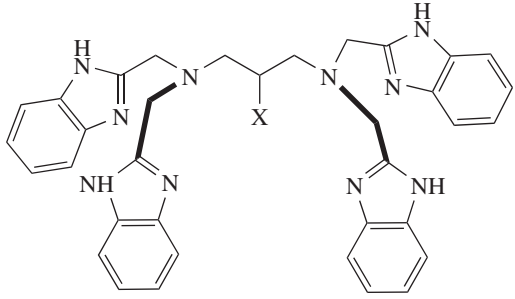
(**107**)

A series of heptameric single-stranded (ss) DNAs and RNAs having a central 9-guanylate ion have been investigated by ^{31}P NMR spectroscopy in order to determine its effect on each of the flanking phosphate moieties. The results showed that the ssRNAs, but not the ssDNAs, were affected, the electronic properties and chemical reactivities of the internucleotidic phosphates being dissimilar in a sequence-specific manner

because of their non-identical microenvironments. To complement these results, preferential cleavages at various phosphates were observed when the heptameric ssRNAs were subjected to alkaline hydrolysis at pH 12.5.[109]

(iii) Phosphate and phosphonate triesters

Homo- and hetero-bimetallic Cu(II), Zn(II), and Co(II) complexes based on the binucleating ligand *N*,*N*,*N*′,*N*′-tetrakis[(2-benzimidazoyl)methyl]-2-hydroxy-1,3-diaminopropane (**108**; X = OH) and its new *p*-toluoyl ester derivative [**108**; X = OC(O)-*p*-Tol] catalyse the hydrolysis of *p*-nitrophenyl diphenyl phosphate at ambient temperature with activities rivalling the fastest known systems. These catalysts are useful in the decontamination of organophosphorus pesticides and nerve agents.[110] Two other papers address the issue of contamination protocols for organophosphorus pesticides and nerve agents. In one, the effects of aqueous mixtures of Pr^iOH, Bu^tOH, and $(CH_2OH)_2$ upon the reactivity of HO^- and HO_2^- towards ethyl *p*-nitrophenyl ethylphosphonate and diethyl *p*-nitrophenyl phosphate were reported. Rates increased as the alcohol content increased for both anions, but the reverse was true for $(CH_2OH)_2$.[43] In the other, kinetic studies of the reaction between a large set of oximate anions and sarin, soman, and di(4-nitrophenyl) methyl- (DNPMP) and phenylphosphonate (DNPPP) were reported. The Brønsted-type plots of these α-nucleophiles revealed a clear tendency for the reactivity of the oximates to suffer a saturation effect with increasing basicity in aqueous solution. In the case of sarin, soman, and DNPMP, this behaviour was reflected in a levelling off at $pK_a \approx 9$, but for DNPPP a decrease in rate at higher pK_a values was seen. However, plots in 70:30 DMSO–H_2O were linear for all four compounds. The result in the latter, less saturating medium supports the view that desolvation of oximates must occur prior to nucleophilic attack.[111]



(**108**)

(iv) Thiophosphates

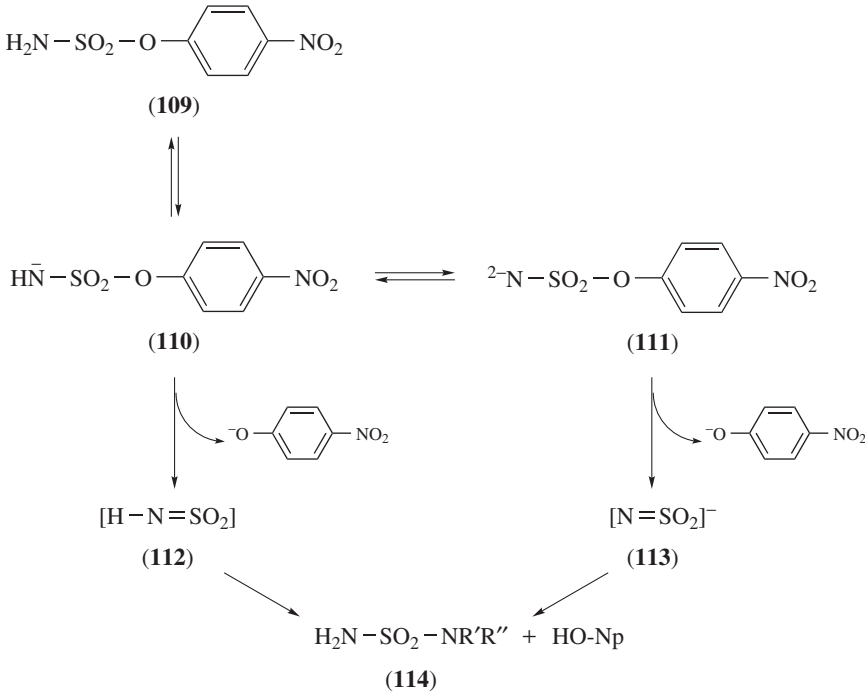
The hydrolysis rates of the dianions of phosphate and phosphorothioate monoesters are substantially accelerated by the addition of polar aprotic solvents such as DMSO and MeCN because the activation barrier $\Delta G^{\neq}$ becomes smaller due to a lowering of the enthalpy of activation. The enthalpy transfer of the transition states in the

two solvents was calculated from the enthalpy of transfer of *p*-nitrophenyl phosphate and *p*-nitrophenyl phosphorothioate from water to 0.6 M aqueous DMSO which were determined calorimetrically. The results show that the reduced enthalpies of activation in both hydrolysis reactions arise not from a destabilization of the reactants in the mixed solvent, but from the fact that the enthalpy of transfer of the transition states to the mixed solvent is significantly more negative than the enthalpy of transfer of the reactants.[112]

(c) Sulfonic Acids and Their Derivatives

(i) Sulfates, Sulfamates, and β-Sultams

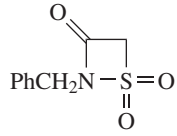
Structure–reactivity and structure–structure correlations of five sulfate monoesters and 11 sulfamate esters determined by low-temperature X-ray crystallography revealed similar ground-state deformations that suggest similar reaction coordinates for sulfuryl and sulfamyl group transfer. The results support a mechanism that proceeds through significant bond lengthening of the scissile S–O_b bond and a dissociative, sulfur trioxide-like transition state. This work suggests a close mechanistic relationship of sulfamyl and sulfuryl group transfer that is similar to but distinct from phosphoryl group transfer.[113]



Scheme 30

Anti-cancer drugs that are sulfamate esters, $ROSO_2NH_2$, appear to act by inhibition of sulfatases. Now, kinetic studies of the aminolysis of *p*-nitrophenyl sulfamate (**109**) by secondary alicyclic amines in MeCN at 310 K are reported that model the enzyme reaction. The Brønsted-type plot was biphasic, the break point at $pK_a \approx 18.2$ more or less corresponding to the pK_a of the ester (**109**) (17.8). The proposed mechanism (Scheme 30) involves a sequential double deprotonation of (**109**) leading first, via (**110**), to the sulfenamine (**112**) and at higher basic strength to (**111**) and thence to a novel anionic sulfenamine (**113**), the products in each case being an *N*,*N*-dialkylsulfamide (**114**) and *p*-nitrophenol.[114]

Theoretical studies of the hydrolysis of *N*-benzyl-3-oxo-β-sultam (**115**) showed that the activation energies for the pathways leading to the products of C–N and S–N cleavage for the uncatalysed hydrolysis were very similar. However, when a second water molecule was involved, cleavage of the C–N bond was preferred.[115] In a review, the mechanisms of reactions of β-sultams have been compared with those of β-lactams, including their reactions with some serine enzymes.[91]



(**115**)

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CHAPTER 3

Oxidation and Reduction

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Oxidation by Metal Ions and Related Species

Chromium, Manganese and Nickel

The experimental data for oxidation of benzyl alcohol,[1] aliphatic primary and secondary alcohols,[2] and cholesterol[3] with cetyltrimethylammonium (CTA) dichromate indicated that the reactions occur in a reverse micelle system produced by the oxidant. Michaelis–Menten-type kinetics were observed with respect to the reductants. The product of the oxidation of cholesterol depends on the solvent. In dichloromethane, the product is 7-dehydrocholesterol, whereas with dichloromethane containing acetic acid the product is 5-cholesten-3-one. A low kinetic isotope effect, $k_H/k_D = 2.81$, was observed in the oxidation of methanol-d_4; this, combined with the rate data and the reverse solvent isotope effect [$k(H_2O)/k(D_2O) = 0.76$], suggests that these reactions

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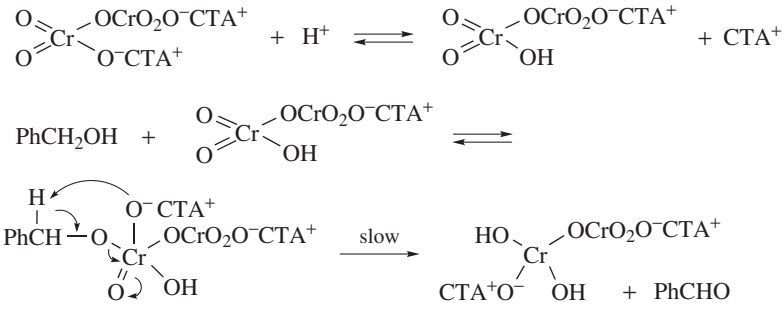


SCHEME 1

proceed through formation of a chromate ester (e.g. Scheme 1), which decomposes in the rate-determining step.

A second-order dependence on both the reductant and acidity was observed in the oxidation of alcohols with butyltriphenylphosphonium dichromate; study of $MeCD_2OH$ and Me_2CDOH indicated the presence of a substantial kinetic isotope effect. The reaction was studied in 19 organic solvents and the rates were correlated with multiparametric equations. The reaction is susceptible to both electronic and steric effects of the substituents. A mechanism involving the formation of a dichromate ester and an α-C–H cleavage has been proposed.[4]

Oxidation of aryl alkyl ketones with quinolinium dichromate (QDC) in acidic medium is proposed to involve a reaction between the enol form of the ketone and protonated QDC in the rate-determining step to form a chromate ester. Subsequently, the ester undergoes a C−C bond cleavage.[5] Although no evidence for the intermediacy of free radicals by ESR spectroscopy was obtained in the oxidation of thio acids with QDC to the corresponding disulfides,[6] the formation of Cr(V) was indicated by ESR spectroscopy in the oxidation of fluorene to fluorenone with QDC.[7] Formation and disproportionation of a chromate ester have been suggested in the oxidation of salicylic acids[8] and pyridinecarboxylic acids[9] with QDC. The kinetic isotope effect ($k_H/k_D = 5.8$) for oxidation of acetaldehyde-d_1 with QDC indicated aldehydic C–H bond cleavage in the rate-determining step. A rate-determining decomposition of a chromate ester of the aldehyde hydrate involving a cyclic transition state has been suggested.[10] Similar mechanisms have also been suggested for the oxidation of unsaturated aldehydes,[11] α-keto acids,[12] salicylaldehydes,[13] and heteroaldehydes.[14] Formation of an acyclic chromate ester has been proposed in the oxidation of dihydric phenols to the corresponding quinines with QDC.[15]

Kinetics and activation parameters for the oxidation of phenol with tetrakis(pyridine) cobalt(II) chromate have been determined.[16] The oxidation of oximes of cyclopentanone, cyclohexanone, and cycloheptanone with pyridinium fluorochromate is first order each in the oxidant and oxime. The observed reactivity sequence has been rationalized on the basis of I-strain.[17]

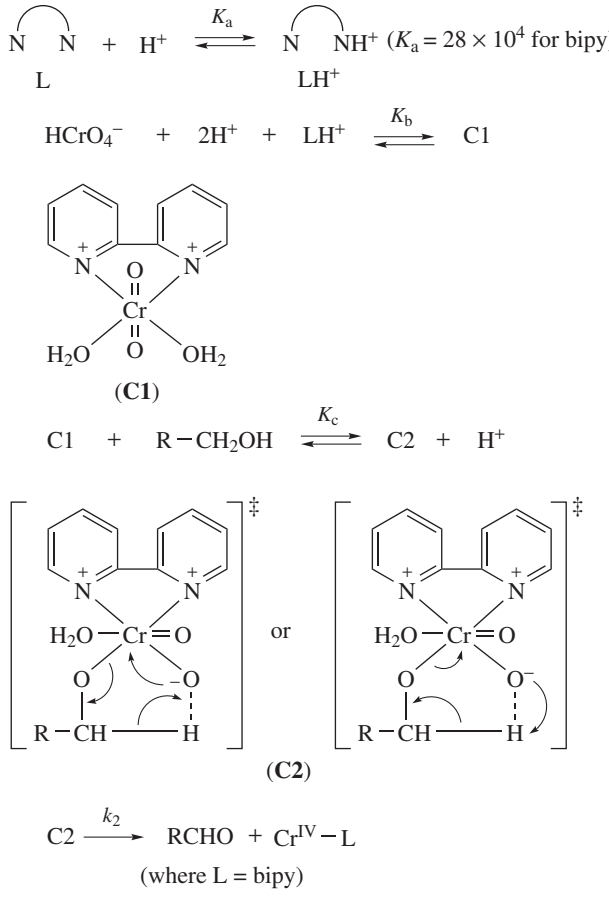
The oxidation of *meta*- and *para*-substituted anilines with imidazolium fluorochromate (IFC)[18] and nicotinium dichromate (NDC),[19] in several organic solvents, in the presence of *p*-toluenesulfonic acid (TsOH) is first order in the oxidant and TsOH and is zero order with respect to substrate. A correlation of rate data in different solvents with Kamlet–Taft solvatochromic parameters suggests that the specific solute–solvent interactions play a major role in governing the reactivity, and the observed solvent effects have been explained on the basis of solute–solvent complexation. The oxidation rates with NDC exhibited negative reaction constants, while the oxidation with IFC did not correlate well with any linear free energy relationships.

Michaelis–Menten-type kinetics were found for oxidation of alcohols with tetramethylammonium fluorochromate indicating the formation of an intermediate. The formation constant and the rate of disproportionation of the intermediate have been determined. A two-electron reaction scheme has been proposed.[20,21]

Michaelis–Menten-type kinetics were observed for alcohols in their oxidation by piperidine chlorochromate. The reaction is first order with respect to Cr(VI) and acidity. The mechanistic aspects have been discussed.[22] The solvent effect on the oxidation of some unsaturated acids,[23] thio acids,[24] methionine,[25] aliphatic aldehydes,[26] and aliphatic alcohols[27] with benzyltriemthylammonium chlorochromate has been analysed in terms of Kamlet's and Swain's multiparametric equations. The hydrogen ion dependence has the form $k_{obs} = a + b[H^+]$. Michaelis–Menten-type kinetics were observed with respect to methionine,[25] whereas a first-order dependence was obtained with other reductants. The oxidation of $MeCD_2OH$ displayed a kinetic isotope effect, thereby confirming the cleavage of a C−H bond in the rate-determining step.[27] A mechanism involving a three-centre transition state has been proposed for the oxidation of unsaturated acids, whereas the oxidation of thio acids, aldehydes, and alcohols is proposed to proceed via a chromate ester.

The rates of oxidation of *ortho*-, *meta*-, and *para*-substituted phenyl methyl sulfides with quinolinium bromochromate (QBC) showed excellent correlation with Charton's LDR/LDRS equations. Oxidation of alkyl phenyl sulfides is sensitive to both polar and steric effects of the alkyl group. The polar reaction constants are negative, indicating an electron-deficient sulfur centre in the slow step. An analysis of the solvent effect with Swain's equation showed that both cation- and anion-solvating powers of the solvent played important roles in the oxidation process. A mechanism involving the formation of a sulfurane intermediate has been suggested.[28] The oxidation of PhCDO with QBC exhibited a substantial primary kinetic isotope effect, confirming the cleavage of the aldehydic C−H bond in the rate-determining step. The results of correlation analysis of the rates of *para*-substituted benzaldehydes indicated an electron-deficient reaction centre in the transition state. Rapid formation of a chromate ester of the hydrated benzaldehyde and its subsequent slow decomposition has been suggested.[29]

Chromic acid oxidation of D-sorbitol and D-mannitol has been studied in the presence and absence of 2,2′-bipyridyl (bipy). A monomeric species of Cr(VI) has been found to be kinetically active in absence of bipy, whereas in the catalysed path the Cr(VI)–bipy complex has been found to be the active oxidant. Sodium dodecyl sulfate



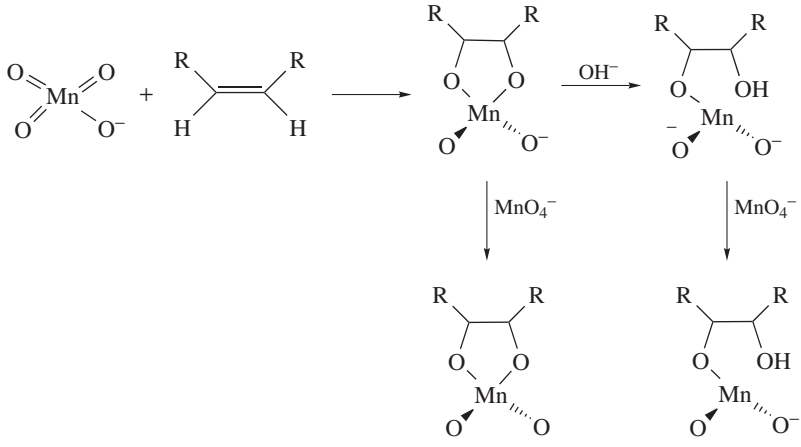
SCHEME 2

has been found to accelerate the oxidation whereas *N*-cetylpyridinium chloride retards it. A mechanism (Scheme 2) has been proposed for the bipy-catalysed reaction.[30]

A Cr(VI)–catalyst complex has been proposed as the reactive oxidizing species in the oxidation of *trans*-stibene with chromic acid, catalysed separately by 1,10-phenanthroline (PHEN), oxalic acid, and picolinic acid (PA). The oxidation process is believed to involve a nucleophilic attack of the olefinic bond on the Cr(VI)–catalyst complex to generate a ternary complex.[31] PA- and PHEN-catalysed chromic acid oxidation of primary alcohols also is proposed to proceed through a similar ternary complex. Methanol-d_4 reacted nearly six times slower than methanol, supporting a hydride transfer mechanism in this oxidation.[32] Kinetics of chromic acid oxidation of dimethyl and diethyl malonates, in the presence and absence of oxalic acid, have been obtained and the activation parameters have been calculated.[33] Reactivity in the chromic acid oxidation of three alicyclic ketoximes has been rationalized on the basis of I-strain. Kinetic and activation parameters have been determined and a mechanism

has been suggested.[34] Hammett's acidity function and the role of water have been examined in the chromic acid oxidation of amoxicillin and 6-aminopenicillanic acid.[35]

It is known that substituent effects on the oxidation of alkenes with permanganate are relatively small. However, a B3LYP/6–311++G** study predicted much larger substituent effects. This was shown to be due to the formation of an initial charge–dipole complex that leads to products via the rate-determining step. PCM calculations indicated that the complex should disappear in aqueous solution and, under these conditions, most of the alkenes were predicted to have about the same activation energy. CCSD/6–311++G** calculations indicated a very early transition state. Kinetic data indicated that the initial reaction between permanganate ion and crotonic acid has a first-order dependence on both reactants and is independent of hydroxide ion concentration. The kinetic and spectroscopic data suggested the process shown in Scheme 3.[36]



SCHEME 3

The oxidation of acetylacetone with permanganate ion in acidic and alkaline solutions has been investigated. The rate constants for the oxidation of keto, enol, and enolate ion forms have been determined. The slow oxidation of the enol has been attributed to π-electron delocalization by conjugation. In acid-catalysed oxidation of the keto form, a nucleophilic attack of permanganate ion occurs on the carbonyl-C atom. The enolate ion suffers a base-catalysed electron abstraction.[37] A mechanism involving the formation of bicyclic intermediates has been suggested for the oxidation of acetylenic compounds with alkaline permanganate. A nucleophilic attack by a permanganate-oxygen on the bridgehead carbon of the triple bond has been contemplated.[38] In the acid permanganate oxidation of propan-1- and -2-ol, permanganic acid is postulated as the reactive species. In the presence of the surfactant Tween-20, the reactants are distributed between the aqueous phase and micellar pseudo-phase before reacting. Compensation between water destruction and substrate–micelle interaction is proposed to play an important role in the oxidation in the presence of the surfactant.[39]

Boron trifluoride forms an adduct, $[BF_3–MnO_4]^-$, with permanganate ion that oxidizes hydrocarbons at rates over seven orders of magnitude faster than that by permanganate alone. The kinetic isotope effects for the oxidation of perdeuterated cyclohexane, toluene, and ethylbenzene, at 298 K, are 5.3, 6.8, and 7.1, respectively. The rate-limiting step for all of these reactions is most likely hydrogen atom transfer from the substrate to an oxo group of the adduct. A good linear correlation between log(rate constant) and C–H bond energies of the hydrocarbons was found. The accelerating effect of boron trifluoride on the oxidation of methane has been studied computationally by the DFT method. A significant decrease in the reaction barrier results from BF_3 coordination to permanganate. The BF_3 coordination increases the ability of the metal centre to achieve a d^1 Mn(VI) electron configuration in the transition state.[40]

Potassium permanganate oxidizes terminal alkenes to the corresponding α-hydroxy ketones in good yields. The reaction is highly chemoselective in the presence of differently protected hydroxy groups and can be utilized for the preparation of polyfunctional compounds.[41] The oxidation of hexamine with alkaline permanganate is proposed to proceed through an intermediate complex, which decomposes in the slow step to generate a free radical. The activation parameters for the slow step have been evaluated.[42]

The oxidation of L-norleucine, L-leucine, L-isoleucine, and L-*t*-leucine with permanganate in strong acid medium showed an autocatalysis by Mn(II), except in the case of L-leucine. For the autocatalytic activity to initiate, a certain concentration of Mn(II) is required. Moreover, the autocatalytic phenomenon vanishes in concentrations of sulfuric acid that are greater than 4.3 mol dm^{-3}. The oxidation showed a good correlation in a biparametric equation, with $\rho = -4.57$ and $\delta^c = 2.23$ at 318 K.[43]

Oxidation of sulfoxides with oxo(salen)Mn(V) complexes follows second-order kinetics. Sodium hypochlorite is used as a terminal oxidant. The oxidation of substituted sulfoxides yielded a reaction constant $\rho = -2.57$. The reduction of substituted Mn(V) complexes showed a reaction constant of 0.50. A valid reactivity–selectivity principle is operative in this system. An S_N2- type mechanism has been proposed.[44]

In aqueous media (pH 2.5–6.0), the Mn(IV) tetramer $[Mn_4(\mu\text{-}O)_6(bipy)_6]^{4+}$ oxidizes both glyoxylic and pyruvic acid to formic and acetic acid, respectively. Kinetic studies suggest that the tetramer, its oxo-bridge protonated form, i.e. $[Mn_4(\mu\text{-}O)_5(\mu\text{-}OH)(bipy)_6]^{5+}$, the reducing acids (RH), and their conjugate bases (R^-) all take part in the reaction. The oxo-bridge protonated form is a stronger oxidant. The *gem*-diol forms of the α-oxo acids are the possible reductants. A one-electron/one-proton electroprotic mechanism operates in the rate-determining step.[45]

Oxidation of some tetrapeptides with manganese(III) acetate showed a first-order dependence on Mn(III), acetate ion, and the peptide. An inverse-order dependence was observed on hydrogen ion. There is no effect of Mn(II). A mechanism involving $[Mn(OAc)_4]^-$ as the active oxidizing species has been proposed. The oxidation by Mn(III) in sulfuric acid medium is found to be faster than that by manganese(III) acetate.[46] Michaelis–Menten-type kinetics and formation of free radicals have been observed in the oxidation of some α-keto esters[47] and 1,3-diketones[48] with Mn(III) pyrophosphate. Manganese(III) porphyrins bearing nitro substituents at β-postions

catalyse the oxidation of activated aromatic compounds with hydrogen peroxide. Yields improved considerably on using imidazole as a co-catalyst.[49]

A convenient enantioselective catalytic oxidation of a variety of differently substituted, cyclic (*E*) and acyclic (*Z*)-enol phosphates with (salen)manganese(III) complex (ee) has been reported. The influence of electronic and steric effects of the enol phosphate substituents on the stereoselectivity of oxidation has been studied.[50]

The oxidation of butane-1,2-diol with dihydroxydiperiodatonickelate(IV) showed a first-order dependence on Ni(IV) and an order between one and two in the reductant. The rate constant increased with increasing concentration of alkali and decreasing concentration of periodate ion. A plausible mechanism involving a two-electron transfer has been proposed.[51]

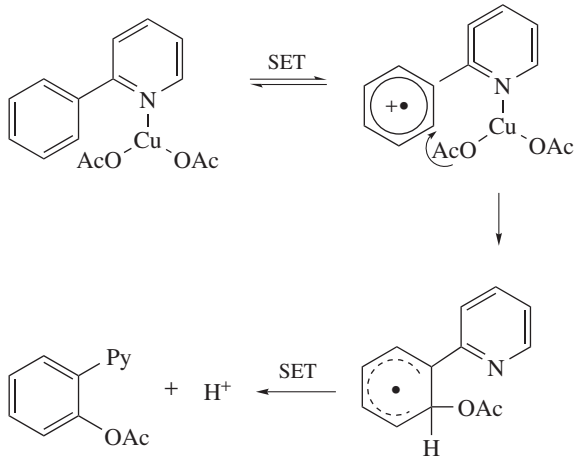
Copper and Silver

(μ-η^2:η^2-Peroxo)Cu(II)$_2$ complex, $[Cu_2(O_2)(H–L)]^{2+}$, is capable of not only intramolecular hydroxylation of the *m*-xylyl linker of the dinucleating ligand H–L but also intermolecular epoxidation of styrene and hydroxylation of THF. Epoxidation of substituted styrenes yielded a Hammett $\rho = -1.9$, indicating a rate-limiting electrophilic attack of the peroxo ligand on the sp^2 carbon of the substrate. Hydroxylation of THF-d_8 showed a very large kinetic isotope effect, confirming that the reaction involves a rate-limiting H-atom abstraction process from THF. Although bis(μ-oxo)dicopper(III) was not detected in the reaction system, a small amount of bis(μ-oxo)dicopper(III) species present in a rapid pre-equilibrium may not be excluded as a reactive intermediate.[52]

Pyridylarenes undergo Cu(II)-catalysed diverse oxidative C–H functionalization reactions. The tolerance of alkene, alkoxy, and aldehyde functionality is a synthetically useful feature of this reaction. A radical-cation pathway (Scheme 4) has been postulated to explain the data from mechanistic studies. A single electron transfer (SET) from the aryl ring to the coordinated Cu(II) leading to the cation-radical intermediate is the rate-limiting step. The lack of reactivity of biphenyl led to the suggestion that the coordination of Cu(II) to the pyridine is necessary for the SET process. The observed *ortho* selectivity is explained by an intramolecular anion transfer from a nitrogen-bound Cu(I) complex.[53]

A mechanism involving the formation of an intermediate complex between the oxidant and reductant has been proposed for the oxidation of isonicotinate ion with diperiodatocuperate(III) in alkaline solution. The activation parameters for the slow step have been evaluated.[54]

The catalytic activity of Os(VIII) is more than that of Ru(III) in the catalysed oxidation of paracetamol with diperiodatoargentate(III) (DPA). The active species of catalysts and oxidant have been identified and a mechanism has been proposed.[55] The oxidation of aspirin, both uncatalysed[56] and catalysed by Os(VIII) and Ru(III)[57] with DPA in alkaline solution is of first order in DPA and has less than unit order in both aspirin and alkali. The order with respect to the catalyst is one. A decrease in the dielectric constant of the medium increases the rate of the reaction. A mechanism has been proposed.



SCHEME 4

The oxidation of butane-1,4-diol,[58] ethanediol, and butane-1,3-diol[59] by dihydroxydiperiodatoargentate(III) (DDPA) in alkaline solution is first order in Ag(III), ethanediol, and butane-1,3-diol. The order with respect to butane-1,4-diol is between one and two. A plausible mechanism involving the formation of an adduct in a pre-equilibrium between the DDPA and reductant is proposed. The activation parameters along with rate constants of the rate-determining step have been calculated. The rate of oxidation of butane-1,2-diol with dihydroxyditelluratoargentate(III), in alkaline solutions, decreases with increase in the concentration of TeO_4^{2-} ions. The dihydroxymonotelluratoargentite(III) species is assumed as the reactive form. A two-electron mechanism has been proposed.[60]

Cerium, Titanium, Vanadium, Cobalt, Tungsten, and Molybdenum

The oxidation of D-fructose with cerium(IV) in sulfuric acid medium is inhibited by an increase in the acidity. A cationic surfactant, CTAB, catalyses the reaction, whereas SDS has no effect. The catalytic role of CTAB has been explained using the pseudophase model of Menger and Portnoy. A mechanism involving the formation of an intermediate complex between β-D-fructopyranose and $Ce(SO_4)_3^{2-}$ has been proposed.[61] The oxidation of cycloalkanones with cerium(IV) in sulfuric acid medium showed a negligible effect of acidity. Formation of an intermediate complex, which decomposes in the rate-determining step, has been suggested.[62]

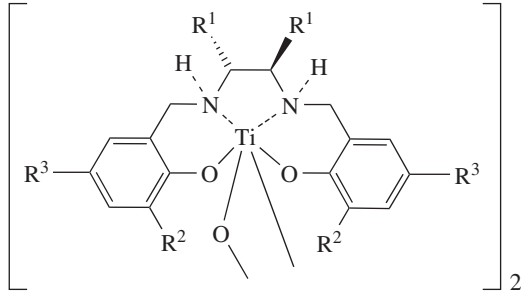
$Ce(SO_4)_2$ is found to be the reactive species in the iridium(III)-catalysed oxidation of *t*-butyl alcohol,[63] cyclohexanol,[64] and methanol[65] with cerium(IV) in sulfuric acid. The reaction is first order in cerium(IV) but of fractional order in the reductants. Induced polymerization of acrylonitrile indicated the generation of free radicals. Mechanisms have been suggested on the basis of experimental results.

The oxidation of benzoin with cerium(IV) in perchloric acid solution is proposed to involve an interaction between Ce^{4+}(aq.) ions and the keto alcohol, resulting in the formation of free radicals. The final product is benzoic acid.[66] The rate of oxidation of crotyl alcohol with cerium(IV) is independent of the concentration of Ce(IV). The reaction induced polymerization of acrylonitrile indicating the formation of free radicals. The kinetics and activation parameters for the reaction have been determined.[67] For the Ir(III)-catalysed oxidation of methyl ketones[68] and cyclic ketones[69] with Ce(IV) perchlorate, successive formation of complex between the reductant and Ce(IV) and then with the catalyst has been proposed. Results showed that in acidic solutions, iridium(III) is a more efficient catalyst than osmium and ruthenium compounds.

The rhodium(III)-catalysed oxidation of maleic acid[70] and fumaric acid[71] with Ce(IV) in acidic medium shows a first-order dependence on Ce(IV), the reductant, and Rh(III). There is no significant effect of ionic strength. Suitable mechanisms have been postulated.

Oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) with ceric ammonium nitrate (CAN) in acetic acid resulted in ethyl 2,4-dioxo-6-phenyltetrahydropyrimidin-5-carboxylates as the major product. However, DHPMs undergo a regioselective oxidation with CAN in the presence of sodium hydrogencarbonate in neutral aqueous acetone solution to yield ethyl 6-methyl-4-aryl(alkyl)pyrimidin-2(1*H*)-one-5-carboxylates. A mechanism involving a nitrolic acid intermediate has been suggested.[72]

A titanium complex (**1**) with a salen ligand is an efficient catalyst for the enantioselective epoxidation of alkenes with hydrogen peroxide as the terminal oxidant. (*ee*) The participation of a titanium–peroxo species, activated by hydrogen bonding, in the reaction, has been postulated.[73]



(**1**)

Kinetics of oxidation of iron(II) by the surfactant complex ions *cis*-chloro/bromo (dodecylamine)bis(ethylenediamine)cobalt(III) have been reported. The second-order rate constant remains constant below the critical micelle concentration (cmc), but increases with cobalt(III) concentration above the cmc. The rate of reaction was not affected by the added hydrogen ions. It is suggested that the reaction proceeds by an inner-sphere mechanism.[74]

Oxidation of promazine and chlorpromazine with hexaimidazolecobalt(III) in acidic solution results in the formation of Co(II) and a cationic radical. The kinetic and activation parameters have been determined and mechanistic aspects have been discussed.[75]

The catalytic action of CDTA complexes of Fe(III), Ni(II), Cu(II), Cr(III), and Mn(II) on the oxidation of L-ascorbic acid with tris(oxalato)cobaltate has been investigated. The rate is proportional to the concentration of the complex. Fe(III)–CDTA is the best catalyst for the reaction.[76]

An oxo–diperoxo tungstate(VI) complex, $PPh_4[WO(O_2)_2(QO)]$, is generated from H_2WO_4, hydrogen peroxide, quinolin-8-ol (QOH), and PPh_4Cl. This complex is highly efficient as a catalyst for epoxidation of alkenes in tandem with sodium hydrogencarbonate as co-catalyst and hydrogen peroxide as as a terminal oxidant. The initial rate of oxidation followed first-order kinetics.[77]

A catalytic asymmetric oxidation of mono-, di-, and tri-substituted alkenes using a chiral bishydroxamic acid (BHA) complex of molybdenum catalyst in air at room temperature leads to good to excellent selectivity. It has been suggested that the Mo–BHA complex combines with the achiral oxidant to oxidize the alkene in a concerted fashion by transfer of oxygen from the metal peroxide to the alkene.[78] The chiral BHA–molybdenum complex has been used for the catalytic asymmetric oxidation of sulfides and disulfides, utilizing 1 equiv. of alkyl peroxide, with yields up to 83% and *ee*s up to 86%. An extension of the methodology combines the asymmetric oxidation with kinetic resolution providing excellent enantioselectivity (*ee* = 92–99%).[79]

Lead, Bismuth, and Palladium

Mn(II)-catalyzed oxidation of cyclic ketones with lead tetraacetate is zero order in the oxidant. The order of reactivity is cyclohexanone > cyclooctanone > cycloheptanone ≈ cyclopentanone. The reactivity has been analysed in terms of the conformation.[80]

The rate of oxidation of acetophenoximes with bismuth(V) fluoride in a mixture of hydrogen fluoride and perchloric acid follows first-order kinetics in both the oxime and Bi(V). The reaction is acid catalysed. A bridged outer-sphere mechanism, involving formation of an iminoxy radical, has been suggested.[81]

Oxidation of methane to acetic acid, catalysed by Pd(II) in concentrated sulfuric acid, has been investigated by DFT calculations. The results show that Pd^{2+} cations in such solutions are ligated by two bisulfate anions and by one or two molecules of sulfuric acid. Methane activation occurs primarily via addition of methane across one of the Pd–O bonds of a bisulfate ligand. A likely route to products involves the oxidation of $Pd(HSO_4)(CH_3)(H_2SO_4)_2$ and $Pd(HSO_4)(CH_3\text{-}CO)(H_2SO_4)_2$ to form $Pd(\eta^2\text{-}HSO_4)(HSO_4)_2(CH_3)(H_2SO_4)$ and $Pd(\eta^2\text{-}HSO_4)(HSO_4)_2(CH_3CO)(H_2SO_4)$, respectively, which then can readily eliminate CH_3HSO_4 or CH_3COHSO_4, respectively. Pd(0) formed as a result of the reaction is reoxidized to Pd(II) by either sulfuric acid or oxygen.[82]

Group VIII Metals

Pentadentate dispidine-based Fe(II) complexes catalyse the oxidation of cyclooctene with hydrogen peroxide to afford the expected epoxide product, with the reaction

rate dependent on the ligand structure. Under anaerobic conditions in acetonitrile *cis*- and *trans*-1,2-diols are also obtained. The data support a mechanism which involves formation of a low-spin Fe(III)–hydroperoxo intermediate that produces (Fe^{IV}=O). Epoxide is formed both by direct transfer of the ferryl oxygen atom and by a radical based process with molecular oxygen. Diols are formed by the reaction of an adduct of the alkene and Fe(IV) with $HO^{\bullet}$ within the solvent cage of the iron complex.[83] Ferrate(VI) oxidation of ibuprofen is slowed with an increase in the pH of the solution and the rates are related to protonation of ferrate(VI). The use of Fe(VI) in removing ibuprofen from water has been discussed.[84]

Bleomycin (BLM), a glycopeptide antibiotic chemotherapy agent, damages single- and double-stranded DNA. The experimental and computational studies on the reaction coordinate of activated bleomycin (ABLM) strongly showed the low-spin (ABLM) Fe^{III}–OOH complex as the active oxidizing species. Kinetic experiments yielded a deuterium isotope effect, $k_H/k_D = 3$, for ABLM decay, indicating the involvement of a hydrogen atom in the rate-determining step. H-atom donors with relatively weak X–H bonds accelerate the reaction rate, establishing that ABLM is capable of hydrogen atom abstraction. Direct H-atom abstraction by ABLM generates a reactive $Fe^{IV} = O$ species, which is capable of cleaving a second DNA strand, as is observed *in vivo*. It has been shown that BLM does not follow the haem paradigm, which involves heterolytic O–O bond cleavage to generate a reactive $Fe^{V} = O$ intermediate.[85]

It has been demonstrated that the oxidation of alcohols with hexacyanoferrate(III) (HCF) shows a hyperbolic variation with HCF concentration, and the reaction order varies from one to zero on increasing the HCF concentration. This rate law is obeyed during the initial moments of the reaction and at any subsequent time. These results rule out the possibility that any substance produced during the course of the reaction acts as an activator or inhibitor of the reaction rate. The mixed order has been attributed to the comparable rates of complex decomposition and catalyst regeneration steps.[86] HCF acts as a selective oxidizing agent for the oxidation of catechols even in the presence of 2-mercaptobenzoxazole, as an easily oxidizable thiol, to produce related catechol thio ethers.[87] Hexacyanoferrate(II) has a retarding effect on the oxidation of vanillin with HCF in alkaline solutions. A mechanism based on the observed kinetics has been proposed.[88]

The reactions of butane-2,3-diol by HCF in alkaline medium using Ru(III) and Ru(VI) compounds as catalysts leads to similar experimental rate equations for both the reactions. The mechanism involves the formation of a catalyst–substrate complex that yields a carbocation for Ru(VI) or a radical for Ru(III) oxidation. The role of HCF is in catalyst regeneration. The rate constants of complex decomposition and catalyst regeneration have been determined.[89] A probable mechanism invoving formation of an intermediate complex has been proposed for the iridium(III)-catalysed oxidation of propane-1,2-diol and of pentane-1,5-diol, butane-2,3-diol, and 2-methylpentane-2,4-diol with HCF.[90–92] The Ru(VIII)-catalyzed oxidation some α-hydroxy acids with HCF proceeds with the formation of an intermediate complex between the hydroxy acid and Ru(VIII), which then decomposes in the rate-determining step. HCF regenerates the spent catalyst.[93]

A zero-order dependence on methionine concentration was observed in the Os(VIII)-catalyzed oxidation by HCF. A slow step consisting of reaction between a hydroxoosmium derivative and HCF to form an intermediate has been suggested. The reaction of this intermediate with methionine in a fast step is postulated to yield a sulfur radical cation.[94]

Novel chiral tridentate ligands, *N*,*N*,*N*-pyridine-2,6-bisoxazolines (pybox) and *N*,*N*,*N*-pyridine-2,6-bisoxazines (pyboxazine) have been synthesized.[95] Asymmetric epoxidation of alkenes with 30% hydrogen peroxide in the presence of ruthenium complexes of these ligands has been studied. Mono-, 1,1-di-, *cis*- and *trans*-1,2-di-, tri-, and tetra-substituted aromatic alkenes with versatile functional groups are epoxidized with this type of catalyst in good to excellent yields (up to 100%) with moderate to good enantioselectivies (up to 84% *ee*). It is shown that the presence (*ee*) of weak organic acids or an electron-withdrawing group on the catalyst increases the reactivity. New insights into the reaction intermediates and reaction pathway of the ruthenium-catalysed epoxidation are proposed on the basis of density functional theory calculation and experiments.[96]

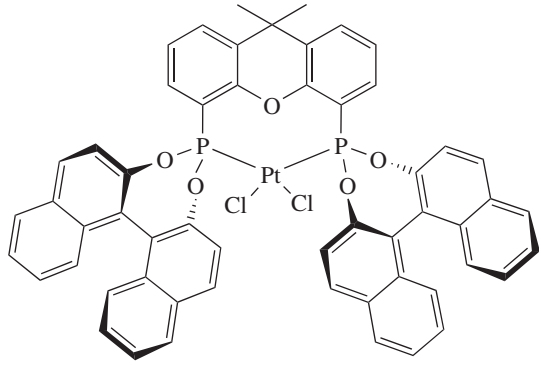
α-Acetoxysulfones were formed in palladium-catalysed asymmetric allylic alkylations of allylic geminal dicarboxylates with sodium benzenesulfinate. The directing ability of this novel functional group has been demonstrated in a series of dihydroxylations, carried out with Os(VIII) and NMO, affording *syn*-diols exclusively *anti* to the acetoxysulfone as single diastereomers in excellent yields.[97]

Application of computaional methods to the enantioselective dihydroxylations of alkenes by osmium complexes have been reviewed with a special focus on methods (*ee*) used to study the origin of high enantioselectivity. The use of a vast number of computational techniques such as QM, MM, Q2MM, QM/MM, molecular dynamics, and genetic algorithms has been enumerated.[98]

1,2-Dioxane-4,5-diols (peroxydiols) are conveniently synthesized in yields up to 98% and with *de* >90% by dihydroxylation of 3,6-substituted 3,6-dihydro-1,2- (*de*) dioxines with osmium tetroxide.[99] Sharpless asymmetric aminohydroxylation has been modified using *N*-sulfonyloxycarbamates as reoxidants for the tethered aminohydroxylation reaction for allylic substrates. The yields are high and the reaction proceeds through an osmium azaglycolate intermediate. The use of *N*-sulfonyloxy carbamates resulted in higher yields than the use of an *N*-halocarbamate salt.[100] In OsO_4-mediated oxidative cleavage of alkenes, OsO_4 can be replaced with alternative, easier to handle, less volatile, and more innocuous osmium sources such as osmium trichloride, potassium osmate, or polymer-bound osmium tetroxide.[101]

Oxidation of α,β-unsaturated nitriles, amide, and acids with pentachlorohydroxoplatinate(IV) in alkaline solution is first order in the oxidant, reductant and alkali. The oxidation takes place with an inner-sphere mechanism. A tentative mechanism involving a two-electron oxidation has been suggested and the activation parameters have been calculated.[102]

Platinum complexes, [$PtCl_2$\{(*R*,*R*)-XantBino}] (**2**) and its *S*,*S* analogue, were treated with tin(II) chloride to form the pre-catalyst for chemo-, regio-, and enantio-selective (*ee*) hydroformylation of styrene, vinyl acetate and allyl acetate. Although the reaction showed good chemo- and regio-selectivities, only moderate *ee* was obtained.[103]



(**2**)

Oxidation by Compounds of Non-metallic Elements

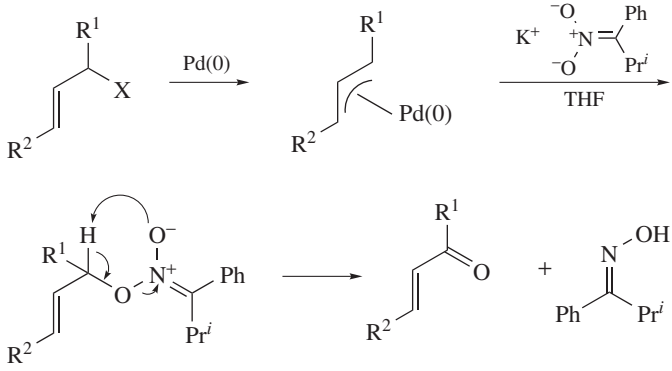
Nitrogen, Sulfur, and Boron

The initial pathways of oxidation of dimethyl sulfide, dimethyl disulfide, and methanethiol with the nitrate radical have been examined using DFT and *ab initio* methods. It is seen that sulfur compounds exhibit a general trend of hydrogen abstraction following the formation of an initial sulfur–nitrate complex. The results are in agreement with experimental work on dimethyl sulfide and methanethiol. Oxygen addition does not seem to be the dominant oxidation pathway in the case of dimethyl disulfide. The rate constants obtained from kinetics calculations are consistent with experimental findings and exhibit a negative temperature dependence. The importance of nitrate radical in the oxidation of reduced sulfur compounds in the atmosphere is confirmed.[104] The importance of the nitrate radical in the troposphere oxidation of dimethyl sulfide has been examined by DFT and *ab initio* methods.[105] A kinetic model of the oxidation of dimethyl sulfide with nitrogen dioxide has been constructed and the parameters thereof were verified by experimental data.[106]

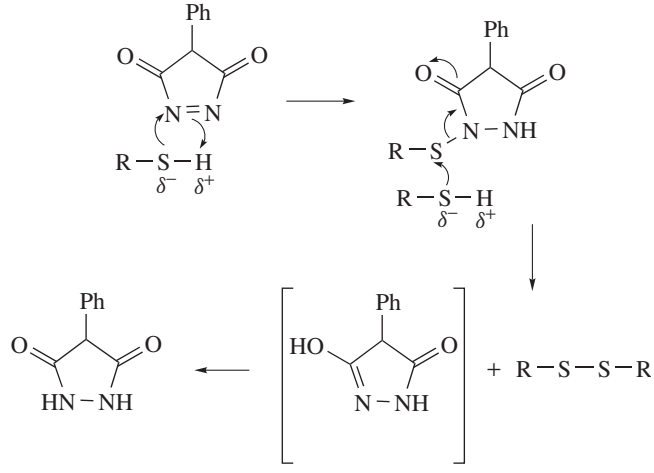
An unexpected aromatization that takes place during the *N*-alkylation reaction performed on several 3-(2-nitrobenzoyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylic acid methyl esters, giving rise to a mixture of 1-alkyl-3-(2-nitrobenzoyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylic acid methyl esters and 1-alkyl-3-(2-nitrobenzoyl)-1*H*-pyrazole-5-carboxylic acid methyl esters is reported. It is suggested that reaction involves both inter- and intra-molecular oxidation by the nitro group.[107]

Palladium-catalysed chemo- and enantio-selective oxidation of allylic esters and carbonates has been achieved using nitronates as nucleophilic oxidants. The products, α,β-unsaturated carbonyl compounds, were obtained in excellent yields and *ee*s. The mechanism in Scheme 5 has been suggested for the reaction.[108]

N-Phenyltriazolinedione is an efficient and chemoselective reagent for the oxidation of thiols to their corresponding symmetrical disulfides. The method is applicable to aromatic, aliphatic, and bifunctional thiols and excellent yields are obtained. A two-step mechanism (Scheme 6) has been proposed.[109]



SCHEME 5

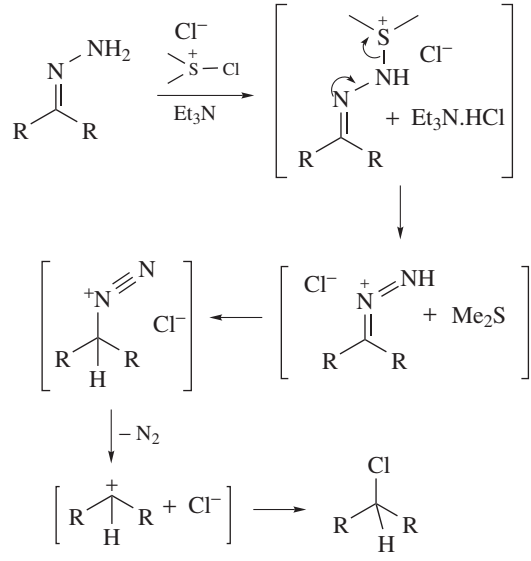


SCHEME 6

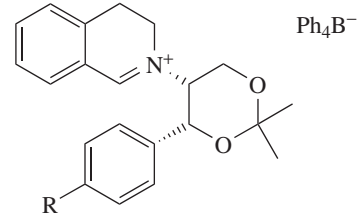
Odourless and non-volatile organosulfur compounds grafted to an imidazolium ionic liquid scaffold has been synthesized. The sulfoxides have been used for an efficient oxidation of primary allylic and benzylic alcohols into aldehydes and secondary alcohols to ketones under Swern oxidation conditions and the corresponding sulfides can be recovered and recycled.[110]

The unsubstituted hydrazones derived from aromatic ketones and aldehydes are converted to the corresponding alkyl chlorides, in high yield, under Swern oxidation conditions. In this unusual oxidation/reduction sequence, the substrate undergoes a net reduction. Unsubstituted hydrazones derived from cyclohexyl ketones yielded elimination products. The mechanism in Scheme 7 has been postulated.[111]

A series of dihydoisoquinolium salts (**3**) based on a dioxane-containing structure have been synthesized and used in the asymmetric epoxidation of alkenes with Oxone (*ee*)



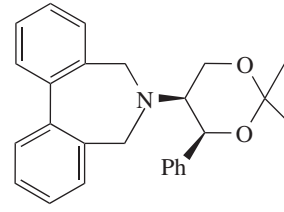
SCHEME 7



(**3**)

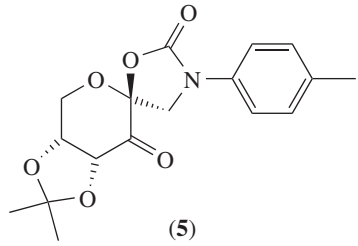
as the terminal oxidation. Almost quantitative yields and *ee*s up to 71% have been realized.[112]

Homologous biphenyl and binaphthyl tertiary azepines (**4**) and quaternary iminium salts, prepared from (+)-(*S*,*S*)-L-acetonamine, behave as effective catalysts for the enantioselective epoxidation of unfunctionalized alkenes with Oxone (*ee* up to 83%).[113]



(**4**)

Oxidative dearomatization of *p*-alkylphenols into 4-alkyl-4-hydroperoxycyclohexa-2,5-dienones (*p*-peroxyquinols) and 4-alkyl-4-hydroxycyclohexa-2,5-dienones (*p*-quinols) using Oxone as a source of singlet oxygen in excellent yields have been achieved in aqueous solutions.[114] Highly enantioselective epoxidation of benzylidene-cyclobutanes[115] and tetrasubstituted benzylidenecyclobutanes[116] has been achieved using a readily available glucose-derived ketone (**5**) as catalyst and Oxone as an oxidant. The epoxidation is likely to proceed mainly via a spiro transition state.



(**5**)

A variety of conjugated dienes are epoxidized with high enantioselectivity using glucose-derived oxazolidinone catalysts and Oxone as an oxidant. The epoxidations are stereospecific and no isomerization is observed, thus *cis*-epoxides are formed exclusively from *cis*-alkenes. The regio- and enantio-selectivity of the reaction are dependent on the substitution pattern of the diene system.[117] Up to 93% *ee* was achieved in asymmetric epoxidation of a series of 6- and 8-substituted chromenes using chiral dioxiranes, generated *in situ* from oxazolidinone and Oxone. Higher *ee*s are obtained when substrates are substituted at the 6-position. The enhanced enantioselectivity is likely due to the van der Waals forces and/or hydrophobic interactions between the 6-substituent of the substrate and the *N*-aryl or alkyl group of the ketone catalyst.[118]

A convenient asymmetric epoxidation of substituted styrenes using chiral dioxiranes generated *in situ* from *N*-aryl-substituted oxazolidinone-containing ketones and Oxone has been reported. High enantioselectivity has been achieved for both electron-rich and electron-poor styrenes.[119] A new class of enantiomerically pure tetrahydropyran-4-ones with an axial α-substituent has been developed as catalysts for asymmetric epoxidation of alkenes using Oxone as the oxidant affording epoxides with up to 83% *ee*. In these monocyclic pyranone derivatives, there is some loss of enantioselectivity compared with bicyclic systems, but good results are still obtained, indicating that an axial heteroatom can be an effective controller.[120] A series of 2-fluoro-8-oxabicyclo[3.2.1]octan-3-ones were prepared and tested as catalysts for alkene epoxidation with Oxone. These catalysts provide *trans*-stilbene oxide with up to 83% *ee*. These are effective catalysts for alkene epoxidation using Oxone, but afford lower enantioselectivities than their monosubstituted counterparts.[121] The *ee* values in the asymmetric epoxidation of *cis*-ethyl cinnamate with arabinose-derived ketones as catalyst and Oxone as the terminal oxidant were found to increase inversely with the size of the catalyst acetal blocking group. The catalyst with the least bulky methoxy acetal group displayed the best enantioselectivity and afforded ethyl (2*R*,3*R*)-3-phenylglycidate in 68% *ee*.[122] Homologous biphenyl and binaphthyl tertiary azepines

and quaternary iminium compounds have been synthesized and used as effective catalysts for the enantioselective (*ee* up to 87%) epoxidation of unfunctionalized alkenes with Oxone as the terminal oxidant.[123]

A V-shaped pH profile (pH = 0–4.73), obtained in the oxidation of furfural with peroxomonosulfuric acid, has been rationalized by considering oxidation of neutral and protonated forms of furfural with HSO_5^- and SO_5^{2-} ions. A suitable rate law has been deduced.[124]

A half-order dependence on hydrogen ion concentration has been observed in the Ag(I)-catalysed oxidation of some alkyl mandalates with peroxydisulfate. A free radical mechanism has been suggested.[125]

The reaction of thiourea[126] with Methylene Blue (MB) is enhanced by an addition of mercaptosuccinic acid. The oxidation of phenylthiourea with MB[127] is unaffected by the addition of the corresponding disulfide. The reactions exhibited a zero-order dependence on MB and a first-order dependence on the thiourea. The kinetic features have been explained in terms of reaction between half-reduced MB radical and the thiourea molecule.

Molybdenum(VI)-catalysed perborate oxidation of sulfides is first order with respect to the sulfide and Mo(VI) but zero order in perborate. The uncatalysed reaction is first order in each the reductant and oxidant. Trichloroacetic acid enhances the oxidation rate. Oxidation of *para*-substituted *S*-phenylmercaptoacetic acids yielded a Hammett ρ of -0.54 at 293 K, indicating an electron-deficient sulfur atom in the transition state. A mechanism involving a diperoxomolybdenum(VI) species as the reactive oxidizing species has been proposed.[128]

Halogens

Oxidation of oxalic acid with dimethyl-*N*,*N*-dichlorohydantoin and dichloroisocyanuric acid is of first order with respect to the oxidant. The order with respect to the reductant is fractional. The reactions are catalysed by Mn(II). Suitable mechanisms are proposed.[129] A mechanism involving synchronous oxidative decarboxylation has been suggested for the oxidation of α-amino acids with 1,3-dichloro-5,5-dimethylhydantoin.[130] Kinetic parameters have been determined and a mechanism has been proposed for the oxidation of thiadiazole and oxadiazole with trichloroisocyanuric acid.[131] Oxidation of two phenoxazine dyes, Nile Blue and Meldola Blue, with acidic chlorite and hypochlorous acid is of first order with respect to each of the reductant and chlorite anion. The rate constants and activation parameters for the oxidation have been determined.[132]

In the oxidation of alkanethiols to disulfides with chloramine-T (CAT), in alkaline solution, the proposed reactive species are hypochlorous acid and $TsNCl^-$ anion. A correlation of reaction rate with Taft's dual substituent parameter equation yielded $\rho^* = -5.28$ and $\delta = -2.0$, indicating the rate-enhancing effect of electron-donating substituents.[133] Michaelis–Menten-type kinetics have been observed in the oxidation of atenolol with CAT in alkaline solutions. TsNHCl is assumed to be reactive species. A mechanism has been suggested and the activation parameters for the rate-determining step were calculated.[134] The Ru(III)-catalysed oxidation of diphenyl

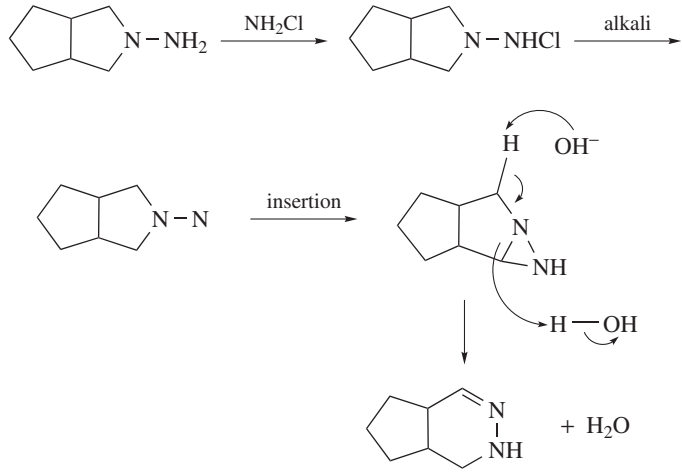
sulfoxide (DPSO) with CAT and chloramine-B (CAB) in acidic solution is first order with respect to the oxidant, hydrogen ions, and Ru(III). The reaction rate is independent of DPSO concentration and increases with added chloride ions. The activation parameters have been determined and mechanisms have been suggested.[135] The kinetics of the oxidation of cyclopentanol and cyclohexanol with CAT, catalysed by ruthenium(III), have been reported.[136–138] Michaelis–Menten-type kinetics have been observed in the oxidation of thiamine with CAT. An inverse fractional order in acidity has been observed. Activation parameters have been determined and a mechanism has been proposed.[139]

A second-order dependence on crotonic acid has been observed in its Os(VIII)-catalysed oxidation with CAT in alkaline solution. The reaction rate varied linearly with the concentration of Os(VIII). A mechanism has been proposed.[140] The kinetics of the ruthenium(III)-catalysed oxidation of the secondary amines with CAT in acidic medium have been obtained and mechanisms have been postulated.[141] Uncatalysed and Ru(III)-catalysed oxidation of ethylenediamine, diethylenetriamine, triethylenetetramine, aminoethylpiperazine, and isophoronediamine with CAT in HCl solution showed a fractional dependence on the amine, hydrogen ions, and Ru(III), and it is independent of CAT concentration. $TsNH_2Cl$ has been postulated as the reactive species and a mechanism has been suggested.[142]

The oxidation of glutamic acid to cyanopropionic acid with CAB in acid solution showed an inverse fractional dependence on acidity. Similarly in alkaline medium, the order in alkali is fractional inverse.[143] Kinetics of ruthenium(III)-catalysed oxidation of diols with CAB have been obtained. The products arise due to a fission of the glycol bond.[144] The oxidation of isatins with CAB, in alkaline solutions, showed a first-order dependence on CAB and isatin and fractional order in alkali. The rates correlate with the Hammett relationship, the reaction constant ρ being -0.31. The observed results have been explained by a plausible mechanism and the related rate law has been deduced.[145] The oxidation of cysteine with CAB in sulfuric acid medium is first order in CAB and cysteine and the rate is decreased with an increase in the hydrogen ion concentration.[146]

The kinetics and mechanism of the oxidation of aromatic aldehydes by *N*-chlorosuccinimide (NCS) have been reported.[147] A zero-order dependence has been observed with respect to maleic and crotonic acids in their Pd(II)-catalysed oxidation with NCS in acid solution. There is no effect of hydrogen ions on the rate.[148] The oxidation of phenylalanine and leucine with NCS, in acidic solution, is retarded by addition of succinimide.[149] A zero-order dependence on the aldehydes was observed in the oxidation of aromatic aldehydes with *N*-chloronicotinamide (NCN).[150] With alcohols,[151] however, the reaction showed a fractional order dependence. A retarding influence of added nicotinamide was observed in both reactions. Suitable mechanisms have been postulated.[150,151] Oxidation of *S*-phenylmercaptoacetic acid with NCN showed a first-order dependence on the reductant, NCN and hydrogen ions.[152] Electron-donating groups accelerate the rate of oxidation of aromatic aldehydes with NCN, whereas electron-withdrawing groups have the opposite effect. Activation parameters were determined and a mechanism has been suggested.[153]

The oxidation of *N*-amino-3-azabicyclo[3.3.0]octane with chloramine follows a second-order rate law and exhibits specific acid catalysis. The nature of the product is pH dependent; in strongly alkaline solutions, the product is 3,4-diazabicyclo[4.3.0]non-2-ene. A mechanism involving a nitrene insertion (Scheme 8) has been suggested.[154]



SCHEME 8

Oxidation of phenothiazines with 1-chlorobenzotriazole followed a first-order dependence on the oxidant and a zero-order dependence on the reductant concentration. Hypochlorous acid has been suggested as the rective oxidizing species. A mechanism consistent with the observed results has been proposed.[155]

The Ru(III)-catalysed oxidation of *o*-, *m*-, and *p*- hydroxybenzoic acids[156–158] with bromamine-B (BAB) in acidic solution showed a first-order dependence on the reductant, BAB, and Ru(III). An inverse first-order dependence with respect to acidity has been observed. Mechanistic aspects have been discussed.

A substantial kinetic isotope effect ($k_H/k_D = 5.88$) has been observed in the oxidation of α-deuteriomandelic acid with *N*-bromobenzamide (NBB) in acidic solution, confirming the cleavage of the C–H bond in the rate-determining step. The oxidation of substituted mandelic acids correlated with Brown's σ^+ with negative reaction constants. A mechanism involving transfer of a hydride ion to the oxidant is postulated.[159] The oxidation of glycolic acid with NBB in the presence of CTAB showed Michaelis–Menten kinetics with respect to the reductant. The oxidation is inhibited by CTAB. The results have been explained by Piszkiewicz model.[160] Iridium (III)-catalysed oxidation of methyl glycol with NBB exhibited a fractional order dependence on the catalyst and a zero-order dependence on the glycol. A mechanism has been suggested.[161] The rates of oxidative cleavage of *para*-substituted benzanilides with *N*-bromoacetamide, in acidic solution, correlate with Swain's *F* and *R* parameters. The rates for *ortho*-substituted compounds correlate well with a

triparametric equation involving steric effects. In this reaction, the field effects are more pronounced than the resonance effects.[162] The oxidation of some dipeptides and the corresponding amino acids with *N*-bromosuccinimide (NBS) is independent of the hydrogen ion concentration. The cationic form of the amino acid or dipeptide is assumed to be the reactive species. The relative reactivity has been correlated in terms of hydrophobicity.[163] The Ru(III)- and Ir(III)-catalysed oxidation of malic acid with NBS show identical kinetics. A suitable mechanism in conformity with the observed kinetics has been proposed.[164]

The reaction between selenium(IV) and tetrabutylammonium tribromide is postulated to involve a direct two-electron transfer as the test for the formation of free radical was negative. The proposed active reacting species are tribromide ion and $HSeO_3^-$ ion.[165]

The uncatalysed Belousov–Zhabotinsky (B–Z) reaction between malonic acid and acid bromate proceeds by two parallel mechanisms. In one reaction channel the first molecular products are glyoxalic acid and carbon dioxide, whereas in the other channel mesoxalic acid is the first molecular intermediate. The initial reaction for both pathways, for which mechanisms have been suggested, showed first-order dependence on malonic acid and bromate ion.[166] The dependence of the maximal rate of the oxidation of hemin with acid bromate has the form $v = k[\text{hemin}]^{0.8}[BrO_3^-]\ [H^+]^{1.2}$. Bromate radical, $BrO_2^{\bullet}$, rather than elemental bromine, is said to play the crucial role. A mechanism has been suggested taking into account the bromate chemistry in B–Z reactions and appropriate steps for hemin. Based on the proposed mechanism, model calculations have been carried out. The results of computation agree with the main experimental features of the reaction.[167]

The Os(VIII)-catalysed oxidation of crotonic acid with bromate ion in alkaline solution showed a zero-order dependence in bromate and the order with respect to crotonic acid is one at low concentration, tending to be zero at higher concentration. A mechanism has been postulated and the rate law has been deduced.[168] Oxidation of diethanolamine and triethanolamine by acid bromate in the presence of ruthenium(III) chloride as catalyst exhibited a first-order dependence on bromate and Ru(III). A first-order dependence on the reductant was observed at lower concentration, which became fractional at higher concentration. An inverse fractional order with respect to hydrogen ion concentration was observed. A mechanism involving the formation of a ternary complex between Ru(III), amino alcohol, and bromate ion prior to the rate-determining step is proposed.[169] Additon of chloride ions increased the rate of Ir(III)-catalysed oxidation of some cyclic alcohols[170] and cyclic ketones[171] with acid bromate. The rate is independent of the acidity of the solution. A change of solvent from H_2O to D_2O had no significant effect on the rate. Suitable mechanisms have been suggested.

A convenient method for the selective oxidation of oximes to carbonyl compounds using *N*-bromo-*N*-benzoyl-4-toluenesulfonamide is reported.[172] A convenient method for the preparation of 2-phenylthio-3-bromopropene by bromination of allyl phenyl sulfide is shown to proceed via the formation of a 1,3-dibromo-2-(phenylthio)propane intermediate.[173]

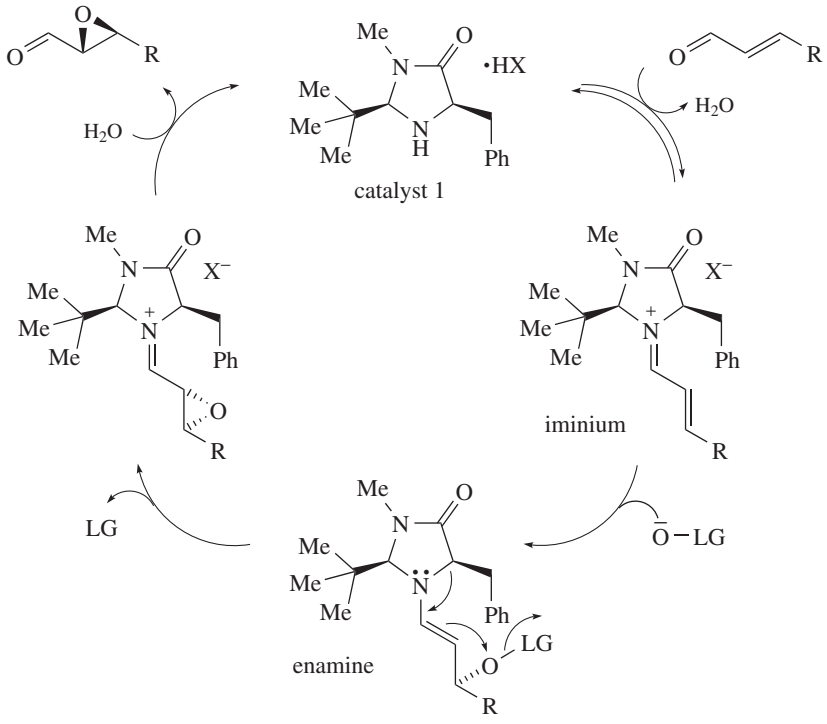
The reactivity of sulfanilic acid towards haloamines, in alkaline solutions, follows the order BAB > bromamine-T > CAB > CAT. This has been attributed to the difference in the electrophilicities of Cl^+ and Br^+ ions and the van der Waal's radii of chlorine and bromine. A probable mechanism has been suggested.[174]

The reactive species in the oxidation of secondary alcohols with benzyltrimethylammonium dichloroiodate, in the presence of zinc chloride, is proposed to be $[PhCH_2Me_3N]^+$ $[IZn_2Cl_6]^-$. The reactions exhibit a first-order dependence on the oxidant, reductant, and zinc chloride. The oxidation of benzhydrol-α-*d* showed the presence of a kinetic isotope effect, indicating a C−H bond cleavage in the rate-determining step. A mechanism involving transfer of a hydride ion from the alcohol to the oxidant has been proposed.[175] The same reactive oxidizing species has been proposed for the oxidation of methionine also. A mechanism involving formation of halosulfonium cation was proposed.[176]

Kinetic and activation parameters for the oxidation of hydroxylamine by iodine have been determined.[177] $Rh_2(OAc)_4$-catalysed oxidative amination of the sulfamate ester of 2-piperidinylmethanol with (diacetoxy)iodobenzene (DAIB) gives rise to seven-membered ring structures. The unusual regioselectivity observed in nitrogen-containing systems has been rationalized on the basis of conformational factors.[178] An unusual enamide–phenol coupling of a 1-methylene-1,2,3,4-tetrahydroisoquinoline derivative with DIAB has been reported. It was found that the formation of the phenoxide is an essential step for the reaction of the phenolic hydroxyl group with DAIB, leading to the formation of the desired product. Better yields are obtained in solvents of low nucleophilicity such as hexafluoropropan-2-ol.[179] Alkoxysulfonyl aziridine heterocycles were prepared through selective intra- and inter-molecular alkene oxidation reactions with DAIB and a rhodium catalyst. For intermolecular processes, trichloroethyl sulfamate was identified as a novel and markedly effective *N*-atom source.[180]

Oxidation of styrene with iodosobenzene is efficiently catalysed by manganese–porphyrin cages confining palladium and gold clusters. Absorption spectroscopic studies indicated that the accumulation of inactive species is efficiently suppressed when the cage catalysts are employed.[181] Asymmetric epoxidation of α,β-unsaturated aldehydes is achieved with iodosobenzene using an imidazolidinone as catalyst. The slow release of monomeric iodosobenzene from an iminoiodinane source provides high levels of reaction efficiency and enantiomeric control in the asymmetric epoxidation of electron-deficient alkenes (Scheme 9, LG = leaving group).[182] (ee)

Reactions of commercially available fluorous alkyl iodides with 80% hydrogen peroxide and trifluoroacetic anhydride gave $CF_3(CF_2)_{n-1}I(OCOCF_3)_2$. These iodides efficiently oxidize aliphatic and benzylic secondary alcohols to the corresponding ketones in the presence of aqueous potassium bromide. Bromide ion activates the reagents and/or generates a relay oxidant such as a functional equivalent of Br^+.[183] A high-yielding method for sulfation of alcohols has been developed, proceeding via sulfite and sulfate diester intermediates. The procedure involves oxidation of sulfite ester with periodate, catalysed by ruthenium(III).[184] A mechanism involving a rate-determining attack by the oxidant on the amine-nitrogen has been suggested in the



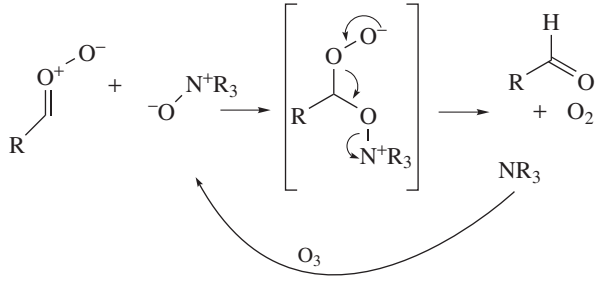
SCHEME 9

acid iodate oxidation of *N*-methyl- and *N*-ethyl-anilines. The faster rate of oxidation of the methyl compound has been attributed to the steric effect.[185]

Ozonolysis and Ozonation

Mechanistic aspects of ozonolysis of saturated organic compounds such as hydrocarbons, alcohols, ethers, cyclic acetals, and organometallic hydrides have been reviewed. The role of alkyl hydrotrioxides and dihydrogen trioxide as key intermediates is discussed.[186] A review has appeared on the kinetic and mechanistic aspects of the ozonization of ketones.[187] Use of ozone as a clean and efficient reagent in chemical reactions has been reviewed. Examples highlighting the successful use of ozone in both academic synthesis and industrial chemical processes have been presented. Generation of interesting new pharmaceutical and fine chemicals using ozone as a reactant has been highlighted.[188]

Ozonolysis of alkenes in the presence of amine *N*-oxides resulted in reductive ozonolysis, i.e, the direct formation of aldehydes in high yields, avoiding the generation and isolation of ozonides or other peroxide products. Use of DMSO and tertiary amines improved the yield of aldehydes but some amount of ozonides remained. This



SCHEME 10

reaction appears to involve an unprecedented trapping (Scheme 10) of the short-lived carbonyl oxide intermediates to generate a zwitterionic adduct, which fragmented to produce the carbonyl group, an amine and $^1O_2$.[189,190]

The rate constants of the reaction of 2,6-dimethyloct-7-en-2-ol separately with ozone and hydroxyl radical, in the gas phase, have been determined. The OH radical can either abstract hydrogen or add to the double bond. Ozone adds to the double bond. The formation of acetone, 2-methylpropanal, 2-methylbutanal, ethanedial, and 2-oxopropanal was discussed.[191] The rate laws and activation parameters for the ozone oxidation of alcohols in aqueous solution have been determined and explained on the basis of formation of an ozone–alcohol complex.[192] The reactivity of alkenes towards ozone, in aqueous solution, correlates well with Taft's equation.[193]

Oxidation with ozone, under physiological conditions, follows the rate order uric acid $\approx$ ascorbic acid $>$ glutathione. The amounts of ozone absorbed and antioxidant consumed have been simulated with a mathematical model and reaction rate constants of the oxidations have been evaluated.[194] Various facets of transition metal-catalysed oxidation of benzylic compounds with ozone have been reported. The correlation of the effect of substituents with Hammett constants and steric factors has been discussed. The reaction seemed to proceed via a radical mechanism.[195]

Ozonation of various silanes and germanes produced the corresponding hydrotrioxides, $R_3SiOOOH$ and $R_3GeOOOH$. Ozone reacts with the H–Si/Ge bond via a concerted 1,3-dipolar insertion mechanism. The hydrotrioxides decompose in various solvents into the corresponding silanols/germanols, disiloxanes/digermoxanes, singlet oxygen, and dihydrogen trioxide (HOOOH), where quantum chemical calculations indicated the importance of catalytic amounts of water. The formation of HOOOH as a decomposition product of organometallic hydrotrioxides in acetone-d_6 is a new and convenient method for the preparation of this simple, biochemically important polyoxide.[196]

Peracids and Peroxides

A new approach to the oxyfunctionalization of alkanes with isolated dioxiranes has been reviewed. Dioxiranes achieve oxidation of alkanes with high selectivity for both

simple and structurally complex targets.[197] The syntheses and synthetic uses of peroxides in the oxidation of sulfides, alcohols, C–H bonds, and organonitrogen compounds and in epoxidation, vicinal dihydroxylation, Baeyer–Villiger oxidation, and oxidative halogenation of hydrocarbons have been reviewed.[198] Recent advances in enantioselective metal-catalysed Baeyer–Villiger oxidation, especially the preparation of chiral lactones, have been reviewed with an emphasis on the role of different ligands.[199] The metal-catalysed asymmetric epoxidation of unactivated terminal alkenes with hydrogen peroxide has been reviewed with an emphasis on recent developments. It has been concluded that the state-of-the-art catalysts for asymmetric epoxidation catalysts using aqueous hydrogen peroxide as the oxidant are [Ti(salalen)] and [Ti(salan)] complexes.[200]

Calculations based on DFT predicted that substitution on the cyclic enol ether influences the level of diastereoselectivity in the epoxidation reaction of dihydropyrans and oxepenes with dimethyldioxirane (DMDO). This is in agreement with the reported experimental results. In all cases, the oxidations are asynchronous and proceed through the spiro-transition state. It is apparent from the calculations that the degree of synchronicity in the transition state is important in the diastereoselectivity.[201] The stereoselectivity of the key epoxidation step, with DMDO, in the synthesis of guanacastepene is shown, by computational study, to be controlled by torsional steering. In this particular epoxidation reaction, the transition structure energetic difference is enhanced by the great asynchronicity of the forming C−O bonds that intensifies the torsional interactions.[202] The oxidation of a series of aliphatic ethers with DMDO is first order in both the ether and DMDO. The competition between oxygen insertion and radical mechanisms has been discussed. DFT calculations of the oxidation of methyl ethers indicated a possible increase in the probability of oxidation via the radical route for substrates containing electron-withdrawing substituents.[203]

Chiral pyrrolidine derivatives, proline, and amino acid-derived imidazolidinones mediate the asymmetric epoxidation of α,β-unsaturated aldehydes. Protected α,α-diphenyl-2-prolinol catalyses the asymmetric formation of 2-epoxyaldehydes, with hydrogen peroxide or sodium percarbonate as the oxygen sources, with 81–95% conversion with up to 96:4 *dr* and 98% *ee*.[204]

Sulfides are oxidized to sulfoxides and sulfones with hydrogen peroxide in the presence of zirconium tetrachloride in methanol at room temperature. Under these conditions, the sulfide function is highly reactive, and various other functional groups such as alkene and ketone remain unaffected.[205] The mechanism of the oxidation of cysteine with hydrogen peroxide has been reformulated based on mathematical models. It has been pointed out that experimental results are not sufficient to make a choice between the two models.[206] A mechanism has been proposed for the oxidation of styrene with hydrogen peroxide in the presence of sodium tungstate and oxalic acid on the basis of the kinetics of the reaction.[207] The oxidation of phenols, cinnamic acids, and methyl aryl sulfides with hydrogen peroxide is efficiently catalysed by manganese 1,4,7-trimethyl-1,4,7-triazacyclononane complexes. The results of spectroscopic and kinetic studies coupled with Hammett correlations and labeling experiments suggested that the active oxidizing species is an electrophilic, mononuclear oxo–Mn(V) species.[208]

The oxidation of benzyl alcohols with hydrogen peroxide showed marked rate acceleration when catalysed by two bridged ketocyclodextrins. These catalysts function as artificial enzymes and show Michaelis–Menten kinetics. The oxidation of *para*-substituted benzyl alcohols exhibited a Hammett $\rho = 1.9$. This value suggests that the transition state is ionic and has some negative charge at the reaction centre. A comparison of 1-phenylethanol with its 1-deuterated analogue reveals a small isotope effect ($k_H/k_D = 1.4$). A suitable mechanism has been proposed.[209] Activation parameters have been determined for the oxidation of α-ethylacrolein and crotonic aldehyde with hydrogen peroxide.[210] A probable mechanism, involving hydroxyl radicals, has been postulated for the gas-phase free radical chain oxidation of pyridine derivatives with hydrogen peroxide.[211] The oxidation of diethyl sulfide with hydrogen peroxide is catalysed by nitrite ions. The observed kinetics indicated the formation of peroxynitrous acid as an intermediate.[212] Alkylated phenol and methoxytoluene derivatives are selectively oxidized to the corresponding 1,4-benzoquinones in good yields with hydrogen peroxide and methyltrioxorhenium in 1-butyl-3-methylimidazolium tetrafluoroborate, a neutral ionic liquid.[213]

Certain dinuclear iron complexes are found to be efficient catalysts for the oxidation of primary and secondary alcohols with hydrogen peroxide.[214] Metalloporphyrins are used as peroxidase mimics in the oxidation of phenol with hydrogen peroxide. A kinetic model has been constructed.[215] New diphosphine–pentafluorophenyl-Pt(II) chiral catalysts epoxidize terminal alkenes with hydrogen peroxide as oxidant, resulting in the production of the corresponding terminal epoxides in moderate to good yields, with *ee* up to 98%, and complete regioselectivity in the case of dienes. The choice of Pt(II) as the metal centre and $-C_6F_5$ as the ligand imparted the proper electronic properties to the metal, while at the same time increasing the rigidity and steric hindrance of the complexes, thereby accounting for the strong steric effect observed with different substrates.[216]

The epoxidation of alkenes by hydrogen peroxide is highly accelerated in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP). Kinetic studies indicated that higher order solvent aggregates are responsible for the rate acceleration. A large negative entropy of activation supported a highly ordered transition state. DFT simulations revealed a pronounced decrease in the activation barrier for oxygen transfer from hydrogen peroxide to ethene with increasing number of coordinated HFIP molecules. The oxygen transfer was unambiguously identified as a polar concerted process. Combined DFT and MP2 simulations of the epoxidation of (*Z*)-but-2-ene are in excellent agreement with the experimental data.[217]

Iodine-catalysed hydroperoxidation of cyclic and acyclic ketones with aqueous hydrogen peroxide in acetonitrile is an efficient and eco-friendly method for the synthesis of *gem*-dihydroperoxides and the reaction is conducted in a neutral medium with a readily available low-cost oxidant and catalyst.[218] Aryl benzyl selenoxides, particularly benzyl 3,5-bis(trifluoromethyl)phenyl selenoxide, are excellent catalysts for the epoxidation of alkenes and Baeyer–Villiger oxidation of aldehydes and ketones with hydrogen peroxide.[219] Efficient, eco-friendly, and selective oxidation of secondary alcohols is achieved with hydrogen peroxide using aqueous hydrogen bromide as a catalyst. Other peroxides such as *t*-butyl hydroperoxide (TBHP), sodium

perborate, and sodium percarbonate are also effective. The following mechanism has been proposed:[220]

$$H_2O_2 + Br_2 \longrightarrow 2HOBr$$

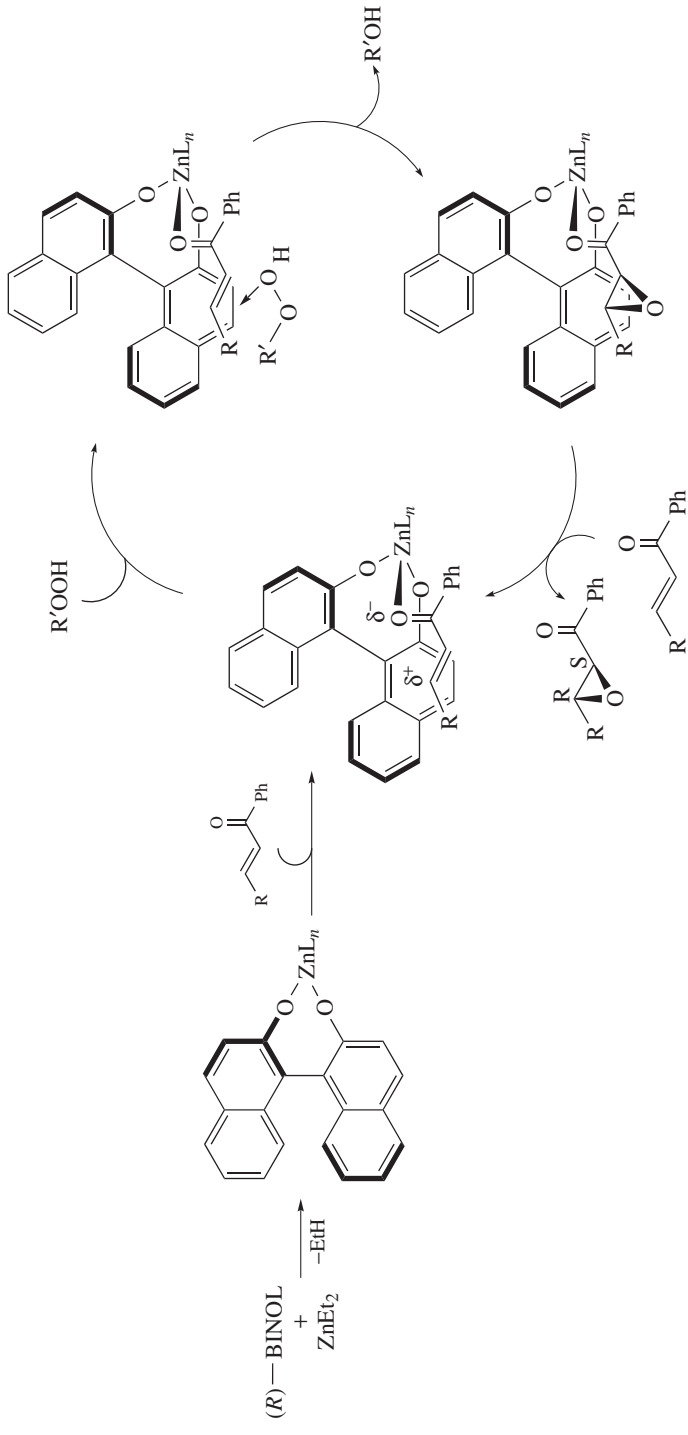
$$R_2CHOH + HOBr \longrightarrow R_2CHOBr + H_2O$$

$$R_2CHOBr \longrightarrow R_2CO + HBr$$

The oxidation of different sulfur compounds (sulfides, dibenzothiophenes, and thiophenes) with TBHP occurs on crystalline molecular sieves CoAPO-5 and Co/H-Y, and on MoO_x/Al_2O_3 catalysts. CoAPO-5 produced the highest organosulfur oxidation rates, reflecting the role of tetrahedral Co^{2+} framework cations that undergo facile redox cycles The relative reactivity of these organosulfur compounds increased with increasing electron density at their sulfur atom (phenyl sulfide > diphenyl sulfide > 4-methyldibenzothiophene > 2,5-dimethylthiophene) on all catalysts.[221] Moderate *ee*s are obtained in the epoxidation of alkenes with TBHP catalysed by a ruthenium(III) complex with a sugar-based ligand and 2,2′-bipyridine. A mechanism in which an Ru(V)–oxo species transfers an oxygen to the alkene through a metalloxetane has been proposed.[222] Catalytic enantioselective epoxidation of enones using a series of chiral pyrrolidinylmethanol-based dendritic catalysts and TBHP as an oxidant has been reported. The epoxides were obtained in good yields and *ee* up to 78%.[223] Catalytic enantioselective epoxidation of α,β-unsaturated ketones promoted by TBHP and diaryl-2-pyrrolidinemethanols has been reported. Investigation on structural modifications of the diaryl-2-pyrrolidinemethanols showed that fine tuning of the stereoelectronics of the substituents on the aryl moiety is important to achieve high efficiency. By employing a structurally optimized organocatalyst, high yields and up to 90% *ee*s have been achieved.[224] The Sharpless asymmetric epoxidation of (+)-zerumbol with TBHP, in the presence of L-diethyl tartrate, gave only an all-*erythro*-bisepoxide which has five stereogenic centres. It is proposed that the reaction proceeds with a diastereoselective but non-enantioselective monoepoxidation at the 2,3-position followed by a second highly enantioselective epoxidation at the 10,11-position giving efficient kinetic resolution.[225] The enantioselective oxidation of β-keto sulfides with TBHP in the presence of a titanium complex with (*S*,*S*)-hydrobenzoin is a convenient route to the corresponding β-ketosulfoxides in terms of reaction conditions, yields and enantioselectivities (*ee* > 98%). Aryl ketosulfoxides on reduction with DIBAL–$ZnCl_2$ yielded the corresponding β-sulfinyl alcohols with a retention of configuration.[226]

Dialkylzinc reagents combine with BINOL to generate, *in situ*, a catalyst for homogeneous epoxidation of (*E*)-α,β-enones to the corresponding *trans*-epoxy ketones. TBHP and cumene hydroperoxide (CHP) are effective terminal oxidants for this process; *ee*s of up to 96% have been achieved. Mechanistic investigations point towards an electrophilic activation (Scheme 11) of the substrates by the chiral BINOL–zinc catalyst and a subsequent nucleophilic attack of the oxidant.[227]

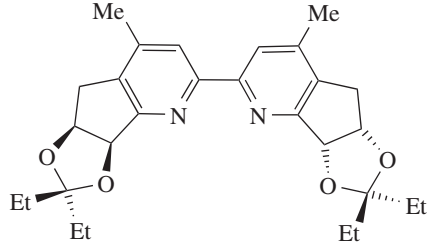
Incorporation of substituted BINOL ligands improved the enantioselectivity of asymmetric Baeyer–Villiger oxidations of prochiral cyclobutanones with CHP and



Scheme 11

catalysed by aluminium-based Lewis acids. NMR studies indicated the formation of non-monomeric reactive species and their relevance in determing the stereochemistry. The involvement of a pentacoordinated aluminium complex has been suggested.[228]

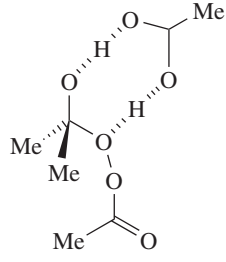
The efficiency of a new chiral non-racemic and C_2-symmetric 2,2-bipyridyl ligand (**6**) in copper(I)-catalysed asymmetric allylic oxidation reactions of the cyclic alkenes with *t*-butyl peroxybenzoate has been evaluated. On performing the reaction of cyclopentene, cyclohexene, and cycloheptene in acetonitrile the corresponding product, (1*S*)-cycloalk-2-enyl benzoate, was isolated in up to 69% yield and in 91% *ee*.[229]



(**6**)

Hydroxylation of alkenes with *m*-chloroperbenzoic acid is efficiently catalysed by an Ni(II)–tris(2-pyridylmethyl)amine complex. The participation of an NiO^+ (nickel–oxo) active species has been suggested.[230]

A new transition state (**7**) of the addition step in the Baeyer–Villiger reaction was found by B3LYP calculations. The role of proton acceptor is played by the carbonyl-oxygen atom, and the free energy barrier is lower than that previously estimated. This finding changes the mechanism for the acid catalysis.[231]

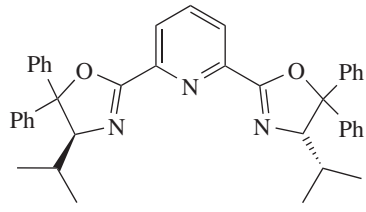


(**7**)

A combined theoretical and experimental study of the Baeyer–Villiger reaction of acetone and pentan-3-one, including their fluorinated and chlorinated derivatives, with performic acid revealed that the first step is rate determining for all substrates examined, even in the presence of acid. Acid catalysts generally decrease the $\Delta G^{\neq}$ of the first transition state (TS1), but increase the $\Delta G^{\neq}$ of the second (TS2). The optimal

reaction path for acetone proceeds over the uncatalysed step for both TS1 and TS2, whereas the reaction with pentanone proceeds best via TS1-cat and TS2. Migration of the ethyl group in pentanone is energetically most favourable. The introduction of a fluorine substituent decreases the migratory aptitude by a moderate amount, both experimentally and theoretically. Both theory and experiment show the migration of a chlorinated substituent to be significantly more difficult than that of the alkyl group.[232] DFT-based quantum chemical calculation has shown that the epoxidation of alkenes with peracids is a proton-catalysed reaction. The protonation site is the carbonyl-oxygen. The transition state and activation barriers to the attack of several peracids and their protonated forms on ethylene have been evaluated. Some important and puzzling kinetic data for epoxidation by peracids have been elucidated.[233]

Allylic oxidation of a variety of cyclic alkenes with copper complexes of different pybox ligands (**8**) and with various peresters shows high enantioselectivity (80–96% *ee*). Use of phenylhydrazine as an additive and acetone as solvent accelerates the reaction. It has been suggested that the phenylhydrazone is responsible for the observed acceleration. Using EPR spectra, it has been shown that the Cu(II) species is reduced to Cu(I) by phenylhydrazine and phenylhydrazone. It has been found that the presence of a *gem*-diphenyl group at C(5) and a secondary or tertiary alkyl substituent at the chiral centre at C(4) of the oxazoline rings is crucial for high enantioselectivity. A stereochemical outcome of the reaction is explained on the basis of a proposed transition state.[234,235]



(**8**)

The rate constants for oxidation of alkanes and alkenes with peroxynitrous acid in aqueous–gas phase are bell-shaped functions of the volume ratio between the liquid and gas phases. The kinetics of the generation of OH radicals and its importance in understanding the mechanism of lipid membrane oxidation has been stressed.[236]

Computational studies showed that the nature of the reactive species in the oxidation of trimethylamine, iodide ion, and dimethyl sulfide with lumiflavin is a C_4 α-hydroperoxide complexed with water. The other two species, C_4 α-hydroperoxide and C_4 α-peroxide, yielded higher activation energies.[237] Kinetic and spectroscopic studies on the effect of basic solvents, ethers, esters, and amides, on the oxidation of thianthrene-5-oxide with substituted peroxybenzoic acids indicated the involvement of the basic solvent in the transition state of the reactions. A solvent parameter, X_{tc}, based on the ratio of the *trans* to the *cis* form of thianthrene-5,10-dioxide, has been introduced.[238]

Photo-oxygenation and Singlet Oxygen

Recent developments in the stereoselective singlet oxygen allylic photo-oxygenations of alkenes have been reviewed. A number of factors, such as solvent, electronic effects, and non-bonded interactions that dictate the ene product selectivity, and also the various mechanisms of this reaction, have been highlighted.[239]

The oxidation of diethyl and diphenyl sulfides photo-sensitized by dicyanoanthracene (DCA), *N*-methylquinolinium tetrafluoroborate, and triphenylpyrylium tetrafluoroborate has been explored by steady-state and laser flash photolysis studies. In the Et_2S–DCA system, sulfide-enhanced intersystem crossing leads to the generation of $^1O_2$, which eventually gives the sulfoxide via a persulfoxide. In all other cases an electron-transfer mechanism is involved. Electron-transfer sulfoxidation occurs with efficiency essentially independent of the sulfide structure, is subject to quenching by benzoquinone, and does not lead to Ph_2SO co-oxidation. Formation of the radical cations $R_2S^{+\bullet}$ has been assessed by flash photolysis and confirmed by quenching with 1,4-dimethoxybenzene. Although it is possible that different mechanisms operate with different sensitizers, a plausible unitary mechanism has been proposed.[240]

Singlet oxygen reacts with binaphthylphosphine derivatives such as 1,1′-binaphthyldi-*t*-butylphosphine to form the corresponding binaphthyl-2-oxide phosphine oxides. This intramolecular arene epoxidation reaction proceeds with complete retention of stereochemistry. The binaphthyl-2-oxide di-*t*-butylphosphine oxide undergoes a slow 'NIH rearrangement' to form the corresponding hydroxylated product. A transient phosphadioxirane intermediate has been directly observed by low-temperature NMR.[241]

A simple route to 1,2-diols by organocatalytic enantioselective α-oxidation of aldehydes with singlet molecular oxygen, catalysed by protected diarylprolinols, has been reported. The oxidation produced α-hydroxy ketones, which are reduced with borohydride to the diols. The 1,2-diols were isolated in high yields with up to 98% *ee*. The oxidant was photo or chemically generated $^1O_2$.[242]

Rates of oxidation of *para*-substituted arylphosphines with singlet oxygen show good correlation with the Hammett σ parameter ($\rho = -1.53$) and with the Tolman electronic parameter. The only products are the corresponding phosphine oxides. However, for *ortho*-substituted phosphines with electron-donating substituents, there are two products, namely a phosphinate formed by intramolecular insertion and phosphine oxide. Kinetic analyses demonstrated that both products are formed from the same intermediate, a phosphadioxirane. VT NMR experiments showed that peroxidic intermediates can only be detected for highly hindered and very electron-rich arylphosphines.[243]

Triplet Oxygen and Autoxidation

The atmospheric oxidation of dimethyl sulfide (DMS) and DMSO has been reviewed. Kinetics of oxidation of DMS and DMSO with OH and NO_3 radicals and with halogen and halogen oxides have been described and the mechanistic aspects have been discussed.[244] A review of recent studies of the mechanism and kinetics of the gas-phase oxidation of dimethyl ether has mentioned the pressure dependence of the

products.[245] Synthetic and mechanistic aspects of catalytic autoxidation using nitroxyls radicals, either alone or in combination with transition metals, have been reviewed. The role of persistent dialkylnitroxyl such as TEMPO and reactive diacylnitroxyls derived from *N*-hydroxyphthalimide or *N*-hydroxysaccharin in the autoxidation of hydrocarbons and alcohols has been discussed.[246] Aerobic oxidation mediated by phosphovanadomolybdates has been reviewed. These aerobic oxidations are selective and synthetically useful in various transformations, notably diene aromatization, phenol dimerization, and alcohol oxidation. The usefulness of newer catalysts including binary complexes of the polyoxometalate and an organometallic compound useful, for example, for methane oxidation, and nanoparticles stabilized by polyoxometalates effective for aerobic alkene epoxidation are described.[247]

Various simulation schemes were examined and a new model is proposed to explain ignition delays found for reaction of *n*-decane and oxygen diluted in argon over a range of temperature (1239–1616 K) and pressure (1.82–10.0 atm).[248]

The radical-chain initiation in the main stage of cyclohexane autoxidation is largely caused by a concerted bimolecular reaction of the primary cyclohexyl hydroperoxide intermediate with cyclohexanone, a major oxygenated product. During this reaction, the breaking of the hydroperoxide O–O bond is assisted by simultaneous abstraction of a weakly bound α-H atom from the ketone by the nascent OH radical as it breaks away from the hydroperoxide. Complementary theoretical and experimental evidence has been produced to suggest that CyOOH initiation proceeds through a similar bimolecular process, involving concerted hydrogen abstraction from a CyH substrate molecule by the nascent OH radical.[249] Incorporation of bismuth greatly enhances the catalytic performance of vanadium–phosphorus oxide catalyst in the liquid-phase oxidation of cyclohexane. It has been suggested that the oxidation of cyclohexane to cycloheanone does not proceed through cyclohexanol.[250]

The use of platinum, heteropoly compounds, and metal-containing heteropoly compounds in the aerobic oxidation of cyclohexane, cyclohexene, and α-pinene in the liquid phase has been reviewed. The catalysts serve to control free radical processes. The role of peroxide intermediate in determining the final products is discussed.[251]

Uncatalysed oxidation of cycloalkanes and alkylarenes by molecular oxygen with acetaldehyde as sacrificial co-reductant occurs efficiently in supercritical carbon dioxide under mild multiphase conditions.[252]

The oxidation of *o*-, *m*-, and *p*-xylenes with oxygen–argon mixtures were measured behind reflected shock waves. The main reaction paths have been determined by sensitivity and flux analyses and have been used to explain the slight differences in the reactivity.[253]

The lowest-lying potential energy surfaces for the $O(^3P) + CH_2{=}C{=}CH_2$ reaction were theoretically characterized using CBS-QB3, RRKM statistical rate theory, and weak-collision master equation analysis using the exact stochastic simulation method. The results predicted that the electrophilic O-addition pathways on the central and terminal carbon atom are dominant up to combustion temperatures. Major predicted end-products are in agreement with experimental evidence. New H-abstraction pathways, resulting in OH and propargyl radicals, have been identified.[254]

The kinetics of the gas-phase reactions of $O(^3P)$ atoms with (*Z*)-CHCl=CHCl, CCl_2=CH_2, CCl_2=CCl_2, and (*E*/*Z*)-CFCl=CHCl were studied using a discharge flow tube system under pseudo-first-order conditions with $[O(^3P)]_0 \ll$ [chloroethene]. Halogen substitution in the alkenes has been discussed in terms of reactivity with $O(^3P)$ and its relation to the ionization potential and the reactivity with OH radicals.[255] Mechanistic aspects of the oxidation of alkenes with molecular oxygen using a Schiff base–Mn(III) complex as catalyst, in the presence of sodium borohydride, have been reported.[256] Mechanisms for the formation of multiple products observed for liquid-phase autoxidation of nonan-5-one have been proposed.[257]

Benzaldehyde is formed in the liquid-phase oxidation of *t*-butyl phenylacetate via a hydroperoxide and also by a non-radical pathway, probably via a dioxetane intermediate; both reactions are catalysed by benzoic acid. The kinetic parameters have been calculated by solving an inverse kinetic equation.[258]

High-yield conversions of thiols into disulfides,[259] alcohols into ketones, benzylic carbons to their ketones, and arenes to their quinones[260] have been achieved in subcritical water with oxygen without any catalyst or supporting materials. A thiol–alkene–co-oxygenation radical chain reaction involving molecular oxygen converts 2′-isopropenylacetophenones directly into cyclic peroxy hemiketal products with three new bonds.[261]

Chiral *N*-salicylidene vanadyl carboxylates are efficient catalysts for asymmetric aerobic oxidation of α-hydoxy esters and amides with divergent substituents. These (ee) catalysts have been explored for the kinetic resolution of secondary alcohols also. The stereochemical origin of the almost total asymmetric control has been probed.[262]

An efficient and convenient methodology for the aerobic oxidation of alcohols catalysed by sol–gel trapped perruthenate and promoted by an encapsulated ionic liquid in supercritical carbon dioxide solution has been reported. The reaction is highly selective and useful for substrates otherwise difficult to oxidize.[263] A four-component system consisting of acetamido-TEMPO–$Cu(ClO_4)_2$–TMDP–DABCO has been developed for aerobic alcohol oxidation at room temperature. The catalytic system shows excellent selectivity towards the oxidation of benzylic and allylic alcohols and is not deactivated by heteroatom-containing (S, N) compounds. The use of DMSO as the reaction medium allows the catalysts to be recycled and reused for three runs with no significant loss of catalytic activity.[264]

A new catalytic system consisting of a persistent macrocyclic aminoxyl radical and the couple $Mn(NO_3)_2$–$Co(NO_3)_2$ for the aerobic oxidation of alcohols to carbonyl compounds has been developed. The rate-determining step has been identified by studying the effect of substituents on the oxidation of benzyl alcohol. The chemistry of aminoxyl, amidoxyl, and imidoxyl radicals has been discussed.[265]

The geometries, vibrational frequencies and energies of all the stationary points for the ketene–oxygen reaction have been calculated. Relationships of the reactants, transition states, intermediates, and products are confirmed by intrinsic reaction coordinate calculations and important aspects of the mechanism have been highlighted.[266]

A theoretical study of the aerobic oxidation of alcohol using a $Pd(OAc)_2$–DMSO catalyst system has brought out the essential role of DMSO in the oxidation process. The transition state of the β-hydride elimination was identified computationally.[267]

Various mechanisms for the aerobic oxidation of alcohols catalysed by (NHC)Pd (carboxylate)$_2$(H_2O) complexes [NHC = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] were investigated using DFT combined with a solvent model. Of these, reductive β-hydride elimination, in which the β-hydrogen of a palladium-bound alkoxide is transferred directly to the free oxygen of the bound carboxylate, provided the lowest-energy route and explained the published kinetic isotope effect, activation enthalpy, reaction orders, and dependence of rate on carboxylate pK_a.[268]

An eco-friendly oxidation of alcohols under an oxygen atmosphere using catalytic amounts of [bis(acetoxy)iodo]benzene–TEMPO–KNO_2 has been reported. The use of a catalytic amount of poly[4-(bis(acetoxy)iodo)]styrene allowed the successful recycling of this catalytic component. The protocol can be used to promote the oxidation of different kinds of alcohols in the presence of other functional groups and also in the oxidation of primary benzylic alcohols in the presence of secondary and aliphatic ones. Primary alcohols can be oxidized to the corresponding aldehydes without any noticeable overoxidation to the carboxylic acids.[269]

The pathways for autoxidation of linalool, leading to hydroperoxides via a linalool–O_2 biradical intermediate state, have been investigated using quantum mechanical and DFT calculations. The major hydroperoxide found both experimentally and by calculations is 7-hydroperoxy-3,7-dimethylocta-1,5-dien-3-ol.[270] Both anionic and cationic cobalt(II)–porphyrin complexes were found to be efficient catalysts for the oxidation of 2-mercaptoethanol with oxygen.[271] The mechanism of base-catalysed oxygenation of phenol derivatives is proposed to involve a one-electron reduction of oxygen to form phenoxy radical. The phenoxy radicals couple with superoxide radical anion to yield peroxy anions and then finally lead to the epoxy alcohol adduct.[272] The temperature dependence of the degradation of dimethyl ether in the presence of oxygen and chlorine has been studied. The main products of the reaction are formaldehyde, methyl formate and formic acid. Formation of formaldehyde shows pressure dependence but that of methyl formate is independent of pressure.[273]

Other Oxidations

Sustainable oxidation of organic compounds, particularly pollutants, has been reviewed. The emphasis is on the catalysed oxidation by molecular oxygen without the use of transition metal ions. A number of less toxic options have been examined.[274] Basics of oxidation involving transition metal ions have been reviewed.[275] Platinum(II)-catalysed rearrangements of carbocations involved in diene cyloisomerizations have been reviewed.[276] Factors influencing the stability of catalysts, enantiomeric excess, (*ee*) and turnover numbers of three classes of chiral metalloporphyrins catalysing asymmetric oxidations have been reviewed. The role of porphyrins in various oxidation reactions such as hydroxylation, alkene epoxidation, *N*-oxidation, *S*-oxidation, and dealkylations has been stressed.[277] The development of mild, general, and selective transition metal-catalysed methods for the oxidative functionalization of carbon–hydrogen bonds has been reviewed. The likelihood of these reactions serving as powerful tools for the rapid and direct synthesis of diverse functionalized products for structure–activity relationship studies in medicinal and materials chemistry has been discussed.[278]

Special properties of water as solvent, with the hydrophobic effect promoting rapid and selective reactions have been reviewed. The use of addition of prohydrophobic and antihydrophobic materials to the water solution to understand the geometry of transition states for a number of classical reactions has been discussed.[279] Guanine bases in DNA are the most sensitive to oxidation. The oxidation of guanine bases by various one- and two-electron processes has been reviewed. Some key intermediates and the description of the oxidation products that can be generated from these intermediates depending on the reaction conditions are described.[280]

The reactions of arene dihydroxylating dioxygenase enzymes, their structure and mechanism, and recent examples of the application of arene *cis*-dihydrodiol bioproducts as chiral precursors in the synthesis of natural and unnatural products and chiral ligands have been reviewed. Alternative mechanisms of arene *cis*-dihydroxylations are discussed. The construction of new designer dioxygenases capable of producing *cis*-diols having unnatural configurations and regioisomers, and in improved yields, is mentioned. The expected applications are in the areas of new and improved synthetic routes to increasingly complex biologically active natural products, e.g. morphine and vinblastine, using a wider range of monocyclic arene *cis*-dihydrodiol precursors.[281]

A comparative study involving singlet oxygen, ozone, and 4-phenyl-1,2,4-triazoline-3,5-dione oxidation of chiral oxazolidinone substituted enecarbamates has shed light on the mechanistic intricacies of the oxidative cleavage of alkenyl double bonds.[282]

Quantitative information on the antioxidant actions of allicin (by radical scavenging through one-step allylic hydrogen transfer) against the oxidation of cumene and methyl linoleate (ML) initiated with 2,2′-azobis(isobutyronitrile) in chlorobenzene has been obtained.[283]

^{13}C kinetic isotope effects (KIEs) of four cinnamyl alcohol oxidations have been determined by ^{13}C NMR spectroscopy using competition reactions with reactants at natural ^{13}C abundance. Primary ^{13}C KIEs of the Pd(II)-catalysed oxidation and of the MnO_2 oxidation are similar ($\sim$1.02) and indicate the C$-$H bond cleavages to be the irreversible and rate-limiting steps in the respective reactions. Low primary ^{13}C KIEs in Swern and Dess–Martin oxidations, however, indicate that the initial C$-$H bond breakings and proton transfers are not the irreversible steps in these mechanisms, which control the rate.[284]

The increase in the rate of oxidation of methanol with supercritical water concentration at 500 °C has been attributed to the increase in the concentration of OH radicals in a quasi-stationary-state.[285]

The outermost surface compositions and chemical nature of active surface sites present on orthorhombic Mo–V–O and Mo–V–Te–Nb–O phases have been determined using methanol and allyl alcohol as probes. It is suggested that the vastly different catalytic behaviours shown by Mo–V–O and Mo–V–Te–Nb–O phases are due to different surface locations of V^{5+} ions.[286]

A theoretical analysis of methanethiol $+^{\bullet}OH$ reaction at the QCISD(T)/6–311+G (2df,2pd)//UMP2/6.311+G(d,p) level indicated that the oxidation proceeds mainly by a direct hydrogen atom transfer. The cysteine $+^{\bullet}OH$ system presented slight variations in major parameters from those of methanethiol. The calculated rate constants, in aqueous solution, are found to be in good agreement with the experimental rate

constants. The calculations indicated that the thiol oxidation is not very sensitive to hydrogen bonding and local electrical polarity.[287]

Oxidation of guanine and 8-oxo-7,8-dihydroguanine with a Mn(IV)=O species, a two-electron oxidant and riboflavin, a known photosensitizer and a one-electron oxidant, was studied. A quantification of the ratio between one- and two-electron oxidation mechanisms of guanine oxidation by electron transfer led to the conclusion that one-electron oxidation predominates and the two-electron oxidation process is a minor pathway.[288]

The major characteristics of excitable media, such as oscillating chemical reactions, and some important concepts necessary for understanding their behaviour have been discussed. The capacity of Belousov–Zhabotinsky (BZ) reactions for spontaneous spatiotemporal auto-organization is described.[289]

The complete metabolic fate of *N*-benzyl-*N*-cyclopropylamine (BCP) and *N*-benzyl-*N*-(1′-methylcyclopropyl)amine with P450 *in vitro* has been determined. 3-Hydroxypropionaldehyde (3HP) was obtained in 57% yield, along with cyclopropanone hydrate (34%), cyclopropylamine (9%), benzaldehyde (6%), benzyl alcohol (12%), and benzaldoxime (19%). *N*-Benzyl-*N*-cyclopropyl-*N*-methylamine was found not to inactivate P450 and not to give rise to 3HP as a metabolite without first undergoing oxidative *N*-demethylation to BCP. These observations argue against a role for single electron transfer mechanisms in the P450 oxidation of cyclopropylamines. It has been suggested that a conventional hydrogen abstraction–hydroxyl recombination mechanism at C–H bonds leads to non-rearranged carbinolamine intermediates and thereby to *N*-dealkylation products including cyclopropanone hydrate.[290] A plausible mechanism for Baeyer–Villiger biotransformations of prochiral bicycloketones promoted by cycloalkanone monooxygenase has been established by means of high-level DFT/B3LYP calculations.[291]

Kinetic isotope effects for C–H hydroxylation of *N*,*N*-dimethylaniline by cytochrome P450 enzymes indicate that a low-spin mechanism applies.[292]

The oxidation of Michler's hydride with 2,3,5,6-tetrabromo-*p*-benzoquinone follows a second-order rate law. It involves a stepwise electron–proton–electron transfer through a charge-transfer complex. The formation of the charge-transfer complex was observed experimentally at low temperature.[293] A stereoselective approach to the precursor of (+)-myriocin, 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-methoxycarbonylamino-α-D-glucofuranose 3-*C*-carboxylic acid, via the [3,3]-sigmatropic rearrangement of allylic thiocyanates prepared from D-glucose, has been reported.[294] It has been found that whether hydrogen transfer from NADH analogues to triplet excited states of 3,6-disubstituted tetrazines (R_2Tz^*) proceeds via a one-step process or sequential electron and proton transfer processes depends on a subtle difference in the electron donor ability and the deprotonation reactivity of the radical cations of NADH analogues and also the electron-acceptor ability of R_2Tz^*.[295]

Two tandem alkene metathesis–oxidation procedures using Grubb's second-generation ruthenium catalyst resulted in unique functional group transformations. Use of sodium periodate and cerium(III) chloride, in acetonitrile–water, furnished *cis*-diols. Oxidation with Oxone, in the presence of sodium hydrogencarbonate, yielded α-hydroxy ketones.[296] Secondary alcohols are oxidized to ketones by a hydrogen

transfer process with dodec-1-ene acting as a hydrogen acceptor and a ruthenium complex as a catalyst.[297]

Reduction by Complex Metal Hydrides

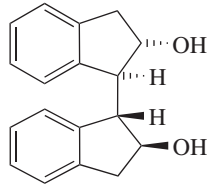
A review describing the major advances in the field of asymmetric reduction of achiral ketones using borohydrides, exemplified by oxazaborolidines and β-chlorodiisopinocamphenylborane, has appeared. Use of sodium borohydride in combination with chiral Lewis acids has been discussed.[298] The usefulness of sodium triacetoxyborohydride in the reductive amination of aldehydes and ketones has been reviewed. The wide scope of the reagent, its diverse and numerous applications, and high tolerance for many functional groups have been discussed.[299] The preparation, properties, and synthetic application of lithium aminoborohydrides (LABs) have been reviewed. The role of LABs, a new class of solid, selective, and air-stable reducing reagents, in the reduction of various organic functional groups is mentioned. Tandem amination–reduction reactions of LAB reagents, which are believed to occur via an S_NAr mechanism, are discussed.[300] (ee)

Hyperforin is not reduced by sodium borohydride. Reduction with hydride-transfer reagents such as lithium aluminium hydride (LAH), RED-AL, and DIBAL-H, gave varied products in good yields. Its two dicarbonyl systems are amenable to reduction or deoxygenation upon treatment with alane reducing agents and pave the way to new and interesting modifications of the natural product.[301]

A series of new chiral lithium aluminum hydrides (BIFAl-Hs) based on biphenyl-2,2′-bisfenchol and various alkyl alcohols has been synthesized and used to reduce aryl alkyl ketones with up to 62% *ee*. The observed enantioselectivities are explained on the basis of computational transition structure analyses. In addition to their application as hydride transfer reagents, the BIFAl-H species are promising chiral Lewis acids.[302] (ee)

S_N2' reduction of the allylic phosphonium salts of cyclic compounds with LAH resulted in the creation of a stereogenic tertiary carbon centre with high selectivity. This protocol has been applied to the formation of *trans*-isomer at the C(3)–C(8) position of the taxol C-ring.[303] The reduction of 2,2,4,4-tetrachloro-8-oxabicyclo[3.2.1]oct-6-en-3-one with LAH yielded the *exo*-alcohol as the dominant product. This is in contrast to most halo-substituted oxabicyclic ketones, which give predominantly the corresponding *endo*-alcohols.[304] (de)

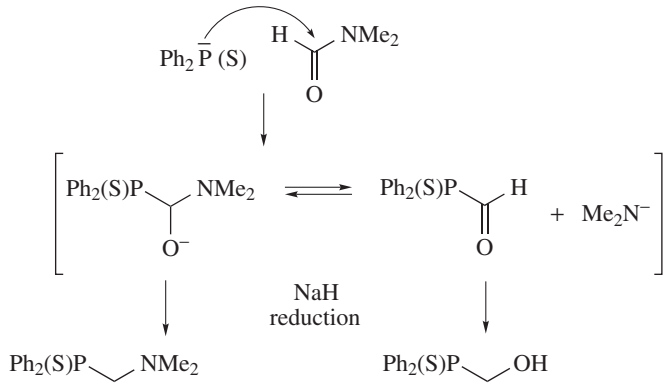
Chiral diol (**9**) and an α-amino alcohol mediated reduction of prochiral ketones with LAH gives alcohols in almost quantitative yields and up to 98% *ee*.[305] (ee)



(**9**)

Enantiopure *N*-*p*-toluenesulfinyl ketimines derived from 2-pyridyl ketones bearing an additional substituent on the 6-position of the pyridine ring are reduced, with DIBAL, to *N*-*p*-toluenesulfinylamines with high yields and diastereoselectivities. (*de*) The reduction of optically active 1-substituted *N*-toluenesulfinyl-1-(6-bromopyridin-2-yl)methylamine in a number of more complex pyridine derivatives with maintenance of the toluenesulfinyl group *N*-protecting group is also reported.[306] Deuterium-labeled experiments indicated that the reduction of secondary alkyl bromides with diisobutylaluminium hydride and ethylmagnesium chloride, catalysed by palladium complexes of chelating diphosphine, does not take place via halogen–metal exchange.[307]

The coupling reaction of diphenylphosphine sulfide with *N*,*N*-disubstituted formamides in the presence of an excess of sodium hydride resulted in the corresponding aminomethyldiphenylphosphine sulfides in good yields. It is suggested that the carbon–oxygen bond is cleaved by sodium hydride (Scheme 12).[308]



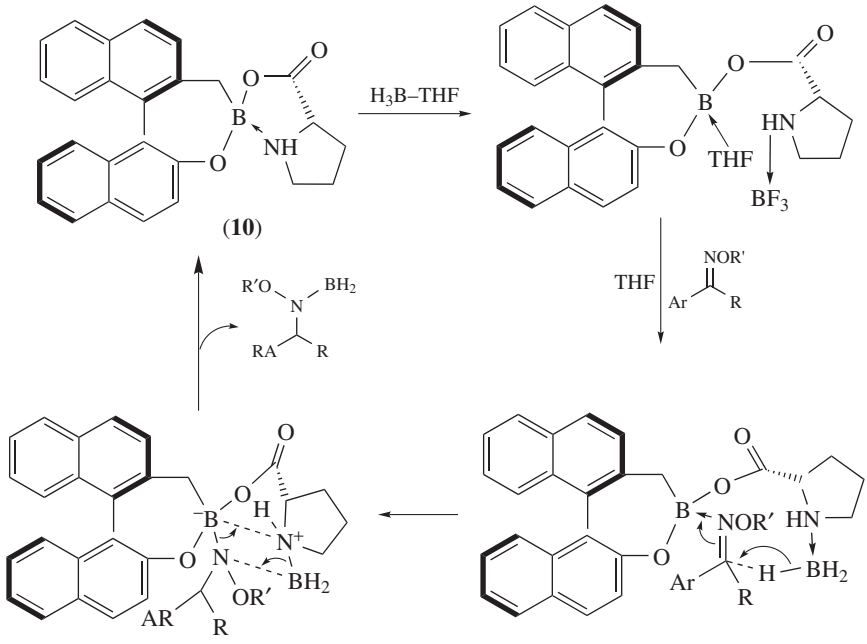
SCHEME 12

Regioselective reductive openings of mixed phenolic–benzylic cyclic acetals, using BH_3–NMe_3–$AlCl_3$, under mild conditions to yield a benzylic ether and free the phenol group have been attributed to association of boron with the more basic oxygen (benzylic) followed by reaction with aluminium chloride.[309]

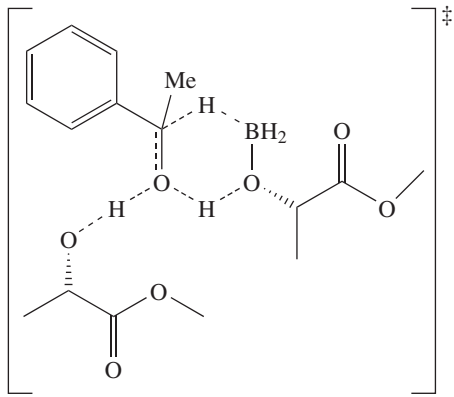
Enantioselective reduction of oxime ethers promoted by chiral spiroborate esters (*ee*) (**10**) with an O_3BN framework is reported. In the presence of (*R*,*S*)-**10**, aralkyloxime ethers are reduced by borane–THF at give (*S*)-1-aralkylamine in high yield and excellent enatiomeric excess (up to 98% *ee*). A possible mechanism (Scheme 13) of the catalytic reduction is suggested.[310]

The hydroboration of acetophenone in the chiral solvent (*S*)-methyl lactate exhibits moderate enantioselectivities. A six-membered transition state (**11**) involving the (*ee*) ketone, the borane, and the lactate as the only chiral source is proposed. Molecular modeling explains the experimentally observed enantioselectivities.[311]

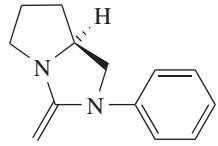
A guanidine derivative (**12**)[312] and (2*S*)-2-anilinomethylpyrrolidine (**13**)[313] have been synthesized and successfully employed as chiral catalytic sources for the



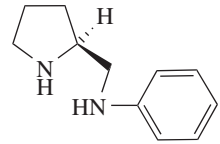
SCHEME 13



(**11**)



(**12**)



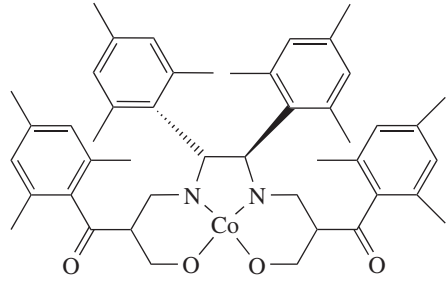
(**13**)

borane-mediated asymmetric reduction of prochiral ketones to provide the corresponding secondary alcohols in high enantiomeric purity. (*ee*)

Reaction of achiral and chiral bis(oxazolines) (BOX) with catecholborane (CATBH) provides boron–BOXate complexes that can be used as catalysts in the enantioselective reduction of ketones. It has been shown that asymmetric transfer of the hydride ion from the boron atom of CATBH to the prochiral carbonyl is the rate-determining step of the catalytic reaction.[314] (*ee*)

A highly enantioselective reduction of α,β-unsaturated nitriles has been conducted by using a $Cu(OAc)_2$–josiphos complex as the catalyst under hydrosilylation conditions. This reaction provides access to valuable β-aryl-substituted chiral nitriles in good yields and with excellent enantioselectivities by employing a stable catalytic precursor and a readily available commercial bisphosphine ligand. The active reducing species is believed to be copper(I) hydride.[315] (*ee*)

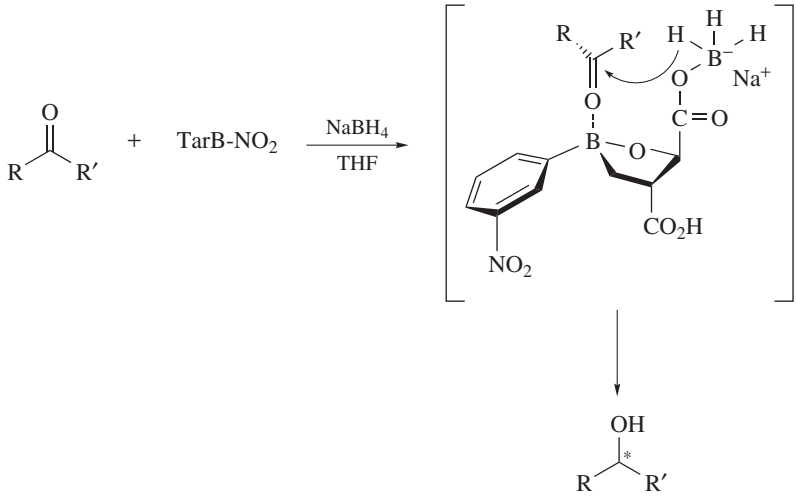
Various benzophenones and aryl alkyl ketones substituted with a fluorine atom on the *ortho* position were effectively converted into the corresponding alcohols with high to excellent enantioselectivities in the presence of the optically active ketoiminatocobalt(II) complexes (**14**). The combination of *o*-F substituent and a modified lithium borohydride reagent contributed to the high yield and high enantioselectivity (88–96% *ee*).[316] (*ee*)



(**14**)

Mechanisms of sodium borohydride reactions with primary, secondary, and tertiary amides have been investigated both at the B3LYP/6–31++G(d,p)//B3LYP/6–31G(d,p) and B3LYP/6–31++G(d,p)//HF/6–31G(d,p) levels of theory. The predicted structures of the key intermediates were then confirmed by experiment.[317] For chemoselective reductions of α-substituted and aromatic esters with sodium borohydride, agreement between experimental results and theoretical computations at the B3LYP/6–31++G(d,p)//HF/6–31G(d,p) levels of theory have been reported.[318]

High enantioselectivities (up to 94%) are obtained in the sodium borohydride reduction of aliphatic ketones using a tartaric acid-derived boronic ester (TarB–NO_2) as a chiral catalyst. A mechanism (Scheme 14) involving an acyloxyborohydride intermediate has been postulated.[319] (ee)



SCHEME 14

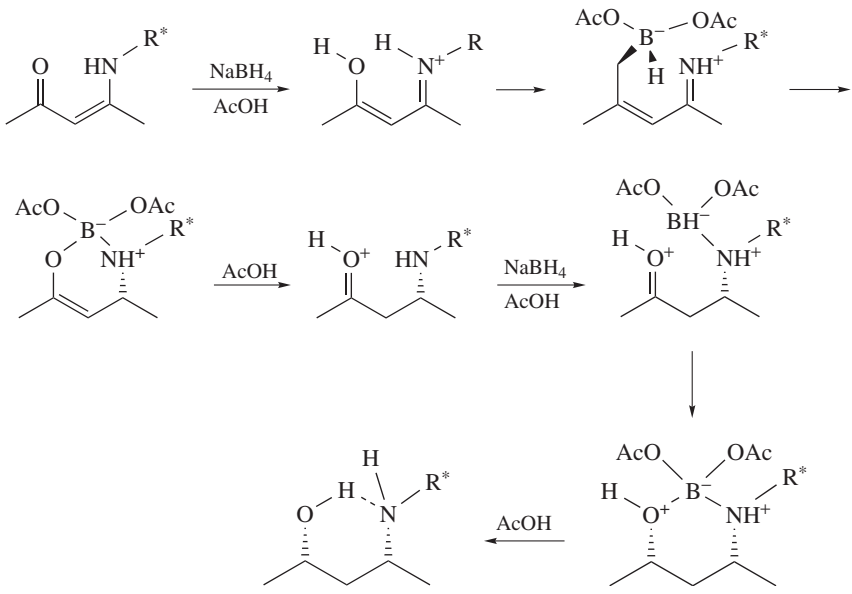
An efficient reduction of alkenes with sodium borohydrde as the reducing agent using 0.5–1.0 mol% $Ru(PPh_3)_4H_2$ as catalyst, in the presence of water, has been reported. The ruthenium complex probably catalyses both the formation of hydrogen from borohydride–water and the subsequent reduction process.[320] (ee)

Reduction of chiral β-enamino ketones with sodium borohydride in acetic acid is convenient, stereoselective, and high yielding and allowed the preparation of enantiopure γ-amino alcohols with *syn* diastereoselectivity. A mechanistic hypothesis (Scheme 15) has been presented.[321] (de)

Substituted 2-azetidinones are reduced with sodium borohydride in aqueous isopropanol giving 3-aminopropan-1,2-diols. The degree of conversion depends on the substitution pattern in the 3- and 4-positions of the 2-azetidinone ring and shows good correlation with carbonyl LUMO energies of starting material.[322]

A variety of *N*-*t*-butanesulfinylimines are reduced with sodium borohydride in THF containing 2% water to the corresponding secondary sulfinamides in high yield and diastereoselectivity. By changing the reductant to L-Selectride, the stereoselectivity is reversed to afford the opposite product diastereomer in high yield and selectivity. It appears that the sulfinyl oxygen atom plays a key role in the delivery of borohydride reagents to give products derived from a closed transition state, whereas L-Selectride reductions proceed via an open transition state.[323] (de)

Nickel boride, generated *in situ* from nickel chloride and sodium borohydride, is an efficient reagent for debromination of *vic*-dibromides to the corresponding (*E*)-alkenes



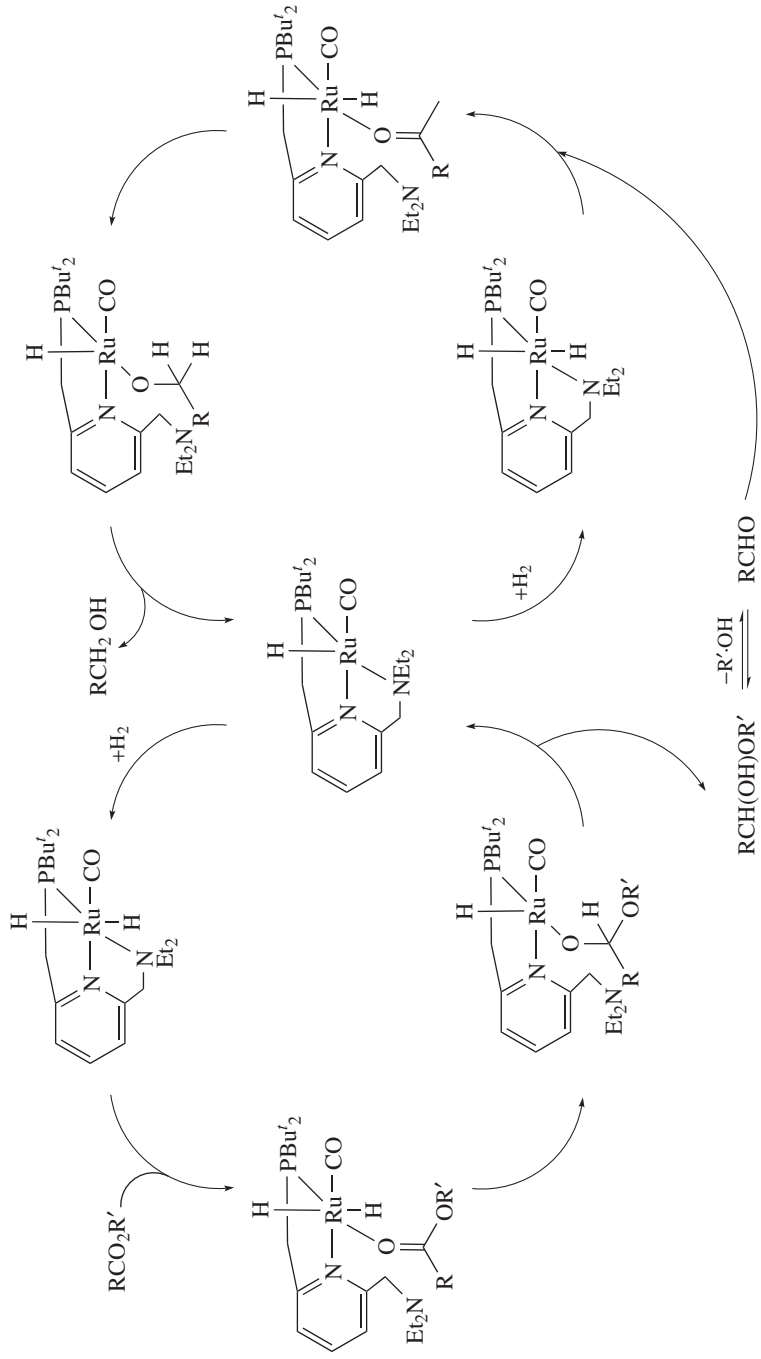
SCHEME 15

and for debromination with concomitant reduction to give dihydro products. Chalcone dibromides and other α,β-dibromo ketones undergo debromination with complete reduction to give alcohols or undergo debromination with selective reduction to give dihydrochalcones.[324]

With sodium borohydride and catalytic amounts of titanyl acetoacetonate, α,β-unsaturated carbonyl compounds give allyl alcohols regioselectively, whereas α-diketones and acyloins are reduced to vicinal diols.[325] Enantioselectivities in the (ee) reduction of acetophenone, catalysed by 1,3,2-oxazaborolidones, have been examined using the AM1-SCF MO method. The optimized geometries, thermal enthalpies, and entropies of *R* and *S* transition states in the stereo-controlling steps of the reduction have been obtained.[326]

Reaction of [2,3,4,5-$Ph_4(\eta^5$-$C_4COH)Ru(CO)_2H$] (HCPRH) with different imines afforded ruthenium–amine complexes at low temperatures. At higher temperatures in the presence of HCPRH, the complexes decomposed to give free amine. Electron-rich imines gave ruthenium–amine complexes with HCPRH at a lower temperature than did electron-deficient imines. The negligible deuterium isotope effect (k_{RuHOH}/k_{RuDOD} = 1.05) observed in the reaction of HCPRH with *N*-phenyl[1-(4-methoxyphenyl)ethylidene]amine shows that neither hydride (RuH) nor proton (OH) is transferred to the imine in the rate-determining step. These results are explained on the basis of an inner-sphere mechanism in which the substrate coordinates to ruthenium prior to hydrogen transfer.[327]

Non-activated aromatic and aliphatic esters have beeen efficiently hydrogenated to the corresponding alcohols under relatively mild, neutral conditions using a [2-(di-*t*-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine]–ruthenium hydride complex



SCHEME 16

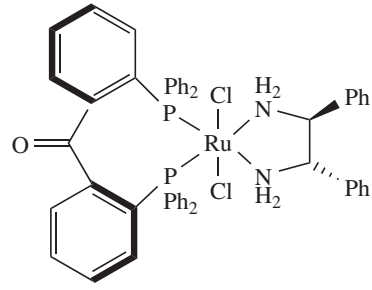
as catalyst. This reaction involves an unusual aromatization–dearomatization sequence (Scheme 16).[328]

The stereochemistry of hydrogen transfer from [2,5-Ph_2-3,4-Tol_2(η^5-C_4COD)]Ru$(CO)_2$D to *N*-arylimines to give amine complexes was shown to be mostly *trans* stereospecific. Stereospecific hydrogen transfer is proposed to generate an amine and a coordinatively unsaturated ruthenium intermediate in close proximity. Coordination of the amine is proposed to occur faster than lone pair inversion of the amine. In contrast, hydrogen transfer to *N*-alkylimines is stereorandom. It is proposed that stereochemistry is lost in part due to the reversibility of the hydrogen transfer being faster than amine coordination.[329]

Hydrogenation

A review of asymmetric hydrogenation of ketones with rhodium complexes as catalysts has been presented.[330] A review of the developments in the asymmetric hydrogenation (ee) of ketones with ruthenium complexes as homogenous catalysts of hydrogenation, with particular emphasis on the work of Halpern, has been presented.[331]

A benzophenone-based ruthenium complex (**15**) afforded high enantioselectivity in the catalytic asymmetric ketone hydrogenation (up to 99% *ee*, >99% yield). It was (ee) found that chirality of benzophenone complexes can be controlled even in the solution phase.[332]

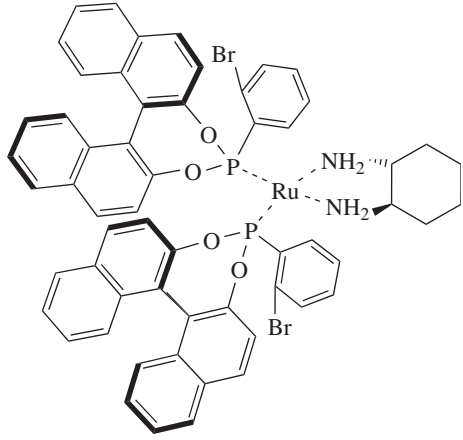


(**15**)

Deuterium labeling experiments, kinetic studies, and rate law analysis have indicated that the (*S*)-BINAP–Ru-catalysed hydrogenation of 2-formyl-1-methylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline proceeds via a monohydride-unsaturated mechanism whereby the two protiums at the α- and β-positions of the enamide substrate are derived from two different hydrogen molecules. The overall rate is limited by the hydrogenolysis step.[333]

Ferrocene-based aminophosphines are shown to be effective ligands in the Ru(II)- (ee) catalysed asymmetric hydrogenation of ketones. The enantioselectivity is mainly determined by the C-centred chirality of the ligands, but the planar chirality is also important, and (R_C,S_{Fc})- or (S_C,R_{Fc})- is the matched combination of chiralities.[334] Dimethyl oxalate is selectively hydrogenated to methyl glycolate with Ru(acac)$_3$,

Zn, and [$MeC(CH_2SBu)_3$] as the catalyst system.[335] Highly enantioselective (up to 93% *ee*) hydrogenation of an α-alkoxy ketone has been achieved using (phosphinoferrocenyl)oxazoline–ruthenium catalysts. Choice of appropriate solvent and base is essential for the success of this reaction.[336] A new ruthenium catalyst (**16**) containing *trans*-1,2-diaminocyclohexane provided improvements in enantioselectivity to asymmetric ketone hydrogenation reactions using Ru–diamine catalysts. Substrates containing halogenated aryl rings are particularly compatible with this catalyst. However, α-chlorinated ketones remain resistant to reduction under any conditions.[337]



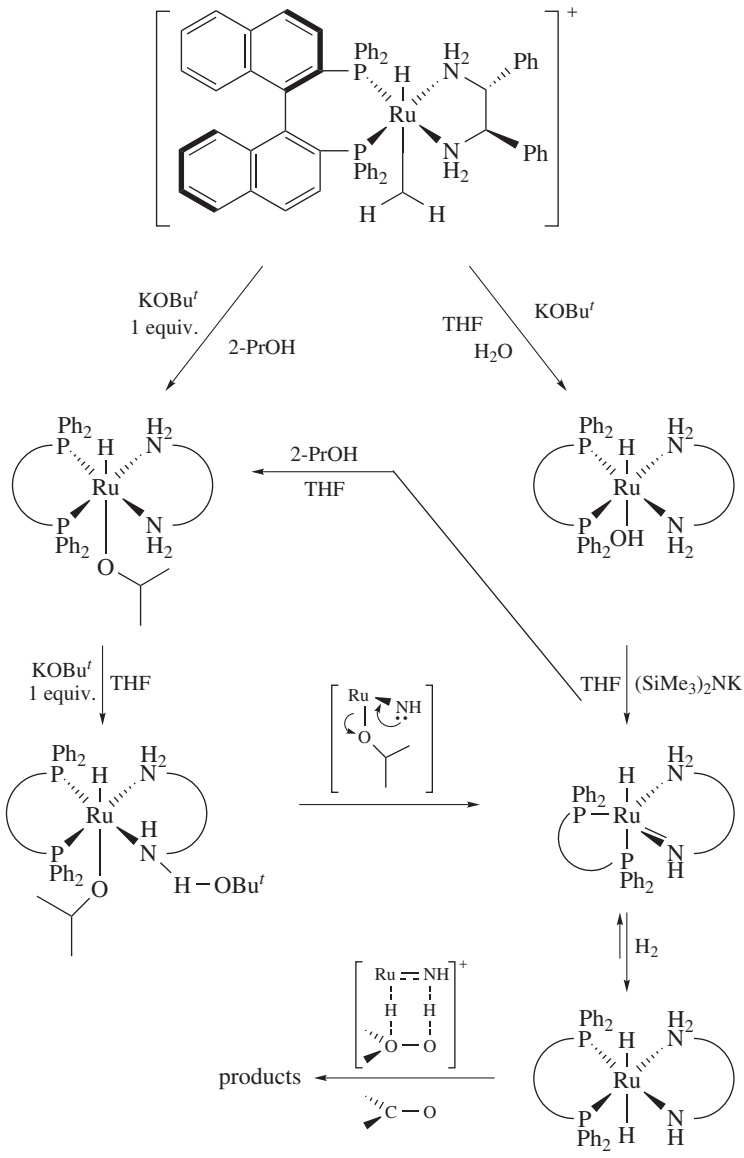
(**16**)

The role of base in the Noyori's asymmetric hydrogenation of ketone catalysed by *trans*-Ru(diphosphine)Cl_2(diamine) has been evaluated. Several catalytic intermediates have been characterized and a mechanism (Scheme 17) has been presented.[338]

Deuterium labeling studies have shown that ruthenium–bis(phosphine)-catalysed enantioselective hydrogenation of α,β-unsaturated acids and esters follows two distinct mechanisms. In each case, a five-membered metallocycle intermediate is formed via alkene–hydride insertion. Hydrogenation of α,β-unsaturated acids proceeds via a heterolytic cleavage of dihydrogen, whereas hydrogenation of α,β-unsaturated esters proceeds via homolytic cleavage of dihydrogen.[339]

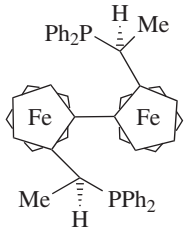
Rh and Ru complexes with electron-rich Tang-Phos and Duan-Phos catalyse a highly enantioselective hydrogenation of *N*-phthaloylenamides. In the hydrogenation of α-arylenamides, up to 99% *ee* has been achieved though a moderate *ee* is obtained in the reduction of α-alkylenamides.[340]

Asymmetric hydrogenation of alkenes is efficiently catalysed by rhodium complexes with chiral diphosphite and diphosphoramidite ligands derived from BINOL or diphenylprolinol. Choice of a proper achiral backbone is crucial.[341] Highly enantioselective hydrogenation of *N*-protected indoles was successfully achieved by use of the rhodium catalyst generated *in situ* from [$Rh(nbd)_2$]SbF_6 (nbd = norborna-2,5-diene)



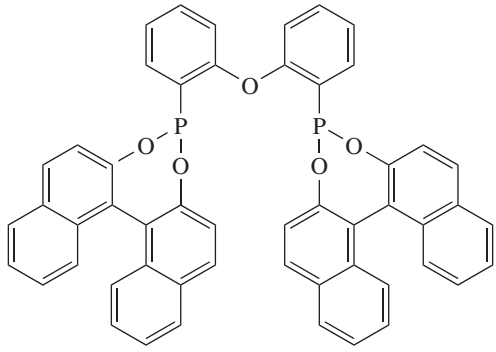
SCHEME 17

and the chiral bisphosphine PhTRAP (**17**). Various 2-substituted *N*-acetylindoles are converted into the corresponding chiral indolines with up to 95% *ee*. The hydrogenations of 3-substituted *N*-tosylindoles yielded indolines possessing a stereogenic centre at the 3-position with high enantiomeric excesses (up to 98% *ee*).[342]



(**17**)

A chiral diphosphonite, derived from BINOL (**18**) and with an achiral diphenyl ether backbone, is an excellent ligand for the iridium-catalysed asymmetric hydrogenation of quinolines. Enantioselectivities ranging from 90 to 94% were obtained.[343] (*ee*)



(**18**)

Mechanistic aspects of the hydrogenation of alkenes catalysed by iridium complexes with a new class of chiral phosphine–oxazoline ligands have been discussed and a selectivity model to help rationalize the results obtained has been presented.[344]

The complex $[IrH_2(\eta^6\text{-}C_6H_6)\ (i\text{-}Pr_3P)]BF_4$ is an effective catalyst for the hydrogenation of *N*-benzylideneaniline under mild conditions by what is postulated to be an outer-sphere, ionic, bifunctional mechanism.[345] Under simple experimental conditions, the dinuclear complex $[Ir_2(\mu\text{-}H)(\mu\text{-}Pz)_2H_3(NCMe)(i\text{-}Pr_3P)_2]$ has been transformed into derivatives such as $[Ir_2(\mu\text{-}H)(\mu\text{-}Pz)_2H_2(L)(NCMe)(i\text{-}Pr_3P)_2]BF_4$ [$L = \eta^2\text{-}H_2$, $NH(Ph)CH_2Ph$] or $[Ir_2(\mu\text{-}H)(\mu\text{-}Pz)_2H_2(OSO_2CF_3)(NCMe)(i\text{-}Pr_3P)_2]$, which are also very efficient catalyst precursors for the hydrogenation of *N*-benzylideneaniline through an ionic mechanism.[346]

The C_2-symmetric diphosphinite and C_1-symmetric phosphinite–phosphate ligands, based on a carbohydrate scaffold, and iridium complexes give catalyst precursors that are active in the hydrogenation of imines. Cationic iridium complexes gave rise to catalytic systems that were more active than the neutral iridium complexes. Enantioselectivities up to 76% were obtained.[347] (*ee*)

Hydrogenation of acyclic aromatic *N*-arylimines, to the corresponding optically active secondary amines with up to 99% *ee*, is catalysed by an iridium(I) complex (*ee*)

of (*S*,*S*)-1,2-bis(*t*-butylmethylphosphino)ethane with tetrakis[3,5-bis(trifluoromethyl) phenyl]borate as the counterion. It has been suggested that the reaction proceeds through a four-membered transition state and the enantioselection is determined at the migratory insertion step.[348] Near quantitative conversion and high *ee* (up to 89%) (*ee*) has been achieved in the asymmetric hydrogenation of methyl α-benzamidocinnamate employing ethylmethylimidazolium trifluoromethanesulfonate as sole reaction solvent using both the achiral and chiral Rh–phosphine catalysts.[349]

The hydrogenation of α,β-epoxy ketones is mediated by a catalytic amount of 1-benzyl-1,4-dihydronicotinamide (BNAH) or BNA^+Br^- to form the corresponding β-hydroxy ketones in high yields. $Na_2S_2O_4$ is used as the reducing agent to convert BNA^+Br^- to BNAH. A radical mechanism has been proposed for this catalytic reaction.[350] Moderate enantioselectivity is obtained in the hydrogenation of aryl alkyl (*ee*) ketones catalysed by $[RuCl_2(p\text{-cymeme})]_2$ and terpene-based β-amino alcohols.[351]

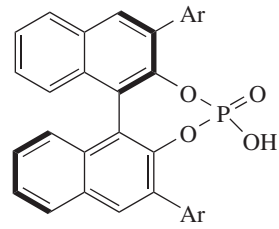
Transfer Hydrogenation

Recent mechanistic studies on transition metal-catalysed hydrogen transfer reactions have been reviewed. Experimental and theoretical studies showed that hydrogen transfer reactions proceed through different pathways. For transition metals, hydridic routes are the most common. Within the hydridic family there are two main groups: the monohydride and dihydride routes. Experimentally, it was found that whereas rhodium and iridium catalysts favour the monohydride route, the mechanism for ruthenium catalysts proceeds by either pathway, depending on the ligands. A direct hydrogen transfer mechanism has been proposed for Meerwein–Ponndorf–Verley (MPV) reductions.[352]

Simulations based on kinetic modelling of the reduction of acetophenone with propan-2-ol, using polymer-enlarged and the unmodified catalysts, revealed that comparable performance cannot be obtained by batch operation. Polymer enlargement allowed a continuous operation of transfer hydrogenation in a chemical membrane reactor.[353]

High yields and enantiopurity have been realized by a highly diastereoselective MPV reduction of protected α-amino aromatic ketones using catalytic amounts of aluminium isopropoxide. The high *anti* selectivity resulted from the chelation of the (*de*) nitrogen anion to the aluminium. In contrast, high *syn* selectivity was obtained with α-alkoxy ketones and other compounds via Felkin–Ahn control.[354]

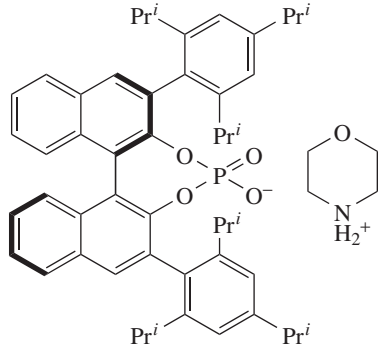
A chiral Brønsted acid (**19**) catalyst system has been developed that induces cascade transfer hydrogenation to provide a direct access to a variety of 2-aryl- and



(**19**)

2-alkyl-substituted tetrahydroquinolines with excellent enantioselectivities and good (*ee*) yields.[355] The acid (**19**) is a highly efficient catalyst for transfer hydrogenation of various aryl-substituted benzoxazines, benzothiazines, and benzoxazinones. This method provides the corresponding dihydro-2*H*-benzoxazine and dihydro-2*H*-benzothiazines (*ee*) in good yields and with excellent enantioselectivities (93–99% *ee*). This methodology has been extended to the enantioselective synthesis of cyclic and linear aryl and heteroaryl glycine derivatives.[356]

A new catalyst salt (**20**) that consists of an achiral ammonium ion and a chiral phosphate anion and which catalyses highly enantioselective transfer hydrogenations of α,β-unsaturated aldehydes to the corresponding saturated derivatives has been developed. The underlying principle, namely asymmetric counteranion-directed catalysis, is claimed to be a new strategy for highly enantioselective synthesis.[357] (*ee*)



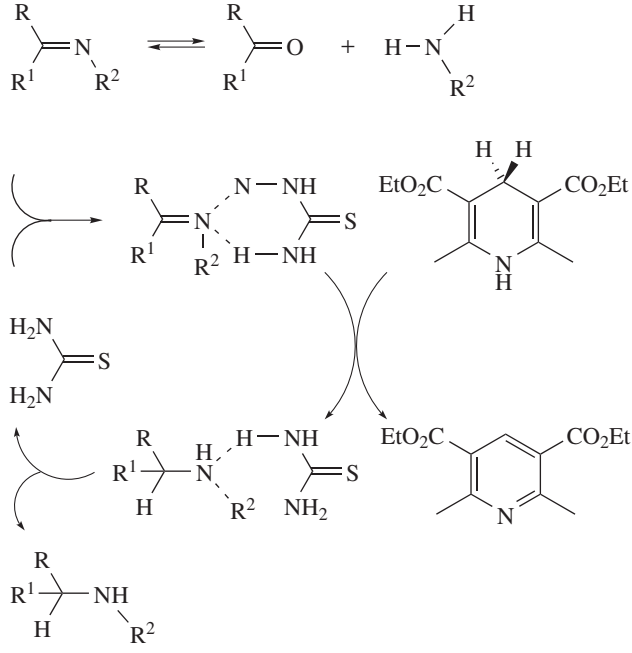
(**20**)

A mild, acid- and metal-free direct reductive amination of ketones has been achieved that relies on selective imine activation by hydrogen bond formation and utilizes the Hantzsch ester for transfer hydrogenation and catalytic amounts of thiourea as hydrogen bond donor. The mechanism in Scheme 18, supported by *ab initio* calculations, has been suggested.[358]

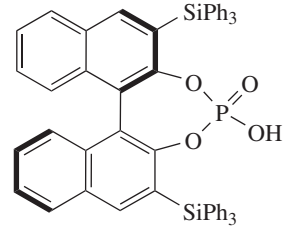
An enantioselective organocatalytic reductive amination has been achieved using (*ee*) Hantzsch ester for hydrogen transfer and compound (**21**) as catalyst. This mild and operationally simple fragment coupling has been accomplished with a wide range of ketones in combination with aryl and heterocyclic amines.[359]

A new, metal-free protocol involving (heteroaryl)oxazoline catalysts for the enantioselective reduction of aromatic ketones (up to 94% *ee*) and ketimines (up to 87% (*ee*) *ee*) with trichlorosilane has been developed. The reaction is characterized by an unusual, long-ranging chiral induction.The enantiodifferentiation is presumed to be aided by aromatic interactions between the catalyst and the substrate.[360] Asymmetric reduction of *N*-arylketimines with trichlorosilane is catalysed by *N*-methyl-L-amino acid-derived Lewis-basic organocatalysts with high enantioselectivity (up to 92% (*ee*) *ee*).[361]

β,β-Disubstituted α,β-unsaturated ketones and esters are reduced with alkoxylhydrosilanes in the presence of chiral rhodium(2,6-bisoxazolinylphenyl) complexes to



SCHEME 18

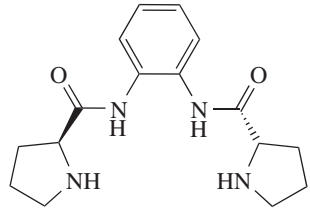


(**21**)

give the corresponding ketones in high yields and high enantioselectivity (up to 98% *ee*). $(EtO)_2MeSiH$ was proved to be the best hydrogen donor.[362]

Reduction of C(5)-substituted 2-hydroxychromans selectively provides 2,4-*cis*-chromans using large silane R_3SiH reductants and 2,4-*trans*-chromans using the smaller silane $PhSiH_3$. The stereochemical outcome has been rationalized on the basis of a Curtin–Hammett kinetic situation arising from hydride delivery to two different conformations of an intermediate oxocarbenium ion.[363]

Pentacoordinate chiral hydrosilanes were generated *in situ* from triethoxysilane and a C_2-symmetric ligand derived from bisproline (**22**). In the presence of a catalytic amount of the ligand, prochiral ketones were reduced in moderate yield with moderate enantioselectivity (up to 64% *ee*). Use of titanium tetrafluoride, a Lewis acid, along with complexes of (**22**) led to higher enantioselectivity and improved yields.[364]



(**22**)

L-Pipecolinic acid-derived formamides have been developed as highly efficient and enantioselective Lewis basic organo-catalysts for the reduction of *N*-arylimines with trichlorosilane. High isolated yields and enantioselectivities up to 96% are obtained under mild conditions with a large substrate spectrum.[365] (*ee*)

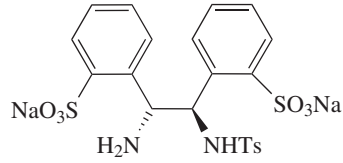
A one-pot reaction has been developed for the reduction of aldehydes, ketones, and primary, secondary and tertiary alcohols into their corresponding alkyl function using either diethylsilane or *n*-butylsilane as the reducing agent in the presence of the Lewis acid catalyst tris(pentafluorophenyl)borane; carbon–carbon double bonds remain unaffected.[366] Aliphatic and aromatic polycarboxylic acids are also conveniently reduced to their corresponding alkanes using the same reagents and catalyst.[367]

Reductions of allylic carbonates, catalysed by $Pd(OAc)_2$–[(n-Bu_3PH)BF_4], with formic acid–triethylamine show excellent diastereoselectivities. Selection of a proper protecting group, the stereochemistry of the aldol adduct, neighbouring substituents, and the alkene geometry can result in formation of three of the four possible diastereomeric triads, namely *syn–syn, anti–syn*, and *anti–anti*.[368] Asymmetric reductions of various classes of fluoroalkyl ketones were achieved under transfer hydrogenation conditions. Chiral α-trifluoromethyl alcohols and their perfluoroalkyl higher homologues were prepared in excellent optical (up to 100% *ee*) and chemical yields (85–100%) through ketone reduction catalysed by Ru(II)–R_2NSO_2DPEN (0.05–0.5 mol%) complexes using formic acid–triethylamine in DMF. Possible transition states for the reaction have been suggested.[369] (*de*) (*ee*)

The role of alkali metal cations in the [{$RuCl_2$(*p*-cymene)}$_2$]-pseudo-dipeptide-catalysed enantioselective transfer hydrogenation of ketones with propan-2-ol has been examined. Lithium salts were shown to increase the enantioselectivity of the reaction when 2-PrONa or 2-PrOK was used as the base. An alternative reaction mechanism for the pseudo-dipeptide-based systems, in which the alkali metal cation is an important player in the ligand-assisted hydrogen-transfer step, has been proposed.[370] (*ee*)

Asymmetric transfer hydrogenation of cyclic imines and iminiums in water was carried out in high yields and enantioselectivities with sodium formate as the hydrogen source and CTAB as an additive, catalysed by a water-soluble and recyclable ruthenium(II) complex of the ligand (**23**).[371] (*ee*)

A class of simple, modular, and highly efficient α-amino acid amides ligands for Ru- and Rh-catalysed asymmetric transfer hydrogenation of aromatic ketones in propan-2-ol has been developed. A remarkable feature with these ligands is the switch of product enantioselectivity observed when the amide functionality is replaced by the corresponding thioamide. The results obtained have significant mechanistic implications (*ee*)



(**23**)

because they pinpoint the structural features which are essential for high catalytic activity and selectivity. Transition states for the reactions have been proposed.[372]

Anomalous concentration dependence observed in the asymmetric transfer hydrogenation of imines with formic acid, catalysed by chiral rhodium–diamine complexes, has been attributed to the participation of both reactant and product in the formation of formate salt. The probable resting state of the catalyst is a rhodium hydride species.[373] (ee)

An Rh(III)–tetramethylcyclopentadienyl complex containing a tethered functionality is found to give excellent results in the asymmetric transfer hydrogenation of ketones in both aqueous, using sodium formate, and formic acid–triethylamine media. Quantitative yields and almost 100% *ee*s are obtained.[374] (ee)

α,β-Unsaturated acids and esters are reduced to the corresponding saturated acid derivatives by hydrogen transfer with formic acid in the presence of Rh(I) complexes with chiral ligand Ph-binepines, an axially chiral binaphthalene-type monodentate *P*-donor ligand. Up to 97% *ee*s were obtained.[375] (ee)

Iridium–monotosylated ethylenediamine [Ts(en)] and Ir–CF_3Ts(en) are highly active and chemoselective catalysts for the aqueous-phase transfer hydrogenation of aldehydes using sodium formate as the hydrogen donor.[376]

Other Reductions

Reductive epoxide opening through single electron transfer has been reviewed. A number of electron-transfer reagents have been compared and a detailed report about titanocene complexes is included. The mechanism of the ring opening, established by cyclic voltammetry, kinetic measurements, DFT calculations, and synthetic studies, has been reported.[377] The fundamental principles of catalytic asymmetric reactions have been reviewed. Various reactions including catalytic hydrogenation of alkenes, ketones, and imines, dihydroxylation and epoxidation, Diels–Alder reactions, and catalytic C−C bond formation have been discussed. Typical catalytic phenomena such as dynamic kinetic resolution, ligand-accelerated catalysis, non-linear effects, and asymmetric autocatalysis are considered.[378] (ee)

Investigation of the mechanism of nitrate reduction by *Desulfovibrio desulfuricans* nitrate reductase at various levels of theory has confirmed the utility of the orbital-free embedding method in the description of enzymatic processes.[379]

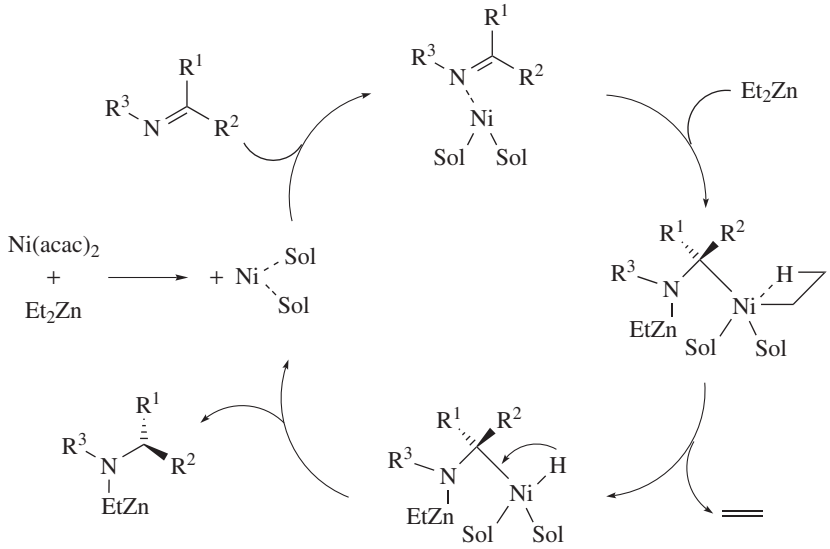
^{13}C Kinetic isotope effects (KIEs) of a xylose reductase-catalysed cinnamaldehyde reduction have been determined by ^{13}C NMR using competition reactions with reactants at natural ^{13}C abundance. The primary KIEs indicated that the chemical reaction steps are only partly rate limiting during reduction of aromatic aldehydes and slow steps occur outside the catalytic sequence. The aldo–keto reductase-catalysed

reductions depend on a hydride transfer from NADH to the carbonyl group, which is not, however, the main step controlling the transformation rate.[284]

Reduction of activated carbonyl groups of α-keto esters, benzils, cyclohexane-1,2-dione, and α-ketophosphonates by alkylphosphines afforded the corresponding α-hydroxy esters or ketones in good to excellent yields. A mechanism has been suggested on the basis of deuterium and ^{18}O labelling experiments.[380]

Reduction of multiple bonds with samarium diiodide has been reviewed. Chemo- and stereo-selective reduction of various compounds such as conjugated alkenes, α,β-unsaturated carboxylic acids, activated alkynes, carbonyl, azides, nitriles, and nitro compounds, under mild conditions, has been discussed. Recent developments in the use of samarium metal in this field have also been discussed.[381]

Electron-deficient imines are reduced with diethylzinc in the presence of $Ni(acac)_2$ with up to 92% yield and moderate to excellent *de*. A plausible mechanism (Scheme 19) has been proposed on the basis of an NMR study.[382]

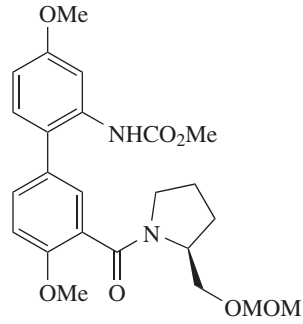


SCHEME 19

Azoarenes are smoothly reduced to hydrazoarenes in excellent yields using tin and hydrazine hydrate. Formation of anilines is not involved.[383] The rate of hydride transfer from 1-(*p*-substituted benzyl)-1,4-dihydronicotinamide (G-BNAH) to *N*-benzylphenothiazine radical cation ($PTZ^{\bullet+}$) decreases as the reaction temperature is increased. It has been attributed to G-BNAH and $PTZ^{\bullet+}$ forming a charge-transfer (CT) complex prior to the hydride transfer and the absolute value of the formation enthalpy for the CT complex being larger than the activation enthalpy of the CT complex. The Hammett reaction constant for the reaction is negative ($\rho = -0.436$). It has been suggested that the reaction of G-BNAH with $PTZ^{\bullet+}$ is initiated by a concerted hydride transfer via a CT complex.[384]

The regioselective debromination of substituted pentabromobenzenes with *t*-BuONa–*t*-BuOH–DMSO is proposed to follow a halophilic mechanism via carbanions.[385]

Birch reductive alkylation of benzamide (**24**) was optimized to give the corresponding cyclohexa-1,4-diene products in 66–78% isolated yield and with high diastereoselectivity.[386] (de)



(**24**)

It has been shown that the reductive ring opening of suitably constituted monocyclic alkylidenecyclopropyl ketones with lithium in liquid ammonia proceeds via distal cleavage and hence offers a novel regio- and stereo-selective route to thermodynamic enolates. Further, stereoelectronic factors dominate the ring opening in a fused bicyclic system, and the degree of regioselectivity is less than in the case of their cyclopropyl congeners.[387]

Reduction of perfluoroalkyl ketones with chiral lithium alkoxides gave chiral α-perfluoroalkyl alcohols in high enantiomeric excesses. The order of steric effects on this reaction is estimated as C_7F_{15} > substituted phenyl > CF_3.[388] (ee)

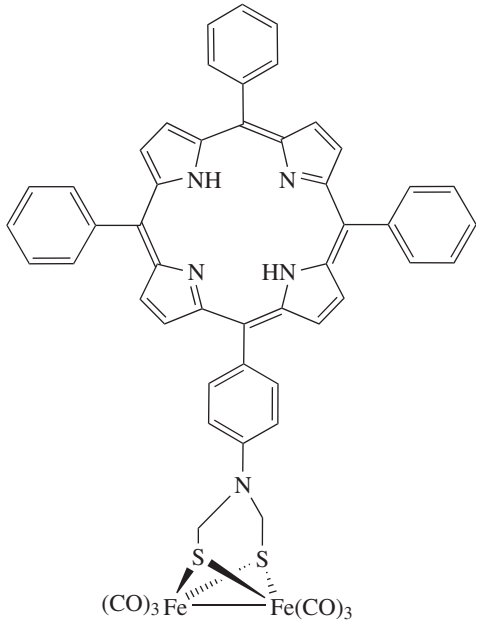
An effective reductive coupling of primary, secondary, and tertiary alkyl bromides and iodides with a wide variety of conjugated alkenes such as acrylates, acrylonitrile, vinyl ketone, and vinyl sulfone in good to excellent yields has been accomplished in the presence of zinc, CoI_2–1,2-bis(diphenylphosphino)ethane complex, and water. The reaction appears to undergo an oxidative addition-driven route rather than a radical route. The reaction is proposed to involve a reduction of Co(II) to Co(I) by zinc followed by the oxidative addition of an alkyl halide to give an alkyl–cobalt(III) intermediate. Subsequent coordination of the conjugated alkene, insertion into the Co–alkyl bond, and protonation give rise to the final reductive coupling product. Co(I) is regenerated by the reduction of Co(III) with zinc powder.[389]

Reduction of diphenylbenzidine with arsenic(III) oxide shows a first-order dependence on hydrogen ions, As(III), and the substrate. The activation parameters have been determined.[390]

Carbonyl compounds and imines are reduced to the corresponding alcohols and amines, respectively, with a mixture of iron(II) chloride tetrahydrate, an excess of lithium powder, and a catalytic amount of 4,4′-di-*t*-butylbiphenyl. α,β-Unsaturated

carbonyl compounds are reduced to the corresponding saturated alcohols. This reducing system exhibited good to excellent diastereoselectivity toward the reduction of different monocyclic and polycyclic ketones.[391]

A light-driven compound containing a photosensitizing tetraphenylporphyrin group linked to a diiron azadithiolate moiety (**25**) has been synthesized as a model compound of iron-only hydrogenases. This compound reduces protons photochemically to hydrogen.[392]



(**25**)

A comprehensive picture at the molecular level has been developed for the titanocene-mediated epoxide ring opening through electron transfer. The investigations, carried out by experimental and computational techniques, have shown that the most reactive Ti(II) species is the dimer in its half-open structure and that the selectivity of the ring opening is governed by steric effects.[393]

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CHAPTER 4

Carbenes and Nitrenes

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Reviews

Diazirines are popular precursors for the formation of carbenes and a review of their synthesis and use has addressed the Graham reaction, the diazirine exchange reaction, and radical-initiated exchange in addition to mechanistic details of the diazirine exchange.[1]

Three Nobel Prize lectures have featured the metathesis reaction in detail, focusing on early results and development from a mechanistic point of view,[2] the development of catalytic metathesis reactions,[3] and the use of metathesis in the preparation of target molecules.[4]

Recent editions of *Organic Reaction Mechanisms* have highlighted a number of carbene and nitrene CH-insertion reactions. This field has now been reviewed with a focus on enantioselective reactions catalysed typically by dirhodium species.[5] The (ee) use of C_2-symmetric 'box' ligands in asymmetric cyclopropanation reactions has been discussed in the context of a wider review of these ligands as a source of asymmetry.[6]

The chemistry of *N*-heterocyclic carbenes (NHCs) features strongly in the section on nucleophilic carbenes. In keeping with this interest, the chemistry and reactivity of these species have been reviewed.[7] Their reactivity towards small molecules and

Organic Reaction Mechanisms 2006. Edited by A. C. Knipe

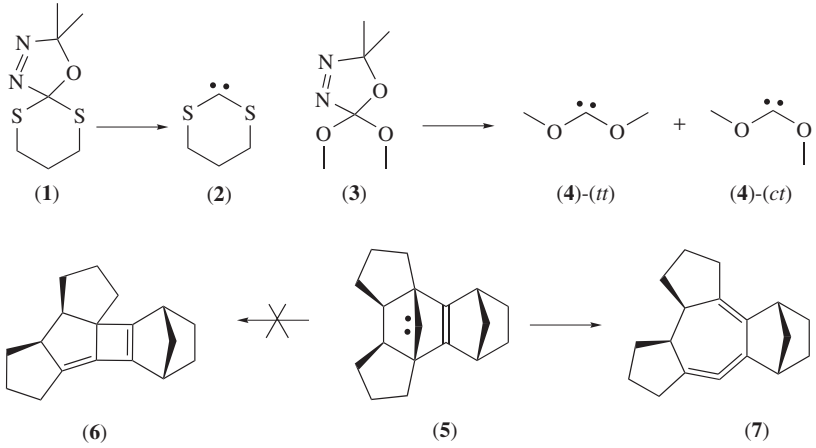
the relevance of the imidazolium salts to ionic liquids are highlighted. NHCs always feature strongly in this publication under the sections on metal-bound carbenes. Normally this is associated with synthesis and transition metals, but their involvement as ligands for *f*-block metals has been highlighted in a review that discusses NHCs with an alkoxide or amine tether, which allows the lability of the ligand to be studied.[8]

Silver is often used as a halophile. In the context of six-electron species, the role of silver atoms in carbene, nitrene, and silylene transfer reactions, including aziridination, CH insertion, ring expansion, and silacyclopropanation, has been reviewed.[9]

Carbenes can be highly reactive but modification of their chemistry through supramolecular encapsulation by cyclodextrins, hemicarcerands, and zeolites has been discussed in a microreview.[10]

Structure and Reactivity

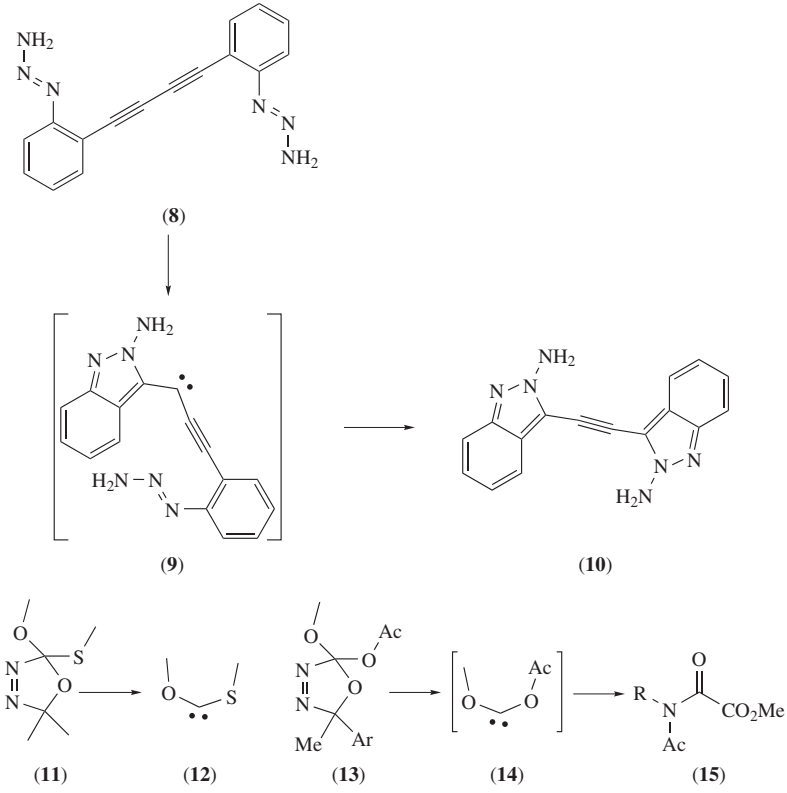
[1,3]Dithian-2-ylidene (**2**) has been trapped in argon and nitrogen and characterized by IR spectroscopy matrixes after high-vacuum flash pyrolysis (HVFP) of (**1**).[11] The sulfur–carbene interaction has been investigated via DFT calculations. Precursor (**1**) was shown to be stable up to 100 K and to decompose under irradiation to CS_2 and cyclopropane in a Corey–Winter-type reaction. Similar acyclic 1,3-heterocarbenes have also been observed and proved to decompose according to a different path. The conformations of dimethoxycarbene (**4**), generated from (**3**), were studied by IR spectroscopy and computations.[12] Only *s-trans*,*s-trans*-(**4**)-(*tt*) and *s-cis*,*s-trans*-(**4**)-(*ct*) were formed in the HVFP, the first being more stable due to dipole moment minimization. Computations have been carried out at the B3LYP/6–311+G(d,p) level of theory on 'foiled' carbene.[13] Studies of the carbene π-orbital interaction have been achieved by determining stabilization energies, singlet–triplet gaps, and lowest transition states for a range of alkenylidenes. Stabilization is enhanced with ring strain and pyramidalization of the electron-rich double bond. In (**5**), the stabilization with respect to vinyl shift is expected to preclude the formation of (**6**) and should favour a retro-Skattebøl rearrangement to allene (**7**).



Theoretical studies indicate that the reaction between CH_2 and SO proceeds by an attack on oxygen leading to HS and HCO.[14] Similar studies on the reaction of CH_2 with HNCO proposed three possible pathways giving different reaction outcomes.[15] The singlet–triplet energy gap, the dimerization activation barrier, the 1,2-hydrogen shift, and intermolecular hydrogen transfer have been determined theoretically for a range of NHCs.[16] Predictions of the hyperfine coupling constants of triplet carbene have been obtained by DFT calculations and compared with experimental ESR data.[17]

Generation

Transient carbene (**9**) is expected to be a reaction intermediate in the transformation of butadiyne-linked triazene (**8**) to alkyne-linked bis-2*H*-indazoles (**10**).[18] Experimental data and DFT calculations support carbene (**9**) as an intermediate in this stepwise, non-synchronous coarctate reaction. Methoxy(methylthio)carbene (**12**) has been observed by UV photoelectron spectroscopy after gas-phase decomposition of oxadiazoline (**11**).[19] The oxadiazoline (**13**) allows the generation of the acetoxy(methoxy)carbene (**14**).[20] The reactivity of the latter with isocyanates has been explored. Such reactions generally yield methyl (acetylamino)oxoacetates (**15**). DFT calculations permitted interpretation of the experimental data.



Cyclopropenylidenelithium (**16**) (the Yoshida–Weiss reagent) has for the first time been isolated and fully characterized.[21] The impact of the counteranion is discussed.

A new approach for the generation of NHCs has been reported using a cyclopentadiene(arene)iron complex (**17**).[22] The method converts imidazolium to the free carbene in the presence of oxygen (peroxyradical anion is the base deprotonating the imidazolium salt). A colour change and precipitation of the oxidized iron complex are evidence for the reaction outcome.

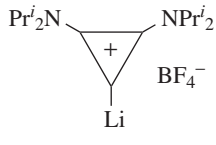
Metal-bound Carbenes

Carbenes as Ligands

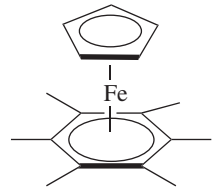
NHCs have become ligands almost as common as phosphines. This is widely exemplified in a book edited by Nolan.[23] We will therefore limit this overview of 'carbenes as ligands' to unusual applications and significant publications regarding their coordination chemistry.

The formation of a carbene from (**18**) in the coordination sphere of $(PCy_3)_2RhCl$ has been studied experimentally and computationally.[24] Evidence for an intramolecular C–H activation is provided by isotope labelling and reaction rate studies. These results have been further confirmed by DFT calculations.

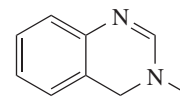
A wide array of ruthenium catalysts for alkene metathesis have been explored using DFT calculations in order to establish quantitative structure–activity and quantitative structure–properties relationships.[25] It has been established that ligands stabilizing the high oxidation state of the intermediate metallacyclobutane (relative to the ruthenium carbene structure) give the most active catalysts. Such a stabilization is achieved for complexes incorporating electron-rich metal (strong σ-donation of the ligand and poor π-back-donation of the metal). Catalytic activity is also enhanced by the bulk of the dative ligand. A fluorine–ruthenium interaction is thought to enhance the catalytic activity of the fluorinated Grubbs II-type catalyst (**19**).[26] This fluorine–ruthenium interaction is expected to take place upon phosphine dissociation. Interestingly, upon similar fluorine substitution, the Grubbs–Hoveyda-type catalyst (**20**) exhibits a native ruthenium–fluorine interaction but its catalytic activity is significantly decreased compared with the non-fluorinated counterpart. Grubbs–Hoveyda-type catalysts have been shown to have an enhanced activity (both in ring-closing metathesis and in cross-metathesis) when the standard isopropyl moiety is replaced by a 2-substituted methyl propanoate as in (**21**).[27] Compound (**21**) is an air-stable complex and exhibits an additional coordination of the carbonyl.



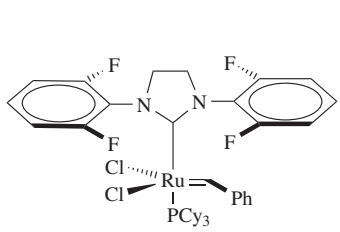
(**16**)



(**17**)



(**18**)



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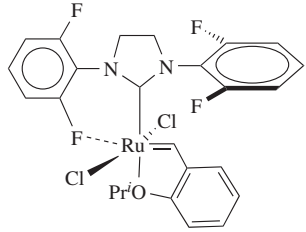

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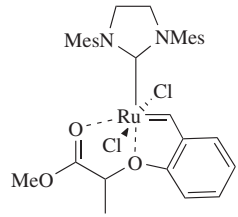
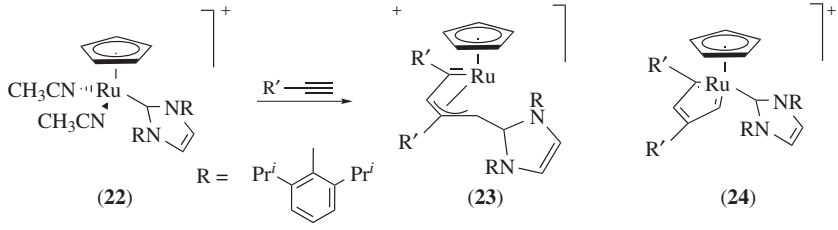


(**21**)

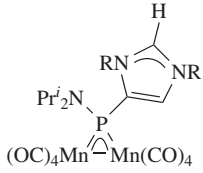
Reaction of ruthenium cyclopentadienyl bisacetonitrile carbene (**22**) with electron-poor acetylenes yields the allylcarbene (**23**).[28] As evidenced from DFT calculations, the reaction is likely to proceed by NHC insertion into the ruthenium–carbene bond in the metallacyclopentatriene (**24**). An unexpected reaction of NHC in the coordination sphere of a metal has been disclosed.[29] In this example, NHC is not coordinating the metal but is linked to a phosphorus atom with a shift of the carbene centre as shown in (**25**).

Combination of an NHC and lithium hexamethyldisilyamide proved highly beneficial for the outcome of the titanium-catalysed hydroamination of alkynes (mainly terminal ones).[30] High yields and complete Markovnikov regioselectivity have been observed. The NHC–Rh(I) (**26**) provided a highly efficient catalytic activity for cycloaddition towards cyclohexadienes and cycloheptadienes.[31] The $4 + 2$-cycloaddition can be carried out almost quantitatively both in intra- and inter-molecular fashion within minutes using 2 mol% of the catalyst; 30 min are required with 0.1 mol%. Similar efficiency (in turnover and yield) is achieved in the intramolecular $5 + 2$-cycloaddition. Interestingly, no intermolecular $5 + 2$-cycloaddition occurs, starting materials being recovered unaltered.



(**22**) (**23**) (**24**)

R′ = CO_2Me, CO_2Et, COMe



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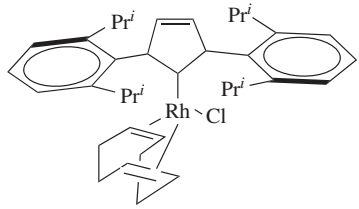


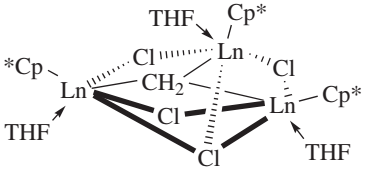
(**26**)

Carbenes as Reagents

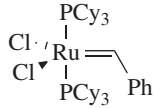
Methylidene–rare earth complexes (**27**) have been synthesized and fully characterized.[32] In these complexes, the methylene should be seen as a doubly charged negative ligand. Nevertheless, these methylidene complexes react as Schrock-type nucleophilic carbenes, (**27**) therefore being analogous to the Tebbe reagent.

Epimerization of vinylcyclopropanes by Grubbs I-type ruthenium catalysts (**28**) has been explored.[33] The reaction can also be effected by the Grubbs–Hoveyda catalyst (**29**) provided that an additional phosphine is added. Mechanistic studies (experimental and theoretical) suggest that the epimerization goes through a ruthenacyclopentene intermediate (**30**).

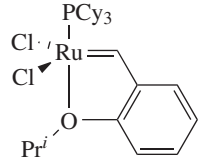
Rhodium-catalysed decomposition of methyl diazoacetate (1.2 equiv.) in the presence of 1,3-dithiolane yields mainly dithiane (**31**) as a mixture of diastereoisomers.[34] Ring-expanded product (**32**) and ring-opened products (**33**) arising from a second condensation of the carbene are also isolated, albeit in low yield. Similar reactivity is observed with 1,3-oxathiolane.



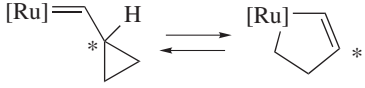
(**27**)



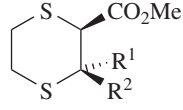
(**28**)



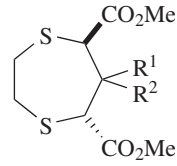
(**29**)



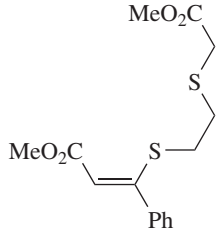
(**30**)



(**31**)



(**32**)



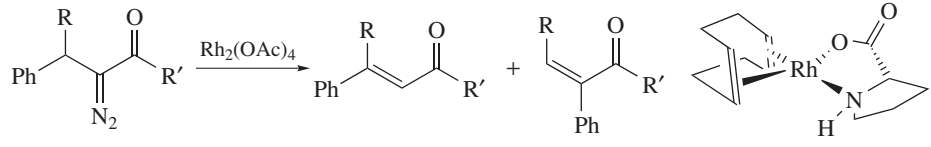
(**33**)

The outcome of Rh(II)-catalysed 1,2-migration from variously substituted diazocarbonyl compounds (**34**) has been explored as a function of R and R′.[35] It appears that the steric effect overrides the electronic effect in the formation of alkenes (**35a**) and (**35b**).

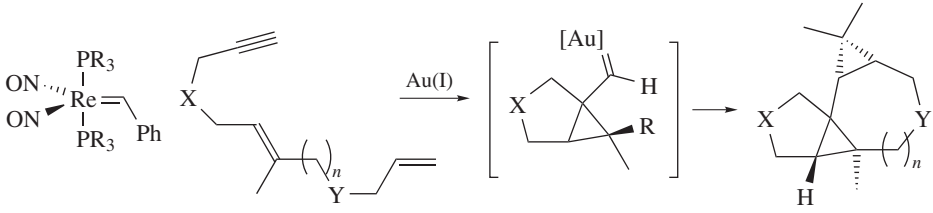
Proline-derived Rh(I) catalyst (**36**) has been involved in ethyl diazoacetate polymerization.[36] The poly(ethyl 2-ylideneacetate) polymers obtained are syndiotactic and have polydispersities slighter higher than 2. Interestingly, switching from rhodium to iridium leads to dimerization, no polymer being observed.

Rhenium complex (**37**) has been used in the ring-opening metathesis polymerization of strained alkenes such as norbornene.[37] The alkenes of the polymer backbone are predominantly *Z*, the polymer exhibiting high molecular weight and polydispersity.

Gold(I)-catalysed cycloisomerizations of enynes (**38**) afford gold–carbene complexes (**39**) that have been trapped in an intramolecular fashion yielding highly strained tetracycles (**40**).[38]



(**34**) (**35a**) (**35b**) (**36**)



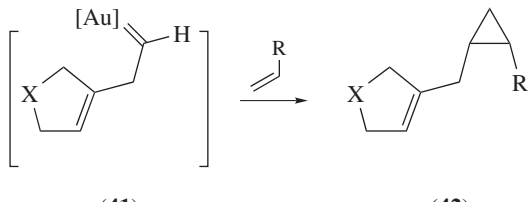
(**37**) (**38**) (**39**) (**40**)

Intermolecular trapping of carbene complexes (**39**) has also been reported. In this case, a second carbene (**41**) arising from a cyclopropyl shift from (**39**) can also be trapped to yield (**42**).[39]

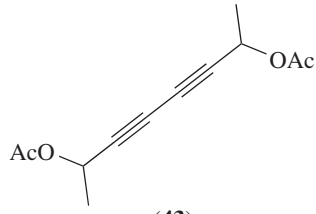
DFT studies of the asymmetric cycloisomerization of enyne catalysed by $PtCl_2$ have been carried out at the B3LYP/6–31G(d,p) level.[40] The formation of the cyclopropylcarbene intermediate represents the chirality-limiting step. (ee)

Rearrangements of 1,3-diynes (**43**) to dienynes (**45a**) and (**45b**) have been carried out; catalytically a metal–carbene intermediate (**44**) is likely to be involved.[41] Interestingly, gold catalysis provides mainly (**45a**) whereas platinum catalysis under a CO atmosphere yields predominantly (**45b**).

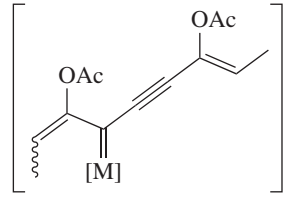
Intramolecular trapping of the transient carbene postulated above has also been achieved yielding polyunsaturated bicycles (**47**) from the diene–diyne precursor (**46**).[42] The intramolecular cyclopropanation is preceded by a [1,3]-metallotropic shift.



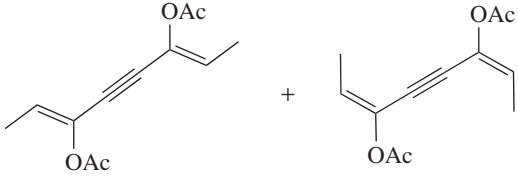
(**41**) (**42**)



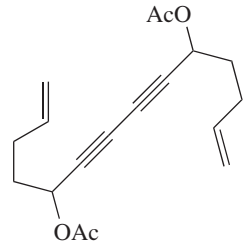
(**43**)



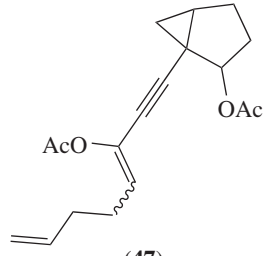
(**44**)



(**45a**) (**45b**)



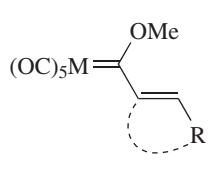
(**46**)



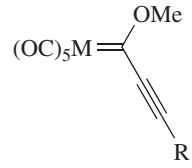
(**47**)

An overview describing the applications of group VI Fischer carbenes in carbo- and hetero-cyclization arising from the Barluenga group has appeared.[43] The reactivity of alkenyl and alkynyl Fischer carbenes (**48a**) and (**48b**) with dimethylaminodiazafulvene (**49**) has been explored.[44] A wide array of imidazole-containing polycycles are accessed in a highly convergent process.

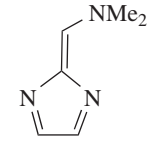
Reaction of crowded chromium alkenyl Fischer carbene (**50**) with bulky ketene acetals provides an interesting entry to 3-substituted pent-1-ynoate (**53**).[45] Formation of the alkyne can be rationalized by a 1,4-nucleophilic addition of the ketene on the unsaturated carbene complex (crowded complexes will not undergo potential 1,2-addition), following by oxonium (**51**) formation and fragmentation to a vinylidene carbene complex (**52**), which undergoes a 1,3-shift to the alkynylchromium complex leading the alkyne after reductive elimination.



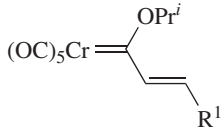
(**48a**)



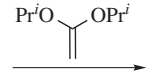
(**48b**)

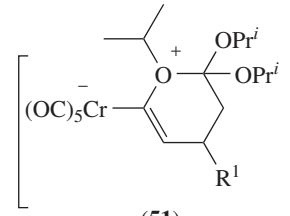


(**49**)

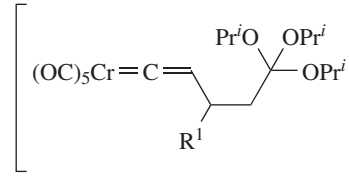


(**50**)

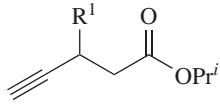




(**51**)



(**52**)



(**53**)

Chromium alkenyl Fischer carbenes have been shown to undergo a 3 + 2-cyclization with allenes under Rh(I) catalysis and a CO atmosphere, yielding 2-alkylidenecyclopentanone (**54**) after acidic hydrolysis.[46] Reactions with electron-rich allenes are carried out with a neutral rhodium complex whereas electron-poor allenes require a

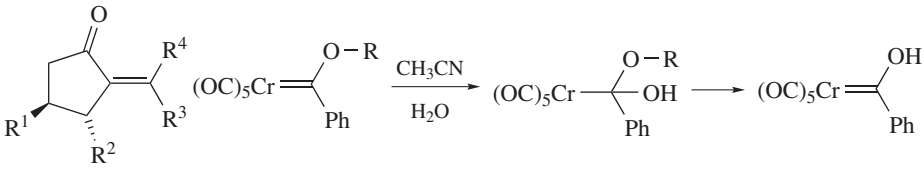
cationic rhodium complex. The mechanism is thought to proceed through a Cr–Rh metal exchange under the CO atmosphere followed by 4 + 2-metallacycloaddition and reductive elimination.

Kinetics of the hydrolysis of chromium Fischer complexes (**55**)–(**57**) in a 50:50 water–acetonitrile medium have been studied.[47] The rate-limiting step is the formation of (**56**), and the rate constant of the addition of water to the carbene is clearly controlled by the steric bulk of the R group in (**55**) varying from 5.3 to 0.01 l mol^{-1} s^{-1}.

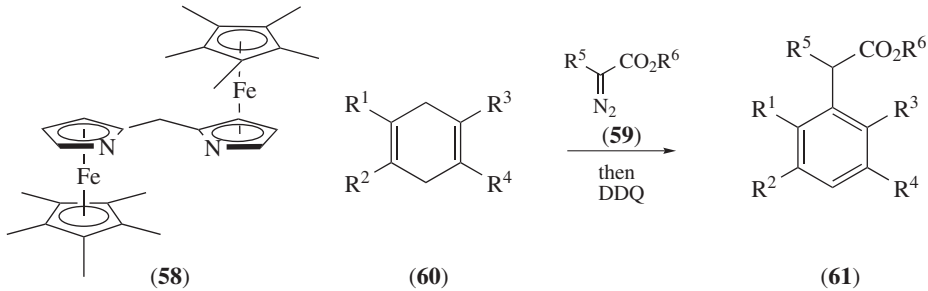
Intermolecular O–H insertions of phenyl diazoacetate with various alcohols have been reported to proceed with high enantioselectivities under catalysis by Cu(II) complexes of (**58**).[48] The presence of water proved crucial to achieving high *ee*s, which correlate linearly with catalyst *ee*. Moreover, a clear isotopic effect has been highlighted.

The Rh(II)-catalysed intramolecular C–H insertion of diazoacetamide in water has been studied.[49] This study assessed the factors governing the preferential intramolecular C–H insertion versus O–H insertion with the solvent. The hydrophobic/hydrophilic nature of the amide substituent appeared to be the most significant contribution driving the reaction towards C–H insertion. The nature of the rhodium catalyst precursor also modifies the reaction outcome [$Rh_2(OAc)_4$ enhancing the O–H insertion].

Intermolecular C–H insertion of diazoacetate (**59**) into the bisallylic position of cyclohexa-1,4-dienes (**60**) followed by DDQ oxidation of the substituted cyclohexadiene gave the polysubstituted arenas (**61**) in medium to very good overall yields.[50]



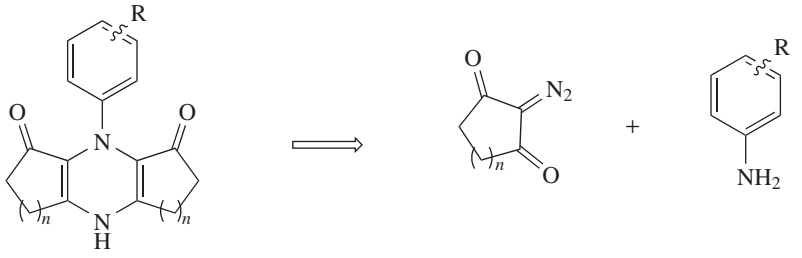
(**54**) (**55**) (**56**) (**57**)



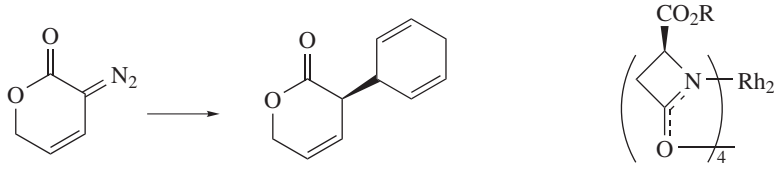
(**58**) (**60**) (**61**)

1,4-Dihydropyrazines (**62**) have been accessed via double Rh(II)-catalysed N–H insertion of 2-diazocycloalkanedione (**63**) on anilines (**64**).[51] Low yields are obtained as a consequence of inefficient double N–H insertion.

Vinyldiazolactone (**65**), a stable vinylcarbene precursor, has been involved in C–H insertion with cyclohexadiene yielding the bicycle (**66**) with moderate yield and good *ee*, especially when azetidinone–rhodium complexes (**67**) were used.[52] Competition between C–H insertion and cyclopropanation is always observed. The cyclopropanation reaction on classical alkenes is more efficient in terms of yields, *de*, and *ee*.



(**62**) (**63**) (**64**)



(**65**) (**66**) (**67**)

Two DFT studies (one in Chinese and one in English) of the cyclopropanation of ethene with samarium(II) carbenoids have been reported.[53,54] The reaction path is likely to involve a methylene transfer rather than a carbometallation with or without coordination of up to two THF molecules to the rare earth.

Double cyclopropanation of furans and pyrroles with aryl diazoacetates catalysed by Rh_2(S-DOSP)$_4$ have been reported to occur with opposite stereochemistry depending on the nature of the heterocycle.[55] Better yields and *ee*s are achieved for tricycles (**69**) derived from furan than for (**68**) derived from more bulky pyrroles. Monocyclopropanation (with high yields and *ee*s) is achieved on the furan ring of benzofuran, whereas double cyclopropanation of the indole is observed.

The effect of substrate structure on enantioselectivity has been explored for the catalytic intramolecular cyclopropanation reaction of α-diazo-β-keto arylsulfones.[56] It has especially been shown that substitution of the phenyl ring by a methyl at the *ortho* position of the sulfonyl group dramatically increased the *ee*s, with values up to 93%.

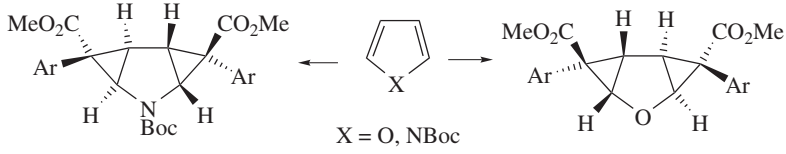
Addition and Fragmentation

In contrast with its reaction with NHC, CO addition to acyclic and cyclic alkylaminocarbenes (**70**) forms aminoketenes (**71**).[57] The structure of the ketene has been

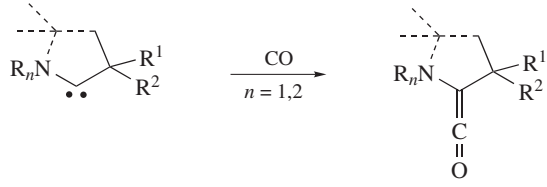
fully studied (experimentally and theoretically). Involving the nitrogen in a cycle allowed its lone pair to conjugate with the ketene moiety; nevertheless, this interaction remains weak.

The mechanism of the cycloaddition of singlet dimethylmethylene to acetone has been explored theoretically.[58] The reaction is thought to proceed in two steps via a high-energy intermediate that isomerizes to the three-membered ring via an energy barrier of 22.2 kJ mol^{-1}.

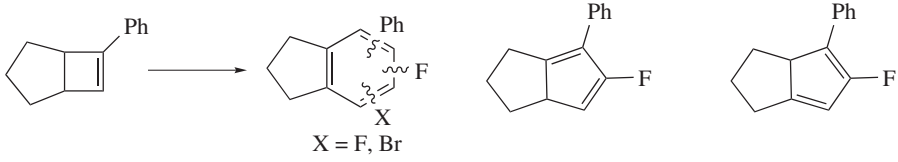
Additions of bromofluorocarbenes to 6-phenylbicyclo[3.2.0]hept-6-ene (**72**) have been shown to yield a mixture of various indanes (**73**), which probably arise from the formal ring expansion (cyclopropanation–ring opening) of (**74**) and (**75**), themselves coming from ring opening of the cyclopropane obtained by addition of the carbene to (**72**).[59]



(**68**) (**69**)



(**70**) (**71**)



(**72**) (**73**) (**74**) (**75**)

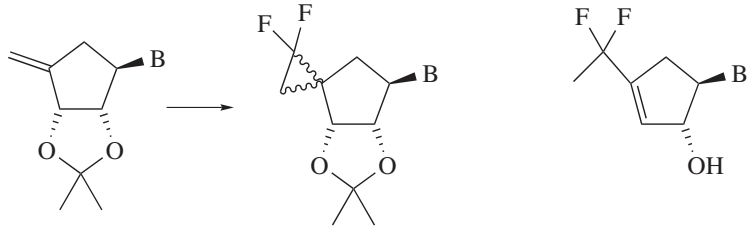
4′-(2,2-Difluorospirocyclopropane) analogues (**77**) of nucleosides have been synthesized by addition of difluorocarbene to (**76**).[60] Radical-mediated deoxygenation of the 2′-position leaves the difluorocyclopropane untouched whereas deoxygenation of the 3′-position induces a ring opening to (**78**).

Difluoro(methylene)cyclopropanes have been obtained in modest yields from allene by difluorocarbene addition.[61] The difluorocyclopropane moiety proved stable upon

functionalization of the remaining double bonds by Heck reaction or through lithiation. Ring opening was achieved using $CuI–I_2$.

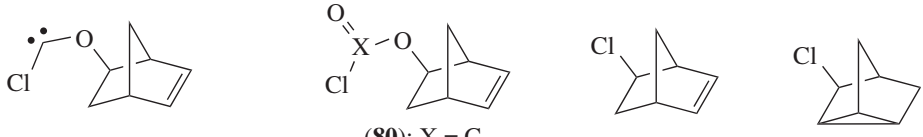
Fluorinated dihalocarbenes have been used as central synthons in the synthesis of fluorinated aromatics from cyclopentadienes.[62] The reaction proceeds via a fluorinated fused bicyclic cyclopropane, which upon heating undergoes a ring opening to achieve the ring expansion of the second cycle.

Ion pairs of similar structure are thought to be generated in polar solvents upon fragmentation of oxychlorocarbene (**79**), chlorocarbonate (**80**), and chlorosulfite (**81**).[63] They all lead to similar mixtures of 2-chloro-5-norbornene (**82**) and 3-nortricyclyl chloride (**83**). The stereochemical outcome of the reaction is mainly due to the tight ion pair, implying least motion chloride return.



(**76**) (**77**) (**78**)

B = adenin-9-yl, cytosin-1-yl, utacil-1-yl



(**79**) (**80**): X = C (**81**): X = S (**82**) (**83**)

Insertion and Abstraction

The insertion of an NHC (**84**) into a non-acidic CH bond has been studied in depth.[64] The mechanism, kinetics, and catalysis by an amide base (K-HMDS) were all investigated. The carbene was found to be stable to dimerization and inserted slowly into a methyl CH bond of toluenes to give aminals (**85**). The rate of aminal formation was strongly dependent on the *para*-substituent (Hammett ρ^- value of 4.8 ± 0.3). The rate-determining step is CH bond cleavage, which occurs with a late transition state.

Abstraction reactions involving alkylidenecarbenes have been characterized by DFT methods.[65] The transition states were examined at the B3LYP/6–311G(d,p) level of theory using the intrinsic reaction coordinate. The electronegativity of the substituents played an important role in predicting reactivity.

Intramolecular C–H insertion reactions, N–H insertion reactions, and intermolecular C–H insertion reactions of aminocyanocarbenes (NCC:NX_2, X = H, CH_3, CF_3) have been studied using restricted and unrestricted CCD, CCSD, QCISD, B3LYP, and MP2 methods with the 6–31G(d), 6–311+G(d,p), cc-pVDZ, and cc-pVTZ basis sets. [66] HC:NH_2, NCC:NH_2, NCC:$N(CH_3)_2$, and NCC:$N(CF_3)_2$ have singlet ground states.

Rearrangement

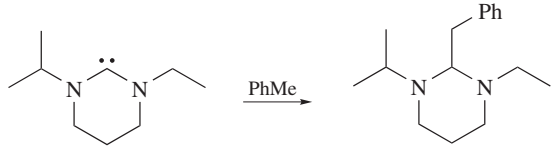
Silver clusters 2.5 nm in diameter displayed unusual electrocatalytic properties in Wolff rearrangements of diazoketones.[67] The reaction proceeds with electron transfer to and from the silver cluster. The presence of an α-ketocarbene/ketene was confirmed using pyridine as a nucleophilic probe and by UV–visible spectroscopy. Electrochemistry was used to support the role of the silver particles in the rearrangement.

The rearrangement of 27 different singlet carbenes to alkenes (or their analogues) was studied by AM1 SCF-MO theory. Four effects were considered: bystander group(s) at the migration origin; various substituent groups at the migration terminus; variations in ring size for cyclic carbenes; and methyl migration instead of hydrogen.[68]

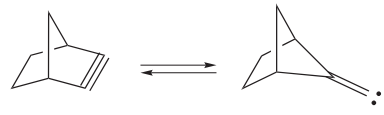
The interconversion of bicyclo[2.2.1]hept-2-yne (**86**) and 5-bicyclo[2.1.1]hexylidenecarbene (**87**) has been studied.[69] The authors claim that their results, in combination with those of an earlier study, give unambiguous support for a rapid equilibrium between the cycloalkyne and the carbene. The results presented comprise careful analysis of product mixtures.

The rearrangements of 3,3-diphenylcyclobutylidene (**88**) and 2,2-diphenylcyclobutylidene (**89**) are revealed to be affected significantly by the diphenyl substitution.[70] The former undergoes a 1,2-hydrogen shift whereas the latter prefers a 1,2-carbon shift. The data were acquired by steady-state and LFP experiments and the mechanism was probed by MRMP2//MP2 calculations.

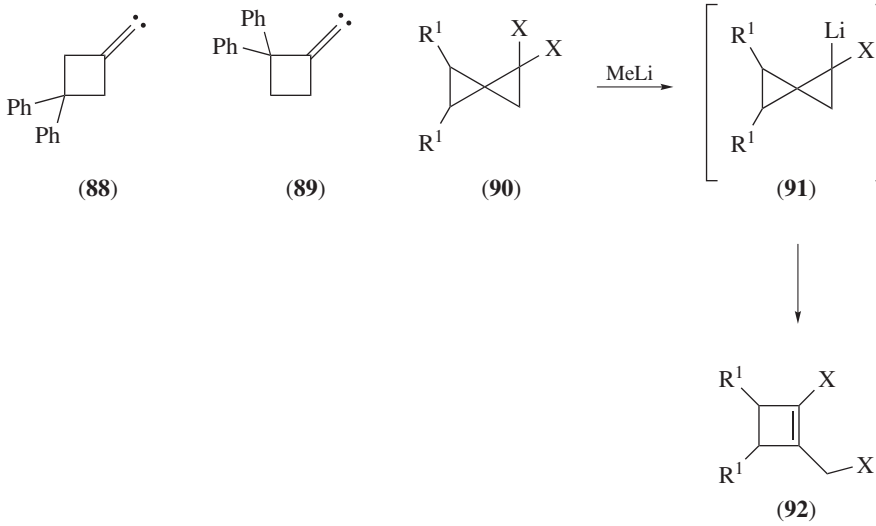
Treatment of dihalospiropentanes (**90**) with alkyllithiums generates carbenoid species (**91**) following metal–halogen exchange.[71] The carbenoids rearrange to cyclobutenes (**92**), which typically undergo a second lithium–halogen exchange before dimerizing in 44–75% yield.



(**84**) (**85**)



(**86**) (**87**)



(**88**) (**89**) (**90**) (**91**) (**92**)

Nitrenes

A substantial 267-article review covers the theoretical treatment of nitrenes.[72] Further reviews address the kinetics, spectroscopy, and computational chemistry of arylnitrenes[73] and the generation of nitrene species catalysed by transition metal complexes.[74]

Optically active sulfonimidamides react with benzylic and allylic methylene groups to give the formal product of nitrene CH insertion.[75] The reaction is catalysed by dirhodium complexes and delivers rather mixed results, both *de* and yield being substrate dependent. The authors finish the transformation by removing the sulfonimidamide by reduction to leave a benzylic or allylic amine.

The singlet–triplet splitting energy was calculated for formylnitrene and for the *syn*- and *anti*-rotamers of carboxynitrene HOC(O)N: by the CCSD(T) method.[76] The results were compared with DFT findings (which overestimate splitting) and with experimental data obtained by photolysis.

The ring expansion of singlet *ortho*-substituted phenylnitrenes (**93**) (X = H, CH_3, CN, NH_2, NO_2, OH, F, SH, Cl) was studied by semiempirical AM1 SCF-MO methods.[77] The two-step rearrangement involves nitrene atom insertion into the phenyl ring to give a bicyclic azirine intermediate (**94**), which undergoes electrocyclic ring opening to yield the monocyclic ketenimine product (**95**). The first step of azepine formation is predicted to be the rate-determining step and is favoured by electron-withdrawing substituents. The ring expansion is predicted to be favoured towards the unsubstituted side of the ring.

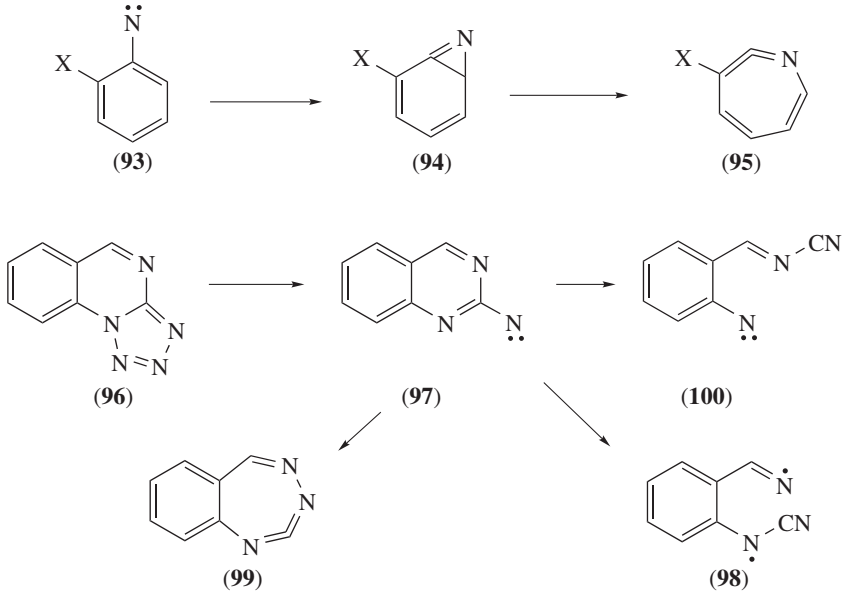
The thermal Curtius rearrangement of formyl, acetyl, and benzoyl azides was studied by DFT.[78] The authors conclude that the reaction occurs by a concerted mechanism and not by the alternative nitrene intermediate.

2,6-Difluorophenylnitrene was reinvestigated in Ar matrices at 10 K by UV–visible and IR spectroscopy. DFT and CASSCF/CASPT2 calculations were also used. Both

neutral rearrangement products (the bicyclic azirine and the cyclic ketenimine) of a phenylnitrene were prepared and characterized for the first time. X-irradiation was used to generate radical cations and it was shown that phenylnitrene and cyclic ketenimine yield stable radical cations, whereas the bicyclic azirine decays to both of these compounds on ionization.[79]

Sulfoximine- and phenanthrene-based *N*-alkoxyaziridines decompose under photochemical conditions to give oxynitrenes.[80] The first EPR spectra of oxynitrenes were reported and were consistent with triplet ground states. Trapping and reactivity studies, nanosecond time-resolved IR investigations, and computational studies all support a triplet ground state.

Argon matrix photolysis of tetrazolo[1,5-*a*]quinazoline/2-azidoquinazoline (**96**) gave a nitrene (**97**) which was observable by ESR, UV, and IR spectroscopy.[81] The reactions of this nitrene were characterized and included fragmentation to radical species (**98**), rearrangement to cycloheptatetraene (**99**), and ring opening to a new nitrene (**100**).



A gold-catalysed nitrene transfer reaction gave aziridine products.[82] The nitrene source was a sulfonamide in combination with a commercially available oxidant [PhI(OAc_2)]. The best catalyst was [Au(4,4′,4″-tri-*t*-butyl-2,2′:6′,2″-terpyridine)]OTf loaded at 3 mol%. The reaction worked well with mono- and di-substituted alkenes but not with alkenes fitted with electron-withdrawing groups. $NsNH_2$ was by far the best nitrene source, other sulfonamides giving significantly worse results. The second aziridination reported in 2006 used a diphenylphosphoryl azide as the nitrene source and was catalysed by a cobalt–porphyrn complex.[83] Yields were modest (< 68%) and the catalyst loading was relatively high at 5–10 mol%.

A Curtius rearrangement was reported as the key step in the synthesis of protected anilines and aromatic ureas.[84] The reaction is a single step from the corresponding carboxylic acid and produces urea or aniline, depending on the conditions.

A nitrene generated from the reaction of *N*-aminophthalimide (**101**) and $PhI(OAc)_2$ was key to the metal-free ring expansion of alkylidenecyclopropanes (**102**) and an alkylidenecyclobutane.[85] The authors propose two plausible mechanisms for these ring-expansion reactions: either an aziridine is formed which undergoes facile rearrangement to form the final 2,2-disubstituted cyclobutylidene hydrazine product (**103**), or reaction of the alkylidenecyclopropane with the nitrene generates an ionic or diradical species which rearranges.

Nitrenes generated from PhINTs and copper acetoacetate react with thietanes to form isothiazolidines.[86] The initially formed S–N donor–acceptor complex undergoes ring expansion with retention of stereochemistry. Yields range from 56 to 76%.

An optically active ruthenium catalyst allows the asymmetric synthesis of aziridines from alkenes and sulfonylazides.[87] Catalyst loadings are 0.1–2 mol% although the yields and *ee*s are rather variable; at best the reaction works well, TsN_3 and $PhCCCH_2$ giving the corresponding aziridine in 98% yield and 98% *ee*. Use of 2-(trimethylsilyl)ethanesulfonyl (SES) azide and styrene gave good results for both yield (99%) and *ee* (92%), but the SES group is easily removed to give the unprotected aziridine.

(*ee*)

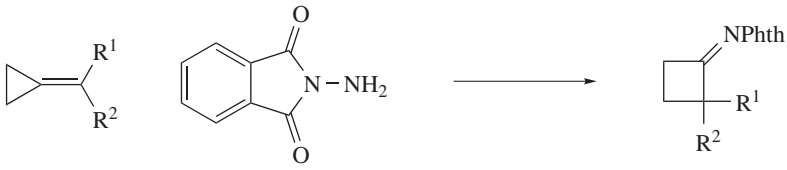
Nucleophilic Carbenes

Asymmetric triazolium salts were employed in synthesis to catalyse benzoin reactions to give optically active benzo-fused cyclohexanes.[88] The triazolium salts are loaded at 10–20 mol% and react *in situ* with base to give the NHCs, which are the real catalytic species. Yields of products were high (85–92%) and *ee*s modest to good (61–98%). This report differs from those discussed in previous editions of ORM in that the benzoin reaction is intramolecular. A reaction with many of the same mechanistic features is the hydroacylation of α-keto esters with aldehydes.[89] Choice of solvent switches the reaction between α-acyloxy- (in CH_2Cl_2) and α-hydroxy ester products (in MeOH/EtOH). The process is tolerant of electron-rich aldehydes, but the yields are generally lower when electron-deficient systems are employed. Using a mixture of deuterated benzaldehyde and non-deuterated 4-methylbenzaldehyde gave all four possible products, implying a reversible reduction step separate from the acylation event. Closely related to hydroacylation is cyanosilylation.[90–93] Yields were above 80% and catalyst loading was between 1 and 0.01 mol%. In one case the reactions were rendered mildly asymmetric by the use of C_2-symmetric NHCs. The formation of cyclopentenes from the reaction of α,β-unsaturated aldehydes with α,β-unsaturated ketones is catalysed by NHCs.[94] Typical yields are 70–90%. Reaction of the carbene with the aldehyde reverses the polarity of the unsaturated aldehyde and allows the β-carbon to act as a nucleophile towards the β-carbon of the ketone.

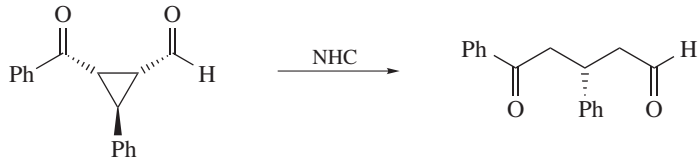
(*ee*)

Thiazolium, imidazolium, and triazolium salts were each investigated as possible precatalysts for the ring opening of cyclopropanes (**104**) to give δ-ketoaldehydes (**105**).[95] Catalyst loading was 5 mol%, the product chirality being derived from the starting material rather than the catalyst. Both diazolium and thiazolium salts were

also used to ring open aziridines with aldehydes.[96] At 20 mol% loading of the carbene precursor, the reaction only barely qualifies as catalytic; however, the reaction works well with a variety of aromatic and aliphatic aldehydes. The reactions were run in air and the products show attack by a carboxylic anion rather than the expected acyl anion. The authors note that exclusion of air yields the expected product of attack by acyl anions. In a second example, the NHC reacts with acid anhydrides to liberate the carboxylic anion, which acts as the nucleophile.[97]



(**102**) (**101**) (**103**)



(**104**) (**105**)

Chiral NHCs formed adducts with aldehydes that underwent enantioselective oxo-diene Diels–Alder reactions with enones.[98] The NHC only needed to be added at 0.5 mol% to achieve yields >70% and *ee*s in the high 90s. (*ee*)

The NHC class of nucleophilic carbenes are also bases. The proton–deuteron exchange of NHCs attached to macromolecules has been studied and the influence of counterion has been explored.[99] Substitution, both directly on the imidazolium unit and on the pre-orientating calixarene backbone, was also studied. The results showed that substitution of the imidazolium salts has a large influence on the H–D exchange rates in wet methanol-d_4. These results were presented as having implications for Suzuki coupling.

An unusual reaction of a diazolium salt was reported during an attempt to form copper complexes of the NHC.[100] The isolated products showed ring expansion of the carbene to form six-membered lactams. The authors verified the product by X-ray crystallography and independent synthesis. It is not clear where the extra carbon comes from. The authors consider a possible mechanism involving a carbene dimer formation, but point out that the carbenes are very hindered. Possible reaction with atmospheric carbon dioxide was not considered. Direct oxidation of the carbene to give a urea is also noted.

Diazolium and triazolium salts have been used in *O*- to *C*-acyl transfer reactions.[101] The reaction works well (67–82% yield) in the presence of <1.5 mol% catalyst. (*ee*) The mechanism involves acyl transfer from the oxygen atom of an enol ether to the

carbene and then transfer back to the enolate carbon. In a related reaction, hydroxyl groups were acylated by NHCs.[102] The catalyst was given C_2 symmetry and used to undertake kinetic resolutions of chiral but racemic alcohols. The total mass recovery was acceptable, but the *ee*s were low ($< 70\%$).

Electrophilic Carbenes

Phenyl chlorocarbene reacts with 2-pyridyl Schiff bases as the first step in the synthesis of imidazo[1,5-*a*]pyridiniums.[103] The reaction mechanism is discussed in detail. The authors consider both attack of the pyridine nitrogen and attack by the imine nitrogen.

The electrophilic carbene CF_2 forms donor–acceptor complexes with 2*H*-azirines.[104] The resulting complexes rearrange to form oxazines and 4*H*-1,3-diazepines. The rearrangements are of general mechanistic interest, but the reactions are not synthetically useful due to very low yields.

Silylenes and Germylenes

Laser flash photolysis of a cyclic trisilane led to three transient species observed by UV–visible spectroscopy.[105] The shortest lived species was monitored at 530 nm and showed chemical behaviour consistent with diphenylsilylene.

The cycloaddition reaction of singlet GeX_2 (X = F, Cl) with formaldehyde was studied employing the HF/6–311+G* theory.[106] The reaction proceeds in two steps: barrierless formation of an intermediate complex followed by rate-determining isomerization to form the product. The results were compared with those from other cycloadditions of germylenes and silylenes.

Methylphenylgermylene was generated by retrocycloaddition from the germanacyclopentane analogue.[107] The germylene was detected directly and by analysis of reaction products. Rate constants for the reactions with amines, acids, silanes, stannanes, oxygen, and unsaturated carbon–carbon bonds were given.

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CHAPTER 5

Nucleophilic Aromatic Substitution

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General

There has been a study of the dediazoniation of 4-nitrobenzenediazonium ions in methanol–water mixtures under acidic conditions using kinetic, spectrophotometric, and chromatographic methods. Two decomposition routes were identified: an ionic pathway yielding nitrophenol and nitroanisole, and a radical pathway involving transient diazo ethers which undergo homolytic fragmentation giving nitrobenzene or 4,4′-dinitrobiphenyl.[1] Catalysis by the Cu(I)–Cu(II)–1,10-phenanthroline system has been reported in the reaction of arenediazonium salts with potassium thiocyanate to yield aryl thiocyanates.[2] Bis(trifluoromethanesulfonyl)amide anions (Tf_2N^-) are usually considered to have very low nucleophilic reactivity. However, in imidazolium ionic liquids this anion has been shown to have higher reactivity than bromide ions in heterolytic dediazoniation reactions.[3]

It has been shown that displacement of the iodo substituent in 4-iodo-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane by arenethiolates or by stabilized enolates occurs by the radical chain $S_{RN}1$ mechanism. The reaction occurs in DMF with photochemical stimulation.[4]

The S_NAr Mechanism

There has been a review of relationships between activation parameters and mechanisms for biomolecular reactions in solution, including both nucleophilic substitutions and additions.[5] Several studies have been reported involving substitutions by amine nucleophiles where both electronic and steric effects may be important. Kinetic studies of the reactions of 2,4-dinitrophenyl 2,4,6-trinitrophenyl ether (**1**) with ring-substituted

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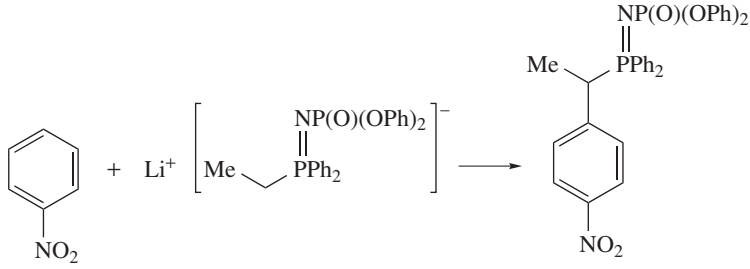
anilines in acetonitrile were interpreted by the mechanism of Scheme 1 and both uncatalysed, k_2 step, and base-catalysed routes, k_B step, were involved. When substituents are at the 3- or 4-positions of the aniline, and hence remote from the reaction centre, there are pronounced electronic effects with values of the Hammett ρ parameter for K_1k_2 of -5.5 and for K_1k_B of -5.4. Steric effects are only important for anilines carrying substituents at the 2- and, particularly, the 2- and 6-positions. These effects are more important for the base-catalysed pathway than the uncatalysed route.[6]

A comparison has been reported of the substitution by aliphatic amines in acetonitrile of 1-chloro and 1-phenoxy groups in ring-activated benzenes. Values of k_1, the rate constant for nucleophilic attack may be affected by steric repulsion at the reaction centre which increases with the orders Cl < OPh and *n*-butylamine < pyrrolidine ≈ piperidine. Ring substituents may also have adverse steric effects, with those of the trifluoromethyl group being particularly serious. Base catalysis in the 1-phenoxy compounds was attributed to rate-limiting proton transfer from the zwitterionic intermediates to base with values decreasing in the order *n*-butylamine > pyrrolidine > piperidine.[7] Kinetic studies have also been reported of the selective substitution of chlorine at the 2-position in methyl 2,4-dichloro-3,5-dinitrobenzoate by aliphatic amines in methanol and in benzene. Here nucleophilic attack is rate limiting and the effect of variations in the nature of the nucleophile and solvent were discussed.[8]

The hydroxy-dehalogenation of activated haloarenes in alkaline water or water–DMF solvents has been shown to be accelerated by the addition of hydrogen peroxide. The mechanism is likely to involve aryl hydroperoxide intermediates.[9] There has been a study of the phenoxy-denitration reactions of 4-nitrophthalonitrile by the R-phenol–potassium carbonate system in DMF and DMF–water solvents. The rate-limiting step is thought to depend on the substituent, R, in the phenol, and changes from phenol deprotonation with weakly acidic phenols to S_NAr substitution with more acidic phenols.[10] Reaction of 4-substituted nitroarenes with alkanethiols in DMSO containing caesium carbonate may result in displacement of the nitro group. Dithiols may yield products resulting from substitutions by both thiol groups.[11]

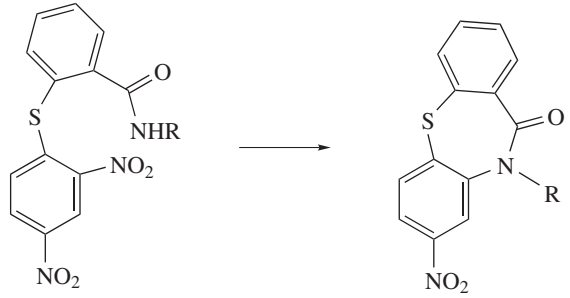
The vicarious amination of nitrobenzene and 5- and 6-nitro-1-methylbenzimidazoles has been reported by use of 4-amino-1,2,4-triazole in DMSO containing potassium *t*-butoxide. In the case of the benzimidazoles the yield was increased on the addition of cuprous chloride and ESR spectroscopy indicated the presence of radical anions derived from the substrates.[12] The oxidative substitution of hydrogen is an alternative to the vicarious mechanism when the nucleophile does not carry a good leaving group. Oxidative substitutions by phosphorus-stabilized carbanions have been reported and an example using a phosphazene derivative is shown in Scheme 2. The addition of dichlorodicyanobenzoquinone (DDQ) may aid the oxidation step.[13] Substitution of hydrogen in nitroarenes by an oxazoline-stabilized carbanion has also been reported. Addition occurs *para* to the nitro group and oxidation of the anionic intermediate with DDQ yields substituted nitroarenes whereas oxidation with dimethyldioxirane (DMD) leads to substituted phenols.[14] Deprotonation of pentafluoroacetonitrile by a guanidine-like base has been shown to yield a carbanion which will displace fluoride from a second molecule, resulting in the formation of a dimer. Further deprotonations may result in trimers and tetramers.[15]

SCHEME 1



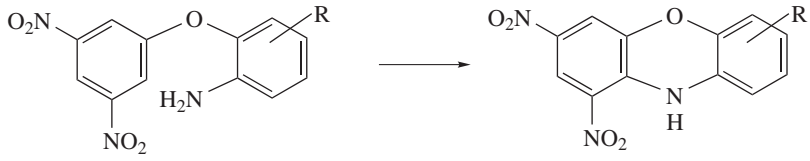
SCHEME 2

There have been several reports of the use of intramolecular displacements of nitro groups in the synthesis of heterocyclic compounds. Thus, reaction[16] of the intermediate (**2**) with a strong base in DMF results in the substitution of a nitro group by the amide function to yield a dibenzothiazepinone derivative (**3**). Nucleophilic addition across the double bond of 2,4,6-trinitrostyrene may occur with thiophenol, aniline, and aliphatic amines. The adducts so formed with primary amines may undergo intramolecular substitution of an *o*-nitro group to give *N*-substituted 4,6-dinitroindoles.[17]



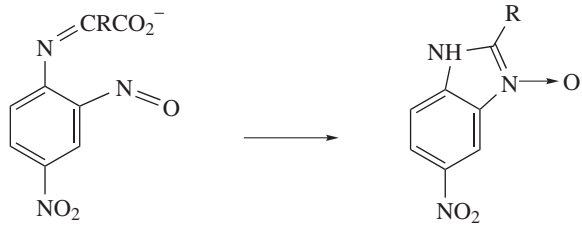
(**2**) (**3**)

Reaction of 1,3,5-trinitrobenzene (TNB) with *o*-aminophenols in the presence of potassium carbonate in dipolar aprotic solvents has been shown to produce 1,3-dinitrophenoxazines (**5**). This reaction is thought to involve nitro group displacement to yield intermediates (**4**), which undergo oxidative substitution of hydrogen by the amino group.[18] The corresponding reaction of TNB with *o*-aminothiophenols yields 1,3-dinitrophenothiazine derivatives.



(**4**) (**5**)

The reaction of *N*-(2,4-dinitrophenyl)amino acids with base in aqueous dioxane has been shown to give benzimidazole *N*-oxides (**7**). The rate-determining step is likely to be formation of an *N*-alkylidene-2-nitrosoaniline intermediate (**6**), which is followed by rapid cyclization and decarboxylation.[19] The loss of carbon dioxide from perbenzoate anions has been investigated by mass spectrometry and electronic structure calculations. The results, including isotopic labelling experiments, support a mechanism involving initial intramolecular nucleophilic attack at either the *ortho*- or *ipso*-ring positions. They also indicate that epoxides may be intermediates en route to the phenoxide products.[20] There has also been a theoretical study of the formation of trichlorinated dibenzo-*p*-dioxins by reaction of 2,4,5-trichlorophenolate ions with 2,4-dichlorophenol.[21]



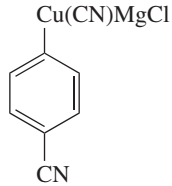
(**6**) (**7**)

The kinetics of the piperidino-defluorination reaction of 1-fluoro-2,4-dinitrobenzene have been studied in non-aqueous reverse micelles consisting of ethylene glycol–AOT–*n*-heptane or DMF–AOT–*n*-heptane. The reaction, which is not base catalysed, is accelerated when DMF, a non-hydrogen bond donor solvent, is used in the micelle core.[22] Catalysis by human glutathione *S*-transferase M 1a–1a of the reaction of glutathione with 1-chloro- and 1-fluoro-2,4-dinitrobenzenes has been investigated. Much stronger enzymatic catalysis was observed in the case of the dechlorination reaction than for the defluorination and a transition-state model was proposed.[23]

Both experimental and theoretical studies have been reported of fluoro-denitration and fluoro-dechlorination reactions using anhydrous tetrabutylammonium fluoride in DMSO. The absences of ion pairing and strong solvation are critical in contributing to the reactivity of the fluorinating agent.[24] Quaternary ammonium salts derived from cinchona alkaloids have been shown to be effective catalysts in an improved asymmetric substitution reaction of β-dicarbonyl compounds with activated fluoroarenes. The products may be functionalized to yield spiro-oxindoles.[25]

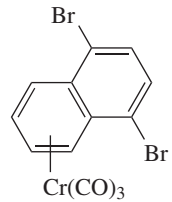
There is continued expansion in the use of metals as catalysts in substitution reactions. Copper(I) iodide in the presence of *N*,*N*′-dimethylethylenediamine has been shown to be effective in the intramolecular substitution of aryl bromides carrying an *o*-1,3-dicarbonyl substituent; reaction may involve either an oxygen centre or a carbon centre of the dicarbonyl moiety.[26] The reaction of aryl halides with sodium trifluoroacetate in the presence of copper(I) iodide may lead to the formation of the trifluoromethylated derivatives, possibly via CF_3CuI^- as an intermediate.[27] There have been theoretical calculations, PM3 and *ab initio*, on complexes formed from copper

chloride and bromobenzene in the presence of either quinolin-8-ol or bipyridyl.[28] It has been shown that the use of copper(II) salts as catalysts with oxygen as the oxidant may be effective in the oxidative substitution of ring hydrogen by nucleophiles including halides and acetoxy ions; a mechanism involving single electron transfer (SET) is likely.[29] Catalysis by cobalt(II) has been reported in the reaction of the aryl copper compound (**8**) with aryl fluorides to produce polyfunctional biophenyls.[30]



(**8**)

There has been a summary explaining how the use of reaction kinetics may help in the interpretation of complex catalytic reaction schemes; examples include palladium-catalysed coupling reactions of aryl halides.[31] A short review has been published on the use of hydrophilic ligands for palladium in aqueous-phase reactions involving aryl halides.[32] A new palladium catalyst containing a rigid tripodal phosphorus-based ligand has been used successfully in Suzuki couplings, such as the reaction of 4-bromoanisole with phenylboronic acid.[33] The use of a new bulky phosphoramidate ligand for the palladium catalyst has been reported in the debromohydrogenation reaction of (**9**), the chromium tricarbonyl complex of dibromonaphthalene; the product is formed in a highly enantiomerically enriched form.[34]



(**9**)

Diastereoselectivity has also been achieved in the intramolecular double-Heck cyclizations of some cyclohexene diamides to form spirocyclic oxindoles; the structural features responsible for imparting diastereoselection in the first[35] and second[36] ring-closure reactions have been examined. The results of studies of the Heck vinylation of aryl bromides with 2-substituted enol ethers using a tetraphosphine–palladium catalyst have been reported; the stereoselectivity of the reaction depends on both steric and electronic factors with the *Z*-isomers being favoured for electron-rich or sterically congested aryl bromides.[37] Use of a $PdCl_2(PCy_3)_2$ catalyst in dioxane in the presence of caesium carbonate has been shown to allow the efficient coupling of aryl chlorides with alkenes to form the *E*-isomers; this catalyst system has the advantage that it

allows reaction with both electron-rich and electron-poor aryl chlorides under mild conditions.[38]

A procedure has been developed for the palladium-catalysed α-arylation of amides by aryl bromides using the zinc enolates of the amides. The reaction works well with bromoarenes carrying a variety of ring substituents and with bromopyridine. In addition, the reaction has been shown to be effective with morpholine amides to give products which are precursors for aldehydes and ketones.[39] A new method has been reported for the allylation of aryl halides using homoallyl alcohols as the allyl source; the palladium-catalysed reaction, which may be both stereo- and regio-sepecific, uses (*de*) a retro-allylation reaction to form a σ-allyl(aryl)palladium intermediate.[40]

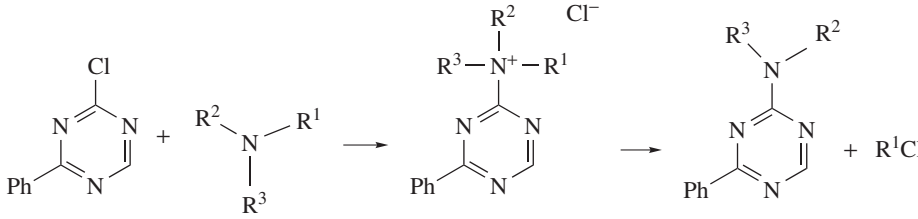
A ruthenium catalyst derived from a secondary diaminophosphine oxide has been used successfully in the arylation of C–H bonds by aryl tosylates.[41]

Heterocyclic Systems

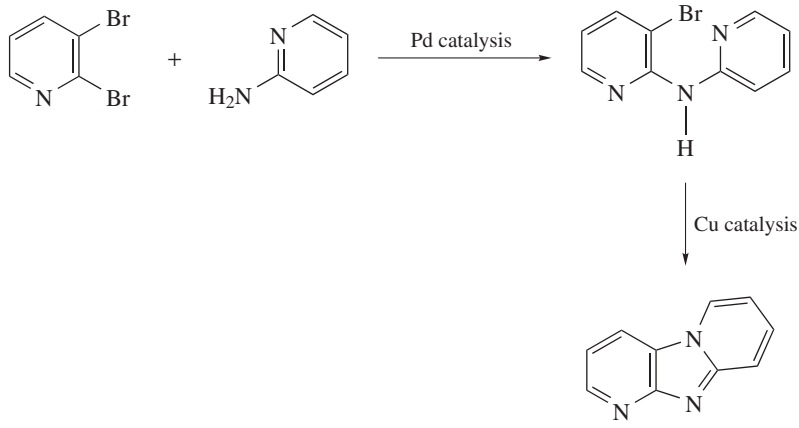
Kinetic studies have been reported of the reactions of a series of 2-substituted-5-nitrothiophenes (substituent = Br, OMe, OPh, OC_6H_4-4-NO_2) with secondary amines in room-temperature ionic liquids. The kinetic behaviour is similar to that of the corresponding reactions in methanol so that most reactions do not show base catalysis. The observation that reactivity is higher in the ionic liquids than in methanol (or benzene) is attributed to relatively poor solvation of the reagents by the ionic liquids. As in conventional solvents, 2-bromo-3-nitrothiophene shows higher reactivity than 2-bromo-5-nitrothiophene.[42] Solvent effects on the kinetics of the alkaline hydrolysis of 2-phenylthio-3,5-dinitropyridine in aqueous organic solvents have been analysed.[43]

Reaction of 9-chloroacridine with aryl sulfonyl hydrazides results in aminodechlorination to give the corresponding *N*-acridinylbenzenesulfonyl hydrazides; kinetic studies in methanol and DMSO have been reported.[44] Reaction of electron-deficient heteroaryl chlorides with tertiary amines may proceed by quaternization and dealkylation, as shown in Scheme 3. These reactions occur under mild conditions, e.g. acetonitrile solvent at room temperature, and in THF may be accelerated by the addition of lithium chloride.[45]

A highly regioselective amination of 6-aryl-2,4-dichloropyrimidines has been developed using palladium catalysis. The reaction which works well with secondary aliphatic amines and with anilines gives the 4-substituted products.[46] Palladium catalysis has also been used in the regioselective coupling of 2,3-dibromopyridine with a series



SCHEME 3

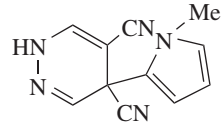


SCHEME 4

of aminoazines including 2-aminopyridines. As shown in Scheme 4, the first step involves palladium-catalysed intermolecular aminodebromination whereas the second, intramolecular, step uses copper catalysis to form dipyrido[1,2-*a*:2′,3′-*d*]imidazole.[47]

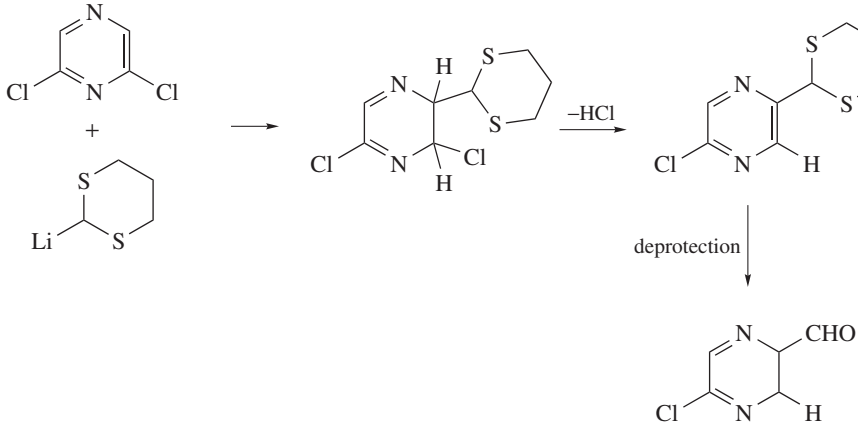
The regioselectivity in the methoxydefluorination reactions of difluoroquinolines has been examined.[48] Studies of the substitution patterns in 2-cyano-3-nitroimidazole[1,2-*a*]pyridine have shown that nitrogen and oxygen nucleophiles substitute the 2-cyano group whereas sulfur nucleophiles replace the 3-nitro group.[49]

4,5-Dicyanopyridazine may react with pyrrole and indole systems as a heterocyclic azadiene in IEDDA Diels–Alder reactions. However, in acetic acid as solvent reaction occurs by substitution of CN at the 4-position and intermediates such as (**10**) may be isolated.[50] Reaction of dichloropyrazines with a dithiane anion in THF may result in a *tele*-substitution process, as shown in Scheme 5, in which initial nucleophilic attack occurs at an unsubstituted ring position. Deprotection of the substituted product yields the corresponding aldehydes.[51]

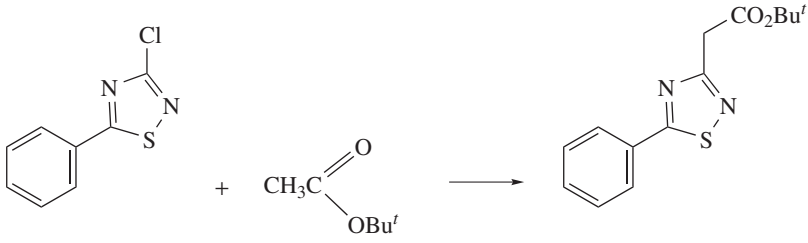


(**10**)

Substitution of chloride in a variety of heterocyclic chlorides by esters, lactones, amides and lactams has been shown to occur in toluene in the presence of hexamethyldisilazide (NaHMDS) acting as a base.[52] An example using a chlorothiadiazole derivative is shown in Scheme 6. There has been a report[53] of a mild and convenient method for the introduction of tetrafluoroethyl substituents into nitrogen heterocycles using the reaction of hexafluoropropane with azine and azole *N*-oxides.



SCHEME 5



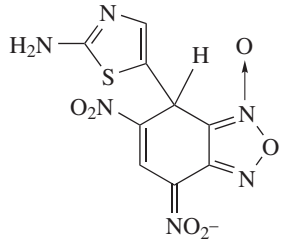
SCHEME 6

A study of the effects of surfactants on the reaction of 2-(4-cyanophenoxy)quinoxaline with hydroxide ions has shown that rate accelerations caused by cetyltrialkylammonium chlorides may be due to reaction in premicellar aggregates or in micelles.[54]

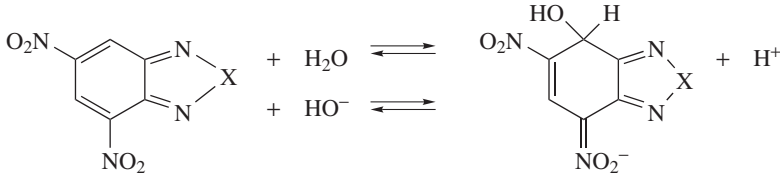
Meisenheimer and Related Complexes

4,6-Dinitrobenzofuroxan (DNBF) is known as a superelectrophile due to its high reactivity both as an electrophile and in its pericyclic addition reactions. NMR studies show that reaction with 2-aminothiazole and its 4-methyl derivative yield anionic carbon-bonded adducts such as (**11**) by reaction at the 5-position, whereas the 4,5-dimethyl derivative reacts via the exocyclic amino group. Kinetic studies of the first two compounds, both in acetonitrile and in 70:30 (v/v) water–DMSO, have been used to assess their carbon nucleophilicities and place them on the Mayr nucleophilicity scale.[55] In a related study, the nucleophilic reactivity, in acetonitrile, of a series of indoles with both DNBF and with benzhydryl cations have been compared and used to determine nucleophilicity parameters for the indoles.[56]

There has been a comparison of the kinetics, in water over a wide pH range, of the formation of hydroxy adducts from 4,6-dinitrobenzofurazan (**12**) with those of its



(**11**)

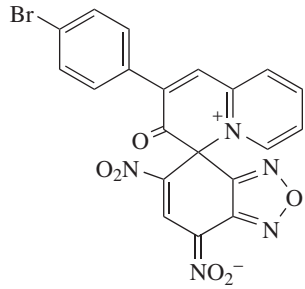


(**12**), X = O
(**13**), X = S
(**14**), X = Se

SCHEME 7

sulfur (**13**) and selenium (**14**) analogues. As shown in Scheme 7, these reactions may involve the attack of water, producing a proton, or direct attack of hydroxide ions. The pK_a values for these processes are 3.92 for (**12**), 6.34 for (**13**), and 7.86 for (**14**), showing (**12**) to be the strongest electrophile of the three. All three compounds also react with dienes to give Diels–Alder mono- or di-adducts and there is a relationship between this pericyclic reactivity and the ability to form σ-adducts. In turn, these abilities are inversely related to the degree of aromaticity in the heterocycles.[57]

The reaction of 7-chloro-4,6-dinitrobenzofurazan with 2-(4′-bromophenyl)indolizine has been shown to result in carbon–carbon bond formation by substitution of the 7-chloro substituent.[58] However, in the reaction of 7-chloro-4,6-dinitrobenzofuroxan the initial substitution is followed by intramolecular oxygen transfer from the *N*-oxide function and by rearrangement to give the zwitterionic spiro-adduct (**15**). An

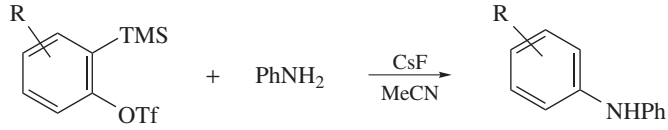


(**15**)

intramolecular substitution involving an oxygen–carbon spiro-adduct has been postulated[59] during a stereoselective two-fold Wittig rearrangement in a 1,1′-binaphthyl derivative. The X-ray crystallographic structure of an anionic 1,3-dioxolane spiro-adduct with a tetrabutylammonium cation has been reported and compared with the structure with a potassium cation.[60]

Benzyne and Related Intermediates

There has been a summary of the use of insertion reactions of arynes into σ-bonds to prepare *ortho*-disubstituted arenes. A key to the success of these processes is the ability to generate benzyne under mild conditions by the reaction of readily available *o*-(trimethylsilyl)phenyl triflate with fluoride ions.[61] Reaction of amines and their derivatives with benzynes generated in this way has been shown to be an efficient method for the production of *N*-arylated derivatives, as illustrated in Scheme 8. The method also works well in the *O*-arylation reactions of phenols and carboxylic acids.[62]



SCHEME 8

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CHAPTER 6

Electrophilic Aromatic Substitution

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General

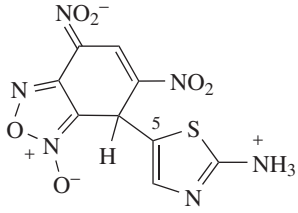
The wide scope of application of the electrophilicity index of Parr, Szentpály, and Liu has been reviewed.[1] Applications to electrophilic aromatic substitutions discussed are few. However, some alkylation and acylation reactions do correlate well with electrophilicity values. In the case of the nitration of toluene and chlorobenzene, correlation is not very good and it is suggested[2] that electrophilicity is a kinetic quantity with inherent thermodynamic information.

A quantitative description of the reactivity of monosubstituted benzenes to electrophilic substitution based on considerations of inductive effect parameters and conjugative effect parameters from the ^{13}C chemical shifts of the aromatic compounds has been proposed.[3] MO calculations on the proton migration in the *ipso* adducts formed in the reaction of CH_3^+ and SiH_3^+ with benzene have been described.[4] With SiH_3^+ the *ipso* adduct is the most stable of possible isomers, whereas for CH_3^+ the *para*-protonated isomer is the most stable.

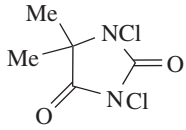
A DFT study of the reactivity of pyridine and the diazabenzenes towards electrophilic substitution, assuming frontier orbital control of the reactions, predicts their low reactivity as the HOMOs of these substrates are not π-orbitals.[5] For pyridine-*N*-oxide, however, the HOMO is an aromatic orbital. DFT studies giving Fukui indices predict[6] the preferred sites of electrophilic attack on pyrrole, furan, and thiophene and calculation of the local softness of the reactive sites rationalizes relative reactivities.

2-Aminothiazole and its 4-methyl derivative react with the superelectrophilic 4,6-dinitrobenzofuroxan at C(5) to form, for example, (**1**) in spite of them exhibiting higher nitrogen basicity than aniline.[7] In the case of 4,5-dimethyl-2-aminothiazole, however, attack did occur at nitrogen.

Organic Reaction Mechanisms 2006. Edited by A. C. Knipe



(**1**)



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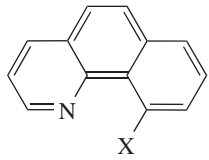


(**3**) **a**; X = H
b; X = Cl

Halogenation

A review indicates that only strong electrophilic fluorinating agents are suitable for the *ipso* fluorodesilylation of arylsilanes.[8] Weaker N–F-type reagents, e.g. Selectfluor®, give low yields together with side products. Kinetic isotope effect studies of the fluorination of aromatic compounds with N–F-type reagents are consistent with a polar S_EAr mechanism where the decomposition of the Wheland intermediate is not rate limiting.[9] Studies of the fluorination of 1,3,5-trideuterobenzene demonstrated the occurrence of 1,2-hydrogen and deuterium migrations in the Wheland intermediates, the first time such a process has been demonstrated in electrophilic fluorination.

The kinetics of the chlorination of phenol and 2-naphthol by 1,3-dichloro-5,5-dimethylhydantoin (**2**) in aqueous acidic media have been interpreted[10] in terms of an initial rate-limiting formation of a charge-transfer complex between the substrate and the chlorinating agent. A kinetic study of the chlorination of nine aryl ethers by 1-chlorobenzotriazole in acetic acid has also led to mechanistic conclusions.[11]

The direct iodination of aromatic compounds has been the subject of a review[12] which, *inter alia*, points out that many of the novel modern methods are less successful with deactivated arenes than with activated aromatic compounds. A new reagent consisting of $NaIO_4$–KI–NaCl in aqueous acetic acid has been found to iodinate a number of activated aromatics, including even 2-nitroaniline.[13] Reaction involving intermediate iodine monochloride is suggested. An MO theoretical study[14] has been made of the iodination of pyridine, quinoline, and their *N*-oxides in neutral and protonated forms by a number of iodinating agents and direct iodination enthalpies have been calculated.

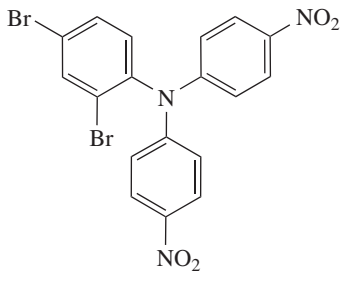
The chlorination, bromination, and iodination of the proton sponge 5,6-bis(dimethylamine)acenaphthylene by halogens and by *N*-halosuccinimides have been studied.[15] With bromine and iodine, reaction gives initial addition at C(1)=C(2). However, chlorination with *N*-chlorosuccinimide is directed *ortho* to the NMe_2 groups, giving 4-chloro- or 4,7-dichloro-substituted derivatives in excellent yields. The scope of palladium-catalysed chelate-directed chlorination, bromination, and iodination of arenes using *N*-halosuccinimides has been explored.[16] For example, compound (**3a**) forms (**3b**) in 95% yield on reaction with *N*-chlorosuccinimide in acetonitrile at 100 °C in the presence of 1–2 mol% palladium acetate.

Nitration

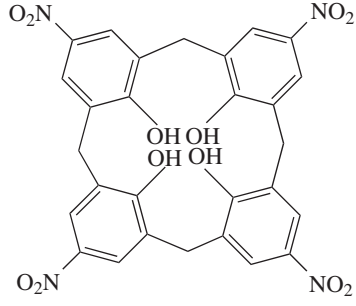
Theoretical calculations and gas-phase mass spectrometric studies have been performed for the reaction of naked and monosolvated nitronium ions with some monosubstituted aromatics, and these lead to a detailed mechanistic scheme for electrophilic aromatic nitration.[17] The scheme comprises a continuum of pathways in which the single electron transfer and the classical polar mechanism are extremes. The importance of either mechanism depends on the ease of transfer of an electron from the substrate to the nitronium ion and this also governs the regioselectivity observed, *meta*-directing groups favouring the classical polar mechanism. MO calculations of the nitrations of benzyl alcohol and benzyl fluoride indicate[18] that both have *ortho–para*-directing substituents but that the presence of the fluorine atom deactivates the system, whereas the hydroxyl group activates the system.

The products and kinetics of nitration of chlorobenzene in a nitric acid–mineral acid system have been investigated[19] to obtain information about possible adjustment of product ratio. The mononitration of phenols by a range of metal nitrates in acetone at 25 °C in the necessary presence of catalytic *p*-toluenesulfonic acid gives highly regioselective *ortho* substitution, phenol, for example, giving an 85% yield of *o*-nitrophenol with Ni(II) nitrate.[20] A PPh_3–Br_2–$AgNO_3$ mixture stirred in acetonitrile at room temperature is a mild and effective chemoselective reagent for the nitration of aromatic amines.[21] *N*-Methylaniline, for example, gives a 100% yield of nitro-*N*-methylanilines (*ortho:para* = 15:78) even in the presence of anisole, which did not react.

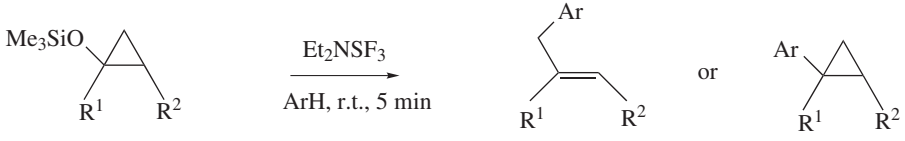
The nitration of triphenylamine derivatives by $Cu(NO_3)_2$ in acetic anhydride at room temperature proceeds readily, introducing up to three nitro groups.[22] Reaction



(**4**)



(**5**)

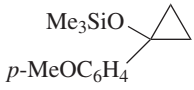


(**6**) (**7**) (**8**)

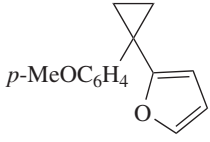
of 4,4′,4″-tribromotriphenylamine gives a complicated mixture of products involving nitrodebromination on one or more rings and bromination at other sites [e.g. to form, *inter alia*, (**4**)]. The nitration of calix[4]arenes and calix[6]arenes by nitrogen dioxide to form *p*-nitro derivatives [e.g. (**5**) in 90% yield] has been investigated.[23]

Alkylation, Acylation, and Related Reactions

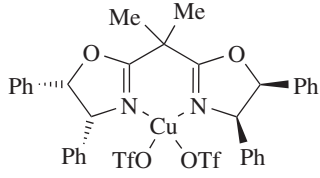
MO calculations on the alkylation of aromatic compounds by alkyl halides catalysed by group 13 trihalides have shown that a pathway involving the dimeric form of the catalyst is more favourable, both thermodynamically and kinetically.[24] This is in agreement with available experimental data suggesting the use of an excess of the metal halide (ratio close to 2:1). The reaction of tertiary cyclopropyl silyl ethers (**6**) with diethylaminosulfur trifluoride in an electron-rich aromatic compound (ArH) as solvent gives alkylated or cyclopropylated aromatic compounds [(**7**) or (**8**)].[25] Compound (**10**), for example, is formed from (**9**) in furan. Enantioselective alkylation of simple aromatic ethers by ethyl 3,3,3-trifluoropyruvate ($CF_3CO.CO_2Et$) occurs using the $Cu(OTf)_3$ complex (**11**) as a catalyst under solvent-free conditions [e.g. (**12**) from *p*-bromobenzyl phenyl ether in 91% *ee*].[26] (*ee*)



(**9**)



(**10**)



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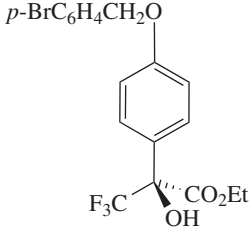
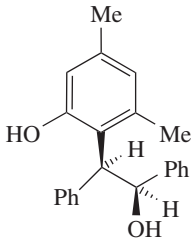
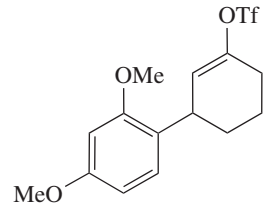


(**12**)

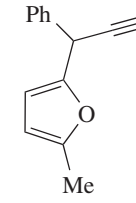
A regioselective and highly *syn*-stereoselective catalyst-free intermolecular alkylation of aryl borates with aryl epoxides under mild, neutral conditions has been reported.[27] The reaction of *trans*-stilbene oxide with tri(3,5-dimethylphenyl)borate gave a 38% yield (>95% *syn*) of the *C*-alkylated product (**13**), easily separated from the *O*-alkylated product(s). Triflic anhydride has been used to activate enones to nucleophilic attack by electron-rich arenes in the presence of a sterically hindered base.[28] Resorcinol dimethyl ether, for example, reacted with cyclohex-2-en-1-one to (*de*)



(**13**)



(**14**)



(**15**)

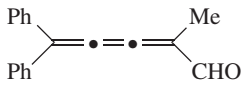
give a 45% yield of the enol triflate (**14**). Intramolecular examples of the reaction were also reported. The alkylation of phenol with *t*-butyl alcohol in supercritical water at 673 K produces some interesting results.[29] The products are 2-isobutylphenol, 2-*t*-butylphenol, and 4-*t*-butylphenol. Isobutene is believed to be a reaction intermediate and the 2-isobutylphenol is formed by an anti-Markovnikov addition to the alkene in which the hydroxyl group participates.

Propargylic alcohols bearing a terminal triple bond react with electron-rich aromatic compounds in the presence of thiolate-bridged diruthenium complexes to give the propargylated aromatic compounds.[30] 1-Phenylprop-2-yn-1-ol, for example, reacts with 2-methylfuran to form (**15**). Intramolecular examples of the reaction were also reported. The process is believed to involve electrophilic attack by the ruthenium-stabilized propargyl cation.

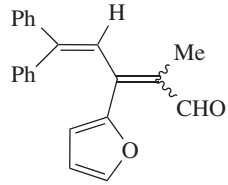
The [3]cumulene derivative (**16**) reacts with electron-rich heteroaromatics (e.g. furan) in the presence of 50 mol% $Yb(OTf)_3$ to form the tetrasubstituted conjugated diene [e.g. (**17**)].[31] Samarium diiodide has been investigated as a catalyst for reaction of various electron-rich aromatics with chelating electrophiles, e.g. alkyl 3,3,3-trifluoropyruvates.[32] With these electrophiles α-hydroxy esters are formed in good yield with complete regioselectivity [for example, (**18**) is formed from the methyl trifluoropyruvate and *N*,*N*-dimethylaniline in 99% yield]. In reactions involving ethyl glyoxylate or a glyoxylic imine, α-hydroxy esters and α-amino esters are obtained, respectively, together with variable amounts of products resulting from further aromatic substitution [e.g. (**19**) from the former reactant with *N*,*N*-dimethylaniline].

A review of catalytic protocols for the ring-closing alkylation and alkenylation reactions of arenes has appeared.[33] Recent enantioselective strategies are covered and it (ee) is noted that the development of effective catalytic systems for practical stereoselective alkylations remains a challenge.

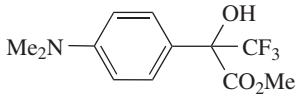
10-(3-Methoxybenzyl)-9,10-dihydroanthacen-9-ols (**20**) undergo a transannular ring closure in the presence of acid to form the corresponding homotriptycenes (**21**) in almost quantitative yields.[34] Reaction of α-alkylcinnamaldehydes with ortho-esters, alcohols, or thiols in the presence of $BF_3.OEt_2$ forms 1-alkoxy-2-alkylindenes [e.g. (**22**) from α-methylcinnamaldehyde and $HC(OMe)_3$].[35] It is suggested that initially alkoxylation of the carbonyl carbon of the aldehyde forms an acetal, which loses alkoxide to give a carbonium ion (**23**) and subsequently a geometric isomer (**24**) in which an intramolecular electrophilic substitution occurs to form the indene ring system.



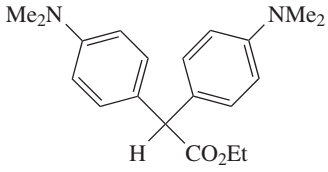
(**16**)



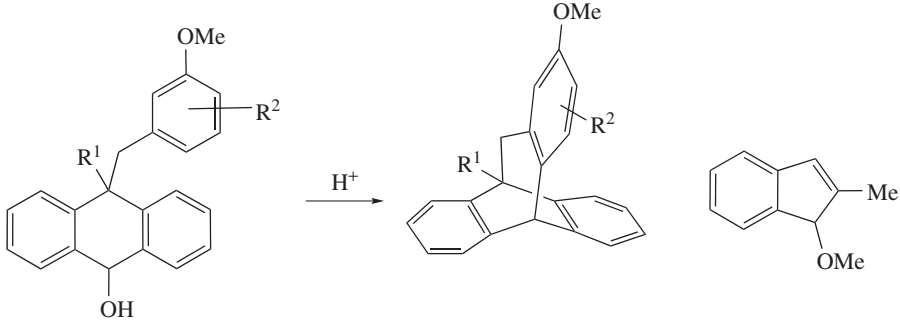
(**17**); *E*:*Z* = 1.0:2.0



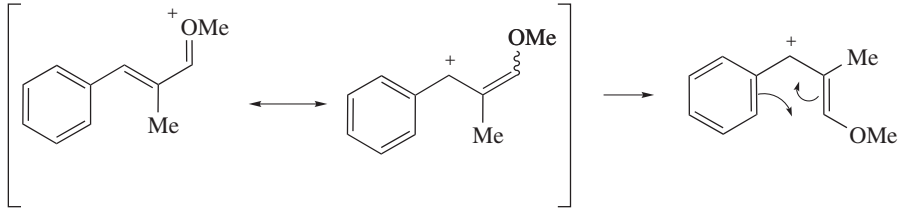
(**18**)



(**19**)

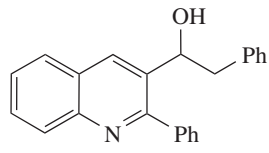


(**20**) (**21**) (**22**)

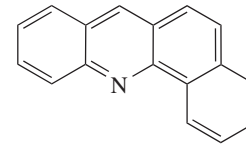


(**23**) (**24**)

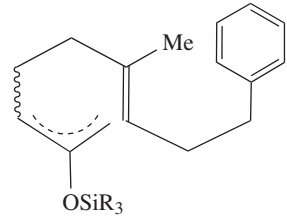
Superacid-catalysed intramolecular reactions of some dicationic electrophiles have been investigated.[36] The positively charged centres migrate apart and this chemistry gives a new synthetic route to aza-polycyclic compounds. The polycyclic compound (**26**) can, for example, be formed from reaction of 2-phenyl-3-(1-hydroxy-2-phenylethyl)quinoline (**25**) with CF_3SO_3H at 25 °C, loss of water and benzene being involved. Highly diastereoselective polycyclization of homo(polyprenyl)arenes [e.g. (**27**) → (*de*)



(**25**)



(**26**)



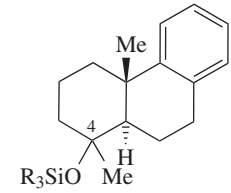
(2*E*)-2-, (2*Z*)-2- and 1-enyl mixture

(**27**)

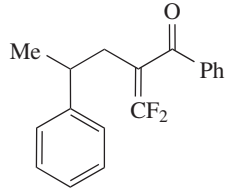
$SnCl_4$

−78 °C

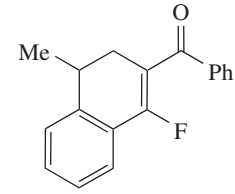
R = Pr^i



(**28**)



(**29**)

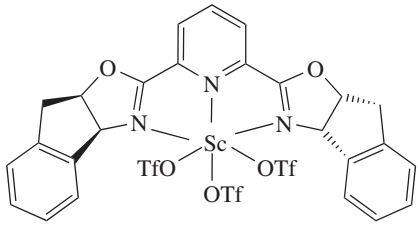


(**30**)

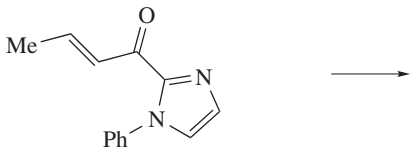
(**28**)] having terminal siloxyvinyl groups is catalysed by 10 mol% tin(IV) chloride.[37] Structural variables, including the bulk of the silyl group, enabled the stereochemistry at C(4) to be altered. 2,2-Difluorovinyl ketones bearing an aryl group [e.g. (**29**)] undergo a facile electrophilic cyclization[38] involving carbocations, which are stabilized by α-fluorine atoms, on treatment with a trimethylsilylating agent to form 4-fluorinated 3-acyl-1,2-dihydronaphthalenes [e.g. (**30**)].

Much work in the review period has concerned enantioselective substitution in five-membered heterocyclics. The enantioselective alkylation of some pyrroles by α,β-unsaturated 2-acylimidazoles catalysed by the bis(oxazolinyl)pyridine–scandium(III) triflate complex (**31**) has been reported.[39] Compound (**33**) is formed in 98% yield and 94% *ee* from the 2-acylimidazole (**32**) and pyrrole at −40 °C. A series of enantiomerically pure aziridin-2-ylmethanols has been tested as catalysts in the alkylation of *N*-methylpyrrole and *N*-methylindole by α,β-unsaturated aldehydes.[40] Enantiomeric excesses of up to 75% were observed for the alkylation of *N*-methylpyrrole by (*E*)-crotonaldehyde using (2*S*,3*S*)-3-methylazirin-2-yl(diphenyl)methanol TFA salt as catalyst to form (**34**).

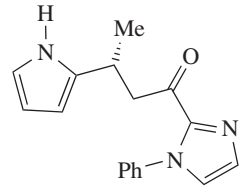
Novel axially chiral bis-arylthioureas [e.g. (**35**)] catalyse the asymmetric substitution of indole and *N*-methylindole by nitroalkenes.[41] 2-Nitroethenylcyclohexane is



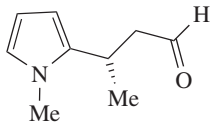
(**31**)



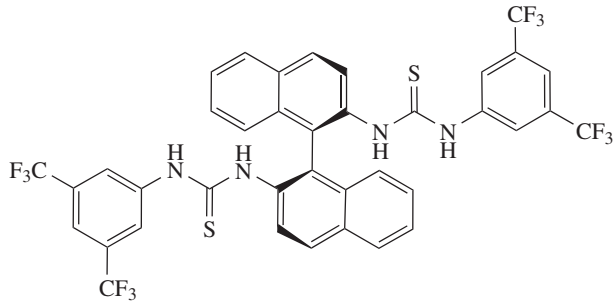
(**32**)



(**33**)



(**34**)

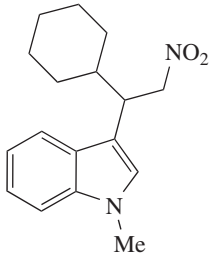


(*s-trans, cis*)

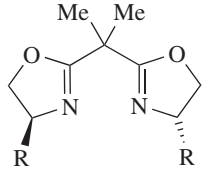
(**35**)

converted on reaction with *N*-methylindole into (**36**) with 43% *ee*. Zn(II) complexes of bisoxazolines [e.g. (**37a**)] catalyse the enantioselective alkylation of indoles by nitroalkenes giving products in up to 90% *ee*.[42] Related catalysts [e.g. (**38**)] also catalyse the alkylation of indoles with nitroalkenes, this time in up to 98% *ee*.[43] The catalyst is believed to act in a bidentate fashion, the nitroalkene being activated through coordination of the nitro group to the Lewis acid centre and the NH group in the catalyst acting as a donor for the NH $\cdots\pi$(indole) interaction.

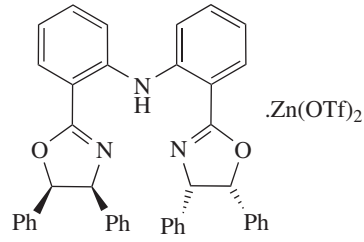
Some bifunctional 6′-OH *Cinchona* alkaloid derivatives catalyse the enantioselective hydroxyalkylation of indoles by aldehydes and α-keto esters.[44] Indole, for example, can react with ethyl glyoxylate to give mainly (**39**) in 93% *ee*. The enantioselective reaction of indoles with *N*-sulfonyl aldimines [e.g. (**40**)] is catalysed by the $Cu(OTf)_2$ complex of (*S*)-benzylbisoxazoline (**37b**) to form 3-indolylmethanamine derivatives, in up to 96% *ee* [e.g. (**41a**)].[45] Some 9-thiourea *Cinchona* alkaloids have been found to catalyse the formation of 3-indolylmethanamines [e.g. (**41b**)] from indoles and *N*-$PhSO_2$-phenylimines in ~90% *ee*.[46] Aryl- and alkyl-imines also give enantioselective reactions.



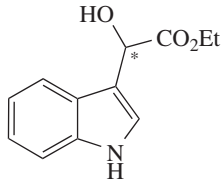
(**36**)



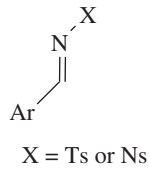
(**37**) **a**; R = Ph
b; R = Bn



(**38**)

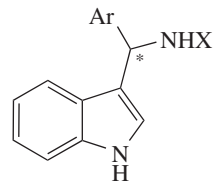


(**39**)

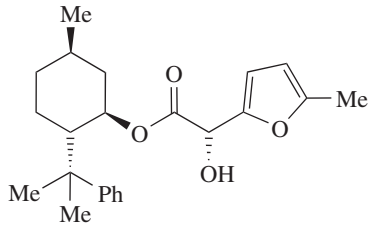


X = Ts or Ns

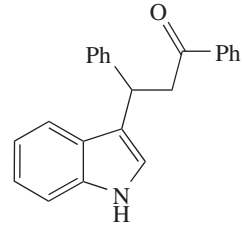
(**40**)



(**41**) **a**; X = Ts or Ns
b; X = SO_2Ph, Ar = Ph



(**42**)



(**43**)

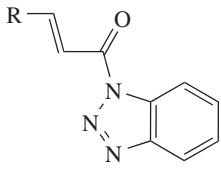
The reaction of (1*R*)-8-phenylmenthyl glyoxylate with various furans catalysed by $SnCl_4$ or particularly magnesium salts (e.g. $MgBr_2$) occurs with high yields and high diastereoselectivities (>90%) to form furan-2-ylhydroxyacetic acid esters [e.g. (**42**)].[47] (*de*)

The heteropoly acids, $H_3PMo_{12}O_{40}$ and $H_3PW_{12}O_{40}$, have been found to be excellent catalysts[48] for the alkylation of a range of indoles and pyrrole by enones and β-nitrostyrene in water as solvent. Chalcone and indole form (**43**) at room temperature. Easy work-up was achieved without the use of organic solvents.

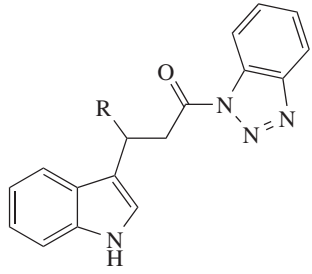
The kinetics of reaction of four indoles with a number of benzhydryl cations has allowed the determination of the nucleophilicity parameters *N* and *S* for these reactions.[49] Kinetic data from the reaction of a number of indoles with 4,6-dinitrobenzofuroxan then allow determination of their *N* values. Correlation of these data with those for protonation at C(3) of 5-substituted indoles and 5-substituted 2-methylindoles

demonstrates that the 2-methyl group sterically hinders the approach of 4,6-dinitrobenzofuroxan to the C(3) position. The quantitative data from reactions of indoles with some other electrophiles were also analysed by this reactivity parameter approach.

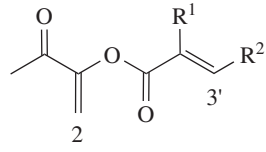
Indoles are alkylated regioselectively by α,β-unsaturated acylbenzotriazoles (**44**) catalysed by samarium(III) iodide under reflux in THF to form new 3-substituted indoles [e.g. (**45**)].[50] The formation of β-(3-indolyl)ketones from the alkylation of indoles by (*E*)-α,β-unsaturated ketones is effectively promoted by 30 mol% of equimolar pyrrolidine and perchloric acid in CH_2Cl_2.[51] MO calculations have been reported on the alkylation[52] of indole by dimethylalkylidenemalonates suggesting that the hydrogen-transfer process becomes rate limiting in alcoholic solvents. Reaction of the 1-acetylvinyl acrylates (**46**) with furan or thiophene in the presence of $BF_3.Et_2O$ at $-78\,^{\circ}C$ occurred solely at C(2) in the vinyl moiety, this position being more reactive than C(3′) in the acrylic moiety.[53] MO calculations are in agreement with this regioselectivity.



(**44**)



(**45**)

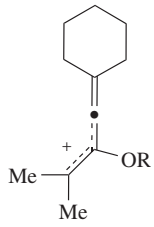


$R^1 = H, R^2 = Me$

(**46**) $R^1 = Me, R^2 = H$

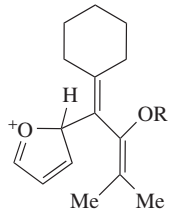
The competing pathways in the reactions of intermediate 1-alkylidene-2-oxyallyl cations (**47**) with furan have been investigated.[54] Cycloaddition pathways compete with the electrophilic substitution pathway which initially forms the cation (**48**) from which a number of products may form.

Recent progress in the palladium-catalysed direct arylation of simple arenes involving both intra- and inter-molecular reactions has been reviewed.[55] The review includes a mention of mechanistic aspects. A new Pd^{II}-catalysed method for the direct 2-arylation of indoles and pyrrole has been reported.[56] This $IMesPd(OAc)_2$-catalysed

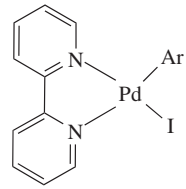


R = Me or $SiMe_3$

(**47**)



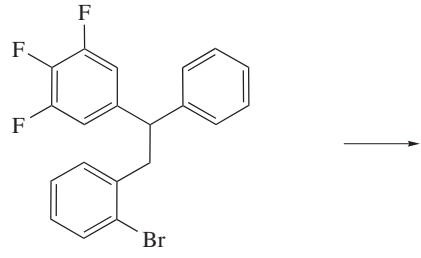
(**48**)



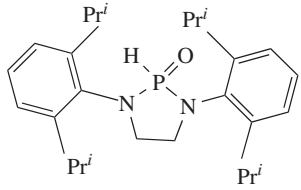
(**49**)

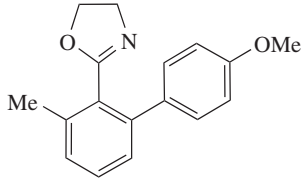
reaction with $[Ph_2I^+][BF_4^-]$ gave regioselectively 2-substitution; the $[Ph_2I^+][BF_4^-]$ could be prepared *in situ* from $PhB(OH)_2$ and $PhI(OAc)_2$. It is believed that initial electrophilic palladation at C(3) is a key step in these reactions.

The reaction of an aryl(iodo)palladium(II)(bpy) complex (**49**) with 2,3-dibromothiophene in the presence of $AgNO_3$–KF gives arylation at C(5).[57] It is suggested that electrophilic palladation, activated by the $AgNO_3$–KF, followed by reductive elimination, occurs. An experimental and theoretical study of some palladium-catalysed intramolecular arylation reactions, including the observation that (**50**) cyclizes mainly to (**51**), precludes an S_EAr mechanism and indicates that proton abstraction by a carbonate or related ligand occurs in the step which determines selectivity.[58] Aryl tosylates have been shown to be arene arylating reagents in the presence of an optimized ruthenium catalyst and potassium carbonate in *N*-methylpyrrolidinone.[59] The catalyst is prepared *in situ* from $RuCl_2(p\text{-cymene})_2$ and (**52**) and could, for example, catalyse the reaction between 2-oxazolinyltoluene and 4-methoxyphenyl tosylate to give (**53**).



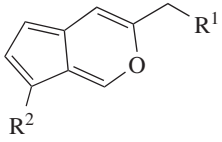
(**50**) (**51**)



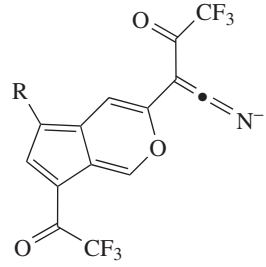


(**52**) (**53**)

The dehydrative acylation of arenes by carboxylic acids has been investigated with a range of Lewis and Brønsted acid catalysts at high temperatures. $Eu(NTf)_2$ shows the best performance at 250 °C and catalyses efficiently the acylation of alkyl- and alkoxybenzenes by aliphatic and aromatic carboxylic acids.[60] $HNTf_2$ is also a useful reagent, catalysing the acylation of anisole in refluxing toluene by carboxylic acids with azeotropic removal of water. Cyclopenta[*c*]pyran-3-yl derivatives (**54a–c**) are acylated by trifluoroacetic anhydride to form the 7-(trifluoroacetyl)cyclopenta[*c*]pyrans, although (**54d**) is the main product from (**54b**).[61] Compound (**54e**), formed from (**54c**), readily undergoes further reaction to form the anions (**55a**) and (**55b**).



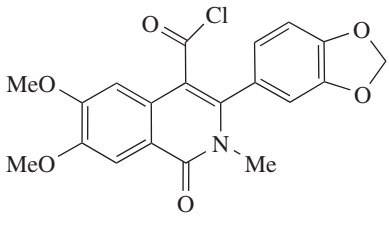
(**54**) **a**; $R^1 = CO_2Me$, $R^2 = H$
b; $R^1 = CH_2OH$, $R^2 = H$
c; $R^1 = CN$, $R^2 = H$
d; $R^1 = CH_2COCF_3$, $R^2 = COCF_3$
e; $R^1 = CN$, $R^2 = COCF_3$



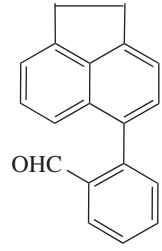
(**55**) **a**; R = H
b; R = $COCF_3$

Details of the sequence of steps in the thionyl chloride-mediated transformation of 4-carboxy-3,4-dihydro-3-phenyl-1(2*H*)-isoquinolines into indeno[1,2-*c*]isoquinolones have been elucidated[62] and it is confirmed that the dehydrogenation precedes the electrophilic cyclization [of (**56**)].

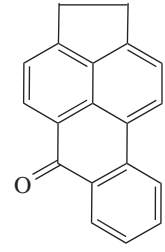
Intramolecular acylation in suitable aromatic aldehydes occurs in the presence of IPy_2BF_4 and HBF_4 to form benzocyclic ketones.[63] For example, (**58**) can be formed by cyclization of (**57**) in 74% yield. Two plausible mechanistic pathways have been suggested.



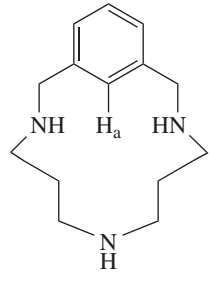
(**56**)



(**57**)



(**58**)



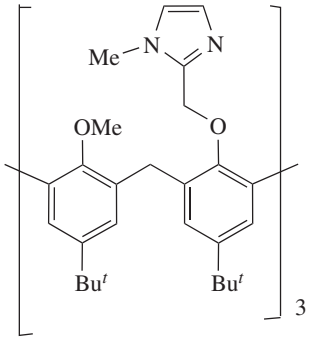
Other Reactions

Recent experimental developments in coupling IR spectroscopy techniques with mass spectrometry, which allow the structural characterization of isolated and microsolvated protonated aromatic molecules in the gas phase have been summarized.[64] Hydrogen–deuterium exchange has been observed at H_a in (**59**) and some closely related substrates when this ligand is complexed to Cu^I in [$^2H_6$]acetone.[65] The process is finely controlled by the precise coordination distance required to form agostic interaction between Cu(I) and the C–H bond and is believed to involve the enol form of [$^2H_6$]acetone and a reversible Cu(I) to Cu(III) interconversion.

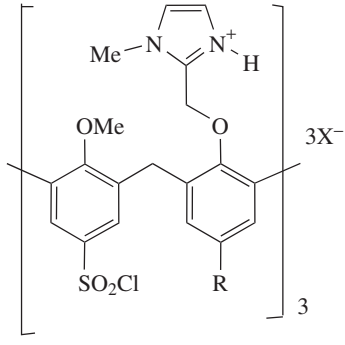
Kinetic data for the *ortho* position azo coupling of substituted benzenediazonium cations with three activated naphthalene derivatives give good correlations with Hammett σ-values of the substituents[66] and the data indicate a transition state near in energy to that of the Wheland intermediate.

MO calculations[67] on the trimethylsilylation of pyrrole and *N*-alkylpyrroles have been reported in full and studies of sulfonation by SO_3 also pursued. Suggestions are made to reconcile the predictions as to regioselectivity with the experimentally observed β-substitution in the reactions.

Studies of the chlorosulfonylation of calix[6]arenes have indicated the importance of *ipso* substitution involving displacement of Bu^t groups.[68] When alternate OH substituents at the small rim are *O*-alkylated by a protonatable imidazole group (**60**), the units containing a methoxy group can be selectively chlorosulfonyldealkylated at room temperature [to give (**61a**)] and further reaction [to give (**61b**)] can take place at higher temperature.



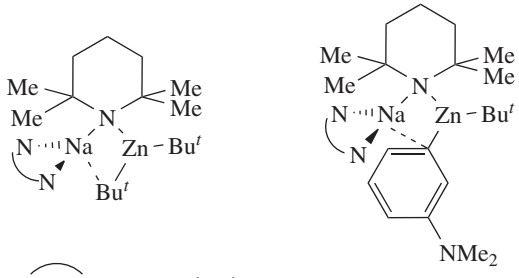
(**60**)



(**61**) **a**; R = Bu^t
b; R = SO_2Cl

Studies of the reactivity of 4,6-dinitrobenzofuroxan with substituted indoles have been mentioned above.[49]

Some reactions involving organometallic species are of interest. Protonation[69] of (ArN=CMe–CMe=NAr)$PtPh_2$ complexes yields Pt(II)phenyl–π-benzene complexes in non-coordinating solvents. The Pt(II) species undergo dynamic exchange processes involving C–H bond cleavage reactions probably involving Pt(IV) hydridodiphenyl



N N = N, N, N′, N′ — tetramethylethylenediamine

(**62**) (**63**)

intermediates giving large kinetic isotope effects. DFT calculations[70] have shown that intramolecular hydrogen bonding to acetate can provide a low energy pathway to C–H activation of some aromatic systems with iridium where a {Cp*Ir(I)} moiety gives electrophilic activation of C–H bonds. The heterometallic species (**62**) induces *meta* deprotonation of *N*,*N*-dimethylaniline, causing *meta* zincation to (**63**) and giving a proposed route to *meta*-substituted derivatives.[71] The reagent can also effect dizincation and monozincation of naphthalene at the 2,6- and 2-positions, respectively.[72]

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CHAPTER 7

Carbocations

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Introduction

Developments in the study of carbocations in superacid media over the past 30 years have been reviewed.[1] The thermodynamics [ΔG(g)] of the reaction $R^+(g) + R_{ref}OH(g) \rightarrow ROH(g) + R^+_{ref}(g)$ involving $R_{ref} = t$-butyl and 21 R^+ has been studied by high-level computation.[2] A plot of ΔG(g) versus ΔG(solution) shows an excellent correlation, except for phenyl-substituted R^+, which form a separate correlation family. The magnitude of the most positive surface electrostatic potential was proposed as an effective measure of the stability of gas-phase carbocations, with results presented for a number of structurally diverse cations.[3] The electrostatic potential directly

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addresses the issue of charge delocalization in the cation, and also relates carbocation stability solely to the properties of the ion, without the need to bring in other reference molecules. Density functional calculations of energy barriers for degenerate 1,2-shifts in long-lived carbocations were reported.[4] When the shift involved a hydrocarbon migrant, there was good agreement with experimental data. Deviations were observed in the case of hydrogen and migrants containing heteroatoms and possible explanations presented. The effect of electrostatic interactions in stabilizing certain conformations of cations was reviewed.[5] These conformational biases, along with stereoelectronic effects, were proposed to be controlling factors in determining the stereoselectivity of reactions involving carbocations.

A review appeared discussing the development and use of superacids, with extremely high acidities in excess of many billion times that of concentrated sulfuric acid.[6] The high acidity and extremely low nucleophilicity have made it possible to prepare in solution long-lived carbocations previously only considered as reactive intermediates. A critical analysis of the use of multi-parameter correlations of solvent effects on solvolytic reactivity appeared.[7] It was suggested that some mechanistic conclusions are unreliable due to systematic errors caused by compensation effects and by comparisons between dissimilar processes. A review commentary considered recent findings of relevance to the mechanism of nucleophilic substitution reactions.[8] Assigning a unimolecular ionization mechanism when racemization is experimentally observed was suggested to be flawed. Front-side bimolecular substitution can occur, especially with larger alkyl groups and with good leaving groups. The use of weakly coordinating anions $[Al(OR^F)_4]^-$ [$R^F = C(H)(CF_3)_2$, $C(CF_3)_3$] as counterions for the preparation of cation salts was reviewed.[9] Carbocations that have been prepared and structurally characterized include C^+X_3 (X = Br, Cl) and $C^+(Br)(SBr)_2$. The mechanisms of bioactivation of modulators of estrogen receptors were reviewed.[10] Various electrophilic intermediates have been identified in these reactions, including carbocations and quinone methides.

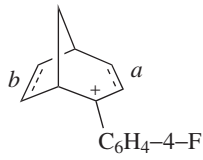
Alkyl and Cycloalkyl Carbenium Ions

A detailed kinetic study of the alkylation of benzene and alkylbenzenes by 1-adamantanol in sulfuric acid solutions was reported.[11] The data clearly point to the 1-adamantyl cation as the intermediate alkylating species. A series of protonated epoxides and their ring-opened cations $R_2C^+–CR'_2OH$ were investigated by a variety of computational methods, with the conclusion that the density functional B3LYP method provides poor agreement with methods such as MP2 and CCSD.[12] The mechanism of the degenerate 1,5-hydride shift in 2,6-dimethyl-2-heptyl cations was investigated by computational methods.[13] In addition to the two equivalent acyclic cations, the potential energy surface consists of a third minimum corresponding to a symmetrically μ-hydrido-bridged carbocation. Incorporation of solvent effects results in good agreement with experiment, for both the relative energies of the minima, and also the energy barriers separating them. The mechanism of the hydroxylation of simple alkanes by hydrogen peroxide in strong acid, investigated by density functional theory, was proposed to involve hydride transfer from the alkane to the superelectrophilic

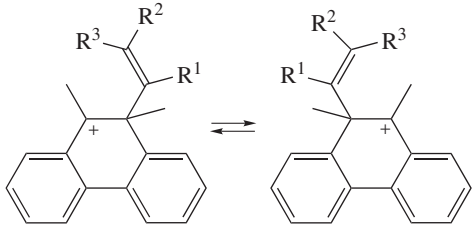
$HO–OH_2^+$.[14] This reaction forms two water molecules and a carbenium ion, which is then hydrated to form the protonated alcohol. The degenerate gas-phase reactions between HF and protonated alkyl fluorides RFH^+ (R = Me, Et, *i*-Pr, *t*-Bu) were investigated by *ab initio* methods.[15] With the exception of $MeFH^+$, the protonated alkyl fluorides can be viewed as weak complexes of the carbocation R^+ and HF. Both frontside and backside substitutions occur, supporting the proposal (see Introduction)[8] that nucleophilic substitution reactions are better understood through such a competition as opposed to the traditional S_N1/S_N2 competition.

Benzyl Cations

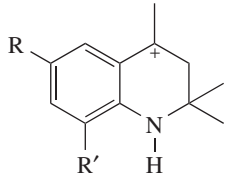
Cations (**1**)–(**3**) were observed in superacid upon addition of the appropriate alcohol precursors.[16] Characterization by NMR and product analysis, combined with quantum chemical calculations, indicates that (**3**) has bishomoantiaromatic destabilization. Kinetics of the degenerate vinyl rearrangement of (**4**) to (**5**) (R^1, R^2, R^3 = H or methyl) were studied by dynamic NMR spectroscopy.[17–19] The presence of methyl groups in certain locations on the migrating vinyl group was shown to have a significant effect on the rate of migration. Two papers appeared discussing the formation of (**6**) by photoprotonation of 1,2-dihydroquinoline precursors in water and alcohol solvents.[20,21] The cation (**6**) was observed with laser flash photolysis, and the kinetics of its further reactions were investigated. Photolysis of stilbenes in CF_3CH_2OH and $(CF_3)_2CHOH$ results in addition of the solvent across the double bond.[22] The proposed mechanism involves initial photoprotonation to form the cation $ArCH^+–CH_2Ar'$. Transients identified as such cations were observed upon laser flash photolysis in $(CF_3)_2CHOH$. Chiral benzylic-type cations (**7**, various Ar) were obtained by acid treatment of the corresponding alcohol at low temperature, and observed to alkylate electron-rich aromatics Ar′H to give products (**8**) with high facial diastereoselectivity.[23] This was



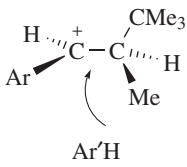
(**1**), *a* = *b* = C–C
(**2**), *a* = C=C, *b* = C–C
(**3**), *a* = *b* = C=C



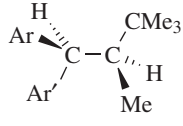
(**4**) (**5**)



(**6**)



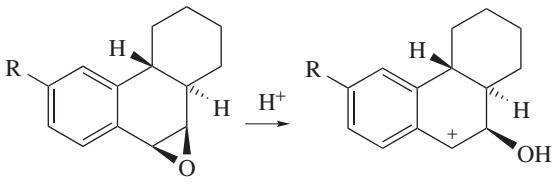
(**7**)



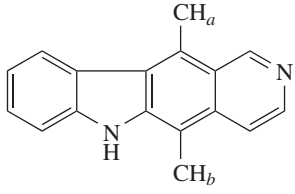
(**8**)

proposed to arise via reaction of Ar′H from the side opposite the *t*-butyl group in the favoured conformation (**7**).

Naphthyl-1-methyl carbocations bearing dimethylamino and methoxy groups at positions 4 and/or 5 were obtained by treatment of the corresponding alcohol with acids, and the products of their subsequent reactions (mainly oligomers) determined.[24] The acid-catalysed hydrolysis of the epoxide (**9**), and its diastereomer with the epoxide on the opposite face, were shown by azide trapping experiments to proceed via free carbocations [e.g. (**10**)].[25] The lifetimes of these cations in water is of the order of 10 ns. A mechanistic study of the TiO_2-photosensitized oxidation of indane and some 1-hetero analogues appeared.[26] The proposed mechanism involved several steps, with the product-forming intermediate being a benzylic carbocation formed by oxidation of the corresponding radical. Energy decomposition analysis based on density functional calculations was performed on a series of *ortho*-, *meta*-, and *para*-substituted benzylic cations.[27] A reasonable correlation with Hammett σ and σ^+ constants was observed, especially for substituents with π-electrons. A computational study of benzyl cations substituted with substituents normally recognized as being π-accepting revealed that there was also a weak π-donating effect, in the order p-NO_2 < p-CHO < p-CN ≪ p-Cl.[28] Ellipticine (**11**), a potent antineoplastic agent, forms covalent DNA adducts upon oxidation by cytochromes P450 and peroxidases. Two carbenium ions, ellipticine-12-ylium (**12**$^+$) and ellipticine-13-ylium (**13**$^+$), were proposed as reactive intermediates.[29,30]



(**9**), R = MeO (**10**)

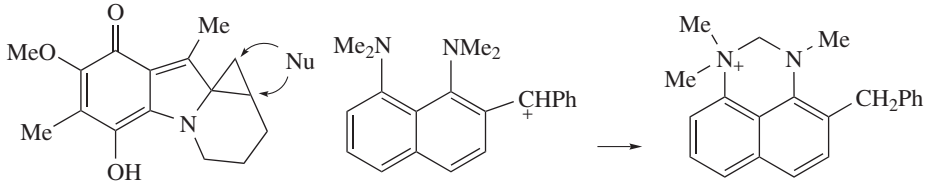


(**11**), $a = b = 3$
(**12**$^+$), $a = 2$, $b = 3$
(**13**$^+$), $a = 3$, $b = 2$

Quinone Methides

o-Quinone methides with both electron-withdrawing and electron-donating substituents were studied by a combination of flash photolysis and product analysis, in the presence of various nucleophiles including nucleosides.[31] Electron-withdrawing substituents significantly increase the reactivity of the quinone methide, and at the same time increase the stability of products, for example with nucleosides, since the reverse reaction regenerating the quinone methide is retarded. UV irradiation of racemic binaphthol derivatives results in quinone methides that were observed by laser flash photolysis.[32] These quinone methides react with L-proline in a highly stereospecific manner to give adducts with >99% diastereoselectivity; these adducts can be further elaborated to single enantiomer binaphthol ligands. Radical formation from 3,5-di-*t*-butyl and

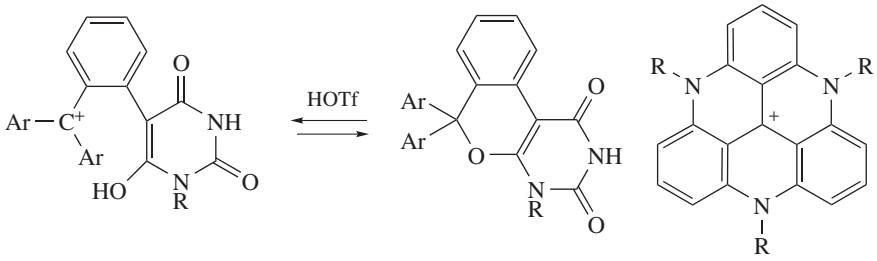
3,5-dimethoxy-4-hydroxycinnamic acids results in stable dimeric *p*-quinone methides with strong visible absorbance.[33] The cyclopropyl quinone methide (**14**) is formed by elimination of a leaving group from the hydroquinone.[34] Reactions with nucleophiles occur at the cyclopropyl group (as shown), rather than in the classic manner of quinone methides, i.e. at the C=C. Study of the products obtained with the diazoparaquinone antibiotics upon reductive activation led to the proposal of an *o*-quinone methide as a key intermediate.[35] A reduced form of a fluoromethylnaphthoquinone eliminates HF giving an *o*-quinone methide, that functions as an irreversible suicide inhibitor of glutathione reductase.[36]



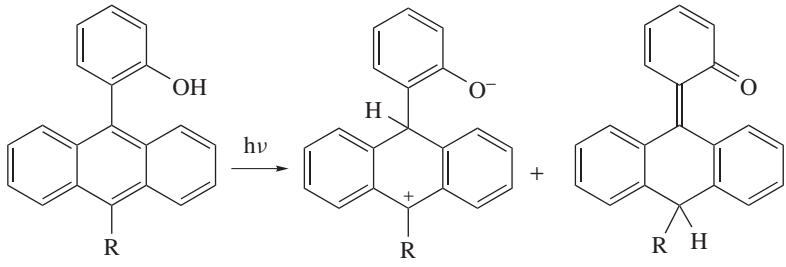
(**14**) (**15**) (**16**)

Benzhydryl, Trityl, and Fluorenyl Cations

Recent advances in the chemistry of triaryl- and triheteroaryl-methanes were reviewed. A significant portion of the review considered carbocations.[37] Cation (**15**) was observed in acidic solutions.[38] This cation rearranged to (**16**) via an initial shift of hydride from one of the methyl groups of the NMe_2 group adjacent to the carbocation centre, followed by cyclization of the neighbouring NMe_2 onto the CH_2^+ so-formed in the hydride transfer. Reaction of benzophenone derivatives with 5-phenylbarbituric acids in the presence of triflic anhydride leads to regioselective formation of *ortho*-substituted products, the triaryl cation (**17**) when Ar is 4-$Me_2NC_6H_4$ and the cyclic ether (**18**) when Ar has less electron-donating substituents.[39] The cyclic ethers are converted to the cation upon treatment with strong acids. Highly stable cations [(**19**), R = $(CH_2)_n$Me, n = 2, 5, 7], with pK_{R^+} higher than 20, were shown to be useful as novel phase-transfer catalysts for several classical organic reactions.[40] The stability of the cation under basic/nucleophilic conditions renders this novel use feasible. Photolysis of anthracene derivatives (**20**) in aqueous acetonitrile results in two intermediates arising by (formal) excited state intramolecular proton transfer, the zwitterionic cation (**21**) and the quinone methide (**22**).[41] These intermediates were observed with laser flash photolysis. The radical cations of the sulfides Ph_3CSPh and $Ph_2C(Me)SPh$ cleave the central C–S bond producing the carbocations Ph_3C^+ or Ph_2C^+Me and the SPh radical.[42] This process has been observed with laser flash photolysis and rate constants for the cleavage process determined. Photolysis of 3-(2,2,2-triphenylethoxy)-3-chlorodiazirine gives 2,2,2-triphenylethoxychlorocarbene (Ph_3CCH_2–OC–Cl), which undergoes heterolytic fragmentation with 1,2-phenyl migration concomitant with loss of CO and chloride.[43] This results in the cation $Ph_2C^+CH_2Ph$, followed by proton loss to give Ph_2C=CHPh. Very fast (ps, fs) laser flash photolysis reveals that 25% of the cation arises directly from the excited diazirine precursor, rather than the



(**17**) (**18**) (**19**)



(**20**) (**21**) (**22**)

carbene. Using the 'cation pool' method, diarylcarbenium ions have been generated by anodic oxidation of diarylmethanes.[44] The thus-generated cations react with various nucleophiles including allylsilanes, ketene silyl acetals and aromatic compounds in a synthetically useful manner. 9-Phenanthryl-type carbocations were proposed as intermediates in a complex transformation of the natural product benaphthamycin B, with support from quantum chemical calculations.[45]

Carbocation Reactivity–Quantitative Studies

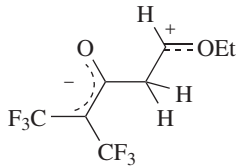
A review by Mayr and Ofial of the reactivity–selectivity principle included a number of examples of carbocation–nucleophile combinations.[46] The conclusion was reached that a decrease in selectivity with increasing reactivity is expected only if diffusion control has been reached. In general, however, selectivity cannot decrease with increasing reactivity. Mayr's group showed that nucleophilicity parameters N derived from the rate constants for carbocation–nucleophile combinations also hold for S_N2 reactions.[47] The result is a general equation for polar reactions, $\log k = s_E s_N(E + N)$, where s_E and s_N are electrophile- and nucleophile-specific slope parameters and E and N are electrophilicity and nucleophilicity parameters. This equation includes as special cases the Swain–Scott equation, the Ritchie single parameter relation, and the Mayr equation developed for carbocations, $\log k = s_N(E + N)$ (since $s_E \approx 1$ for carbocations). Back-to-back papers appeared discussing a quantitative nucleofugality scale.[48,49] The analysis, presented in the first paper, was based on the kinetics of S_N1 ionization of benzhydryl derivatives; the second paper extended the discussion to other types of substrates. The data were correlated by the equation $\log k_{sol} = s_f(N_f + E_f)$,

where k_{sol} is the rate constant for ionization of R–X, E_f is an electrofuge-specific parameter dependent on R, and s_f and N_f are nucleofuge-specific parameters dependent on X and, importantly, also on the solvent. Since $s_f \approx 1$, rate constants for solvolysis reactions can be estimated knowing the values of N_f and E_f. The three-parameter relation for k_{sol} presented above was re-evaluated by Bentley, who proposed additivity methods for obtaining E_f and N_f parameters that avoided multi-parameter optimizations.[50]

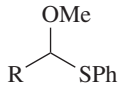
The kinetics of the reactions between benzhydrylium ions and 11 carbanions (nitronates and malonates) led to the determination of nucleophilicity parameters N and s for the latter.[51] The N parameters show poor correlations with the acidity constants of the conjugate CH acids, and also with Hammett σ^- constants. Nucleophilicity parameters were determined for a series of substituted indoles,[52] and for the azide ion in different alcohol solvents.[53] A study of the kinetics of the gas-phase combinations of benzhydrylium cations with amine nucleophiles concluded that the Mayr equation, $\log k = s(E + N)$, determined in solution also applies in the gas phase, albeit with different electrophilicity and nucleophilicity parameters E and N.[54] The electrophilicity parameters E show a good correlation with those determined in solution, although the sensitivity to substituent change is considerably attenuated in the gas phase. A detailed review analysed the mechanism and kinetics of carbocationic polymerization.[55] An attempt was made to explain the 10^4–10^5-fold discrepancy between propagation rate constants measured using (a) polymerization rates and (b) competition kinetics, where there is an assumption of diffusion limit trapping with nucleophiles. Kinetic hydrogen isotope effects were determined by computational methods for several identity hydride transfers involving carbenium ions, for example the hydride transfer between CF_3H and CF_3^+, and the intramolecular hydride transfer in HCF_2–CF_2^+.[56] Correlations of the rates of solvolysis with solvent parameters show that 1- and 2-naphthoyl chlorides react by an ionization mechanism via an acylium ion intermediate.[57]

Oxonium Ions

The zwitterion (**23**) was observed during the 2 + 2-cycloaddition reaction of the ketene $(CF_3)_2C{=}C{=}O$ and $CH_2{=}CHOEt$.[58] Thioacetal (**24**) reacted at low temperature with electrochemically generated (**25**) to give the cation (**26**), which was observed by NMR, and employed in synthetically useful reactions, e.g. with allyltrimethylsilane.[59] The HCl-induced ring-opening reactions of (**27**) were explained by a competition between initial protonations at oxygen (a) leading to the cation (**28**) and carbon (b) leading to the cation (**29**).[60]



(**23**)



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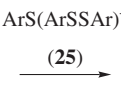
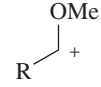
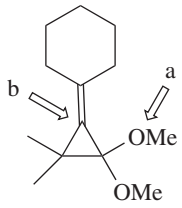
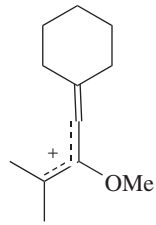




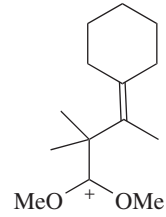
(**26**)



(**27**)



(**28**)



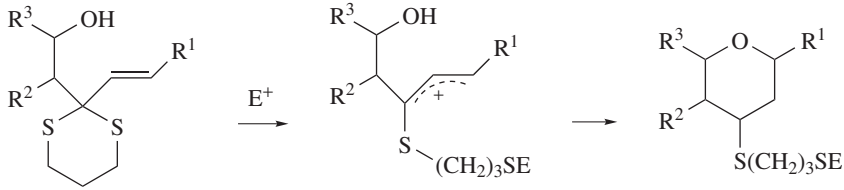
(**29**)

Conformational analysis of the arabinofuranosyl carbenium ion led to a model where the conformation was locked such that nucleophiles approached with a high selectivity from the β face.[61] This prediction was borne out by synthesis, where excellent β selectivities with a variety of nucleophiles were observed. In conjunction with a systematic study of the *C*-glycosylations of mannose derivatives, conformational preferences of the intermediate oxocarbenium ions were investigated, along with the energetics of the transition states for nucleophilic addition to these cations.[62] In a similar study, the stereoselectivity of the reactions of cyclohexanone acetals with thiophenyl groups (and other heteroatoms) was examined both experimentally and through computation.[63] The *trans* selectivities were explained by the reactions of oxocarbenium ions, without the need to invoke episulfonium ions. In yet a further related paper, the nucleophilic substitution reactions of 4-substituted cyclohexanone acetals were examined, with the results being explained by the electronic nature of the 4-substitutent, and its preference for either the equatorial or axial position in the intermediate oxocarbenium ion.[64] Stereoselective glycosylations were achieved by employing a chiral auxiliary at C(2) of a glycosyl donor.[65] The mechanism proposed involved *trans*-fused or *cis*-fused dioxolenium ion intermediates, the nature of the fusion being controlled by the stereochemistry in the chiral donor. Density functional theory was employed to address the origin of stereoselectivity in intramolecular Diels–Alder reactions of vinyl oxocarbenium ions.[66] Torsional steering, the preference for the staggered conformation about incipient σ-bonds, was found to determine the preferred transition states. Isotopic labelling experiments led to a mechanism for the racemization in Prins cyclization that involves an oxocarbenium ion intermediate undergoing a reversible oxonia-Cope rearrangement prior to nucleophilic capture.[67] 5′-Hydroxy-*N*′-nitrosonornicotene undergoes decomposition in the presence of 2′-deoxyguanosine to give products with the nucleoside that are consistent with an oxocarbocation that reacts as an onium ion and a carbenium ion.[68] A mechanistic study of the reversible oligomerization of cyclophane formaldehyde acetals concluded that the ring fusion/ring fission processes involve oxonium ion intermediates undergoing S_N2 reactions.[69] The alternative pathway involving carbenium ions generated by S_N1 cleavage of oxonium ions is not consistent with the experimental data.

Carbocations Containing Sulfur

The stabilization of carbocations by sulfur was studied by computational methods, and compared using isodesmic reactions to the stabilization by oxygen, fluorine,

and chlorine. Sulfur substitution stabilizes carbocations similar to oxygen, whereas halogen substitution leads to destabilization.[70] The intermediate $ArS^+(OE)CH_2R$ in the Pummerer reaction of sulfoxides $ArSOCH_2R$ with electrophiles E^+ fragments the CH_2–R bond to form the carbocation R^+ when R^+ is a very stable carbocation ($pK_R{}^+ > 14.5$).[71] A review of the Pummerer reaction has emphasized modern applications.[72] Many of these take advantage of the sulfur-stabilized carbocation intermediate, and the possibility of reacting this with various nucleophiles in both inter- and intra-molecular reactions. Thioacetals (**30**) react with electrophiles to give cyclic ethers (**32**).[73] The proposed mechanism involves an initial ring opening of the acetal to give the allylic sulfur-stabilized cation (**31**) that undergoes an intramolecular reaction with the neighbouring OH group, forming a six-membered ring as opposed to a four-membered ring.

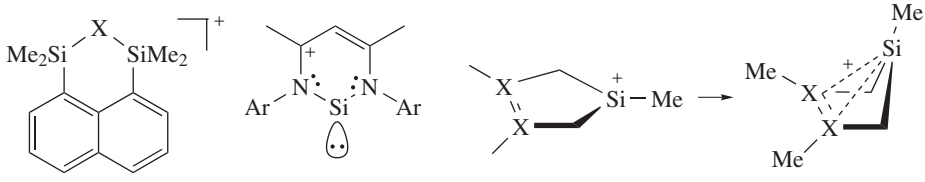


(**30**) (**31**) (**32**)

Carbocations Containing Silicon

The novel bridged disilyl cations (**33**), X = H, F, were synthesized as their $B(C_6F_5)_4{}^-$ salts and characterized by NMR and X-ray methods.[74] In both cations the Si–X–Si linkage is symmetrical, corresponding to a single minimum potential. The novel cation (**34**), Ar = 2,6-^{i}PrC$_6$H$_3$, with a formal divalent silicon was obtained as a $B(C_6F_5)_4{}^-$ salt.[75]

Bishomoaromatic stabilization energies [(**35**) → (**36**)] were obtained by computational methods; this study was part of a paper describing the experimental preparation of a zwitterionic analogue of such compounds (i.e. where X is boron).[76]

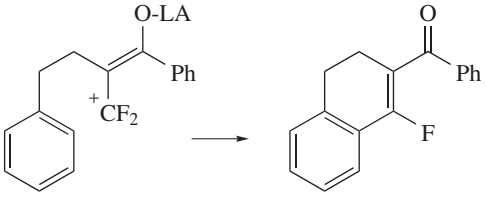


(**33**) (**34**) (**35**), X = C, Si (**36**)

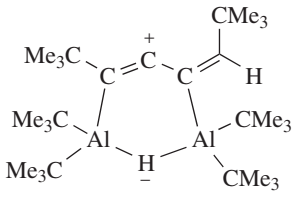
Halogenated Carbocations

The cations CH_2I^+ and CD_2I^+ were observed in the gas phase, and their electronic spectra recorded.[77] Quantum chemical calculations for semibullvalene bromination

show that the reaction involves concerted bromine addition and cyclopropane ring opening to form an allylic cation, without the intermediacy of either a bromonium ion or a cyclopropylcarbinyl cation.[78] Under treatment with a Lewis acid (LA), 2,2-difluorovinyl ketones bearing an aryl group form carbocations [e.g. (**37**)] stabilized by α-fluorines.[79] These cations undergo Friedel–Crafts cyclization to give, after ketonization and loss of fluoride, dihydronaphthalenes such as (**38**).



(**37**) (**38**)



(**39**)

Carbocations Containing Other Heteroatoms and Metals

The interesting zwitterionic compound (**39**) with the cationic component a butadien-2-yl cation was obtained by reaction of 1,4-di(*t*-butyl)butadiyne with 2 mol of di(*t*-butyl)aluminium hydride, with the structure being established by X-ray analysis.[80] The reactions of the 1,2-diferrocenyl-3-(methylthio)cyclopropenylium ion with carbanions derived from active methylene compounds were investigated.[81] Products were derived by ring opening of the cyclopropene ring after the initial carbanion addition. The bis(ferrocenylethynyl)phenylmethylium cation $(Fc–C{\equiv}C–)_2C^+Ph$ (Fc = ferrocenyl) was prepared.[82] This cation proved to be much less stable than its bis-ethenyl analogue $(Fc–CH{=}CH–)_2C^+Ph$.

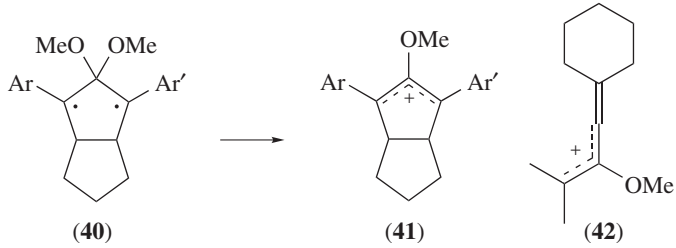
Carbocations in Zeolites and Other Materials

The following papers relate to carbocation-mediated reactions catalysed by zeolites and other solid-state catalysts where the paper places a clear emphasis on mechanism, moreover, a mechanism with a carbocationic intermediate. Zeolite-catalysed reactions of *n*-butane, investigated through ^{13}C labelling, were rationalized in terms of rate-limiting hydride transfer between an initiating carbenium ion and the parent *n*-butane.[83] Methanol is converted to hydrocarbons over zinc iodide at high temperature, with the highly branched alkane being formed with high selectivity.[84] A mechanistic study, including various labelling experiments, proposed various carbocationic intermediates being formed through the methylation of alkenes. Gas-phase multiply methylated benzenium ions fragment by both loss of H_2 and loss of methane, the latter being the dominant process for higher homologues.[85] This latter finding is consistent with a proposed reaction cycle in the mechanism of the zeolite-catalysed conversion of methanol to hydrocarbons. Density functional computations and explicit-contact modelling were employed to investigate the mechanisms of β-scissions of chemisorbed carbenium ions, e.g. $C_5H_{11}^+ \rightarrow C_2H_5^+ + C_3H_6$.[86] Density functional theory was

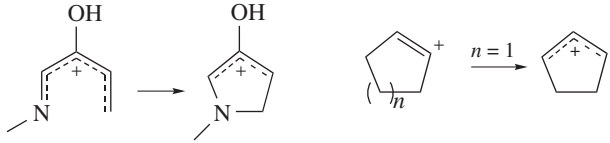
employed to model the role of carbonium and carbenium ions in acid-catalysed hydrocarbon conversions that occur over phosphotungstic acid.[87,88]

Allylic Systems

The singlet diradical (**40**), obtained by photolysis of a diazo precursor, was found to undergo C−OMe bond heterolysis in methanol to produce the allylic cation (**41**).[89] Transient signals assigned to both the diradical and the cation were observed with laser flash photolysis. The gas-phase cyclobuten-3-yl cation was reacted with amine bases to give cyclobutadiene and with electron donors to give the cyclobuten-3-yl radical.[90] The success or failure of these reactions, depending on the strength of the amine or electron donor, led to the experimental determination of the proton affinity of cyclobutadiene (undergoing protonation to form the cyclobuten-3-yl cation), and the ionization potential of the cyclobuten-3-yl radical (losing one electron to form the cyclobuten-3-yl cation). An (alkylidene)allyl cation $R_2C{=}C^+{-}CH{=}COR'$ was generated by Lewis-acid mediated ring-opening of the (alkylidene)cyclopropanone acetal.[91] Reaction with (siloxy)alkenes gave products that are the results of nucleophilic addition to the sp^2 centre of the cation, with no sign of nucleophilic addition at the *sp* centre. The oxyallyl cation (**42**) was obtained as an intermediate by acidic ring opening of an alkylidenecyclopropane acetal; this cation reacts with furan to give 3 + 2- and 4 + 3-cycloadducts, in addition to an electrophilic substitution product.[92] Photolysis of cinnamyl acetates $ArCH{=}CHCH_2OAc$ (Ar = 3- and 4-$MeOC_6H_4$) in methanol solvent results in high yields of the ether products $ArCH{=}CHCH_2OMe$ and $ArCH(OCH_3)CH{=}CH_2$.[93] The cinnamyl cation $ArCH{=}CHCH_2^+$ is proposed as the intermediate, the cation forming by C–OAc bond heterolysis in the singlet excited state. Treatment of α-alkylcinnamaldehydes with orthoesters, alcohols and thiols in the presence of BF_3 results in 1-alkoxy-2-alkylindenes.[94] Mechanistic studies suggest a sequence of reactions, with a γ-alkoxyallyl cation as the key intermediate. A computational scheme expressing the wavefunction in terms of Lewis structures was tested on the allyl cation, leading to a resonance energy of 63 kcal mol^{-1}.[95] Density functional theory was employed to investigate the Nazarov reaction, the cyclization of a 3-hydroxy- or 3-alkoxy-pentadienyl cation to a 2-hydroxy- or 2-alkoxy-cyclopentenyl cation.[96] Of particular interest were the factors that control the torquoselectivity of the cyclization. Computation predicts that the aza-Nazarov reaction (**43**) → (**44**) proceeds with high exothermicity and a modest activation barrier; several experimental examples were then examined, verifying the prediction.[97]



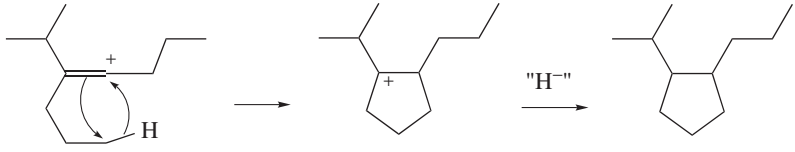
(**40**) (**41**) (**42**)



(**43**) (**44**) (**45**) (**46**)

Vinyl Cations

Photochemical solvolysis of cyclopentene-1-I^+Ph and 1-cyclohexene-1-I^+Ph gave products consistent with the formation of the geometrically destabilized C_5- and C_6-ring cations (**45**).[98] Allylic products derived from the cation (**46**) were also observed with the C_5-ring system. These were argued to arise from a 1,3-hydride shift. Protonated polyacetylenes, observed in 6 K neon matrices, were shown to have the structure $HC{\equiv}C(C{\equiv}C)_nC^+{=}CH_2$ by analysis of their electronic and vibrational spectra.[99] The protonation of arylethynyl halides or halogen addition to arylethynes was investigated through a computational study of the possible intermediates, an α-aryl-β-halovinyl cation, a β-aryl-α-halovinyl cation, a halogen-bridged cation, and a spirocyclic phenyl-bridged cation.[100] Except with strongly electron-withdrawing substituents in the aryl ring, the β-aryl-α-halovinyl cation is the cation of lowest energy. The addition of HCl to two buta-1,3-diyne units held in close proximity results in a double cyclization leading to dichloro-substituted cyclooctatetraenes.[101] A quantum chemical investigation of this process found several vinyl cations as energy minima. Vinyl cation (**47**), obtained by addition of the isopropyl cation to oct-4-yne, reacted in the presence of hydride donors to give cyclopentane (**49**).[102] The mechanism proposed involved a concerted cyclization–hydride transfer resulting in the tertiary cyclic cation (**48**).

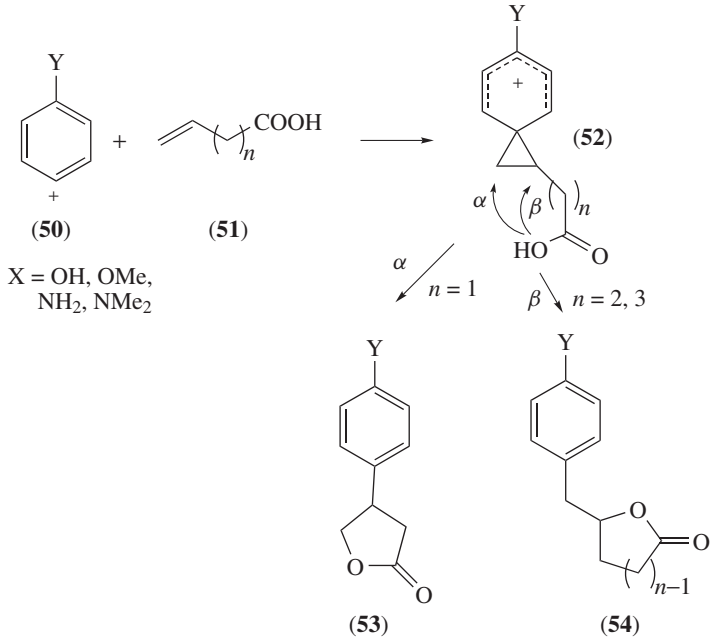


(**47**) (**48**) (**49**)

Aryl Cations

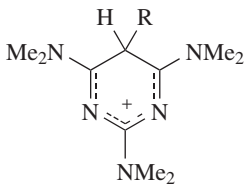
The parent phenyl cation has been prepared in an argon matrix at 30 K, and characterized by IR spectroscopy.[103] Co-deposition with nitrogen or carbon monoxide leads to a decrease in the IR signals for the phenyl cation, with new signals identified as being due to the products of addition of the diatomic nucleophiles, the benzenediazonium ion from N(2) or the benzoyl ion from CO. Nanosecond laser flash photolysis of neutral aqueous solutions of the quinolone antibacterial agent lomefloxacin and an 8-chloro analogue resulted in transients that, based on quenching by halide nucleophiles, were assigned to the aryl cations.[104] Such cations may be responsible for the photosensitivity of this class of compounds. The dediazoniation of the 4-nitrobenzenediazonium

ion in acidic methanol–water mixtures was shown to involve a competition between homolysis and heterolysis, the latter proceeding by way of an aryl cation.[105] Triplet aryl cations, obtained by acetone-sensitized irradiation of *o*-chlorophenyl allyl ethers, reacted to afford dihydrobenzofurans or chromanes through addition of the cation onto the tethered double bond either in 5-*exo* or 6-*endo* modes.[106,107] Aryl cations (**50**), obtained by photoheterolysis of various precursors in acetonitrile–water, reacted with carboxyalkenes (**51**) to afford lactones (**53**) or (**54**) in good yield.[108] A phenonium ion (**52**) was proposed as an intermediate.



Arenium Ions

A review summarized recent developments that have allowed the unambiguous structural characterization of arenium ions in the gas phase and under microsolvated conditions.[109] C(5)-substituted 2,4,6-trimethylaminopyrimidines undergo protonation at the N(1) position and also at C(5), the latter resulting in the arenium cation (**55**).[110] C(5) protonation is favoured over N(1) when R = alkyl, since the carbon protonation relieves steric congestion by pushing the alkyl group out of the plane of the aromatic ring. Cation (**56**), stabilized by palladium complexation, was obtained as its triflate salt, and characterized by NMR and X-ray methods.[111] A solution of $H_3O^+.CHB_{11}C_{11}^-$ in benzene was obtained.[112] IR spectroscopy suggests the formation of a trisolvated species $H_3O^+.3C_6H_6$ with the three OH bonds hydrogen bonded to the benzene π system, i.e. as π complexes. A combined theoretical and gas-phase experimental study of the nitration of monosubstituted aromatics led to the proposal of a general mechanism whereby the polar Ingold–Hughes mechanism and single electron transfer are



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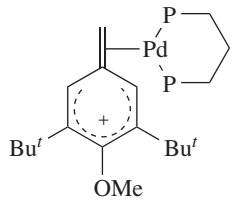
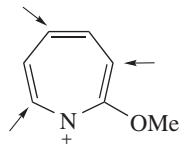


(**56**)



(**57**)

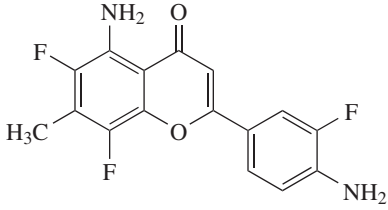
extremes of a continuum.[113] The fraction of each is determined by the ability of the aromatic compound to transfer an electron to the nitronium ion. A kinetic study of the electrophilic fluorination of aromatic compounds with NF reagents was reported.[114] The results are consistent with rate-limiting formation of an arenium ion. An example of a 1,2-hydrogen shift in this intermediate was also revealed. A study of gas-phase toluenium ions formed by protonation of perdeuterated toluene provided evidence for the occurrence of ring hydrogen shifts, in particular evidence for the interconversion of isotopomers bearing either one D-atom and one H-atom or two D-atoms on the tetrahedral ring carbon.[115] Benzenium ions bearing alkyl groups undergo carbon atom scrambling between ring carbons and the alkyl carbons.[116] A theoretical study into this reaction has revealed that it occurs via a ring expansion into a seven-membered ring. A quantum chemical investigation was reported into the mechanism of the Scholl reaction, an intramolecular dehydrogenative aryl–aryl bond formation of synthetic utility in the preparation of oligophenylene compounds.[117] The favoured mechanism involves ring protonation to form arenium ion intermediates, which react intramolecularly with neighbouring phenyl rings. The alkylation of phenol was investigated by density functional theory.[118] A phenolic ether is the most energetically favourable product, but under acidic conditions the alkyl group migrates via arenium ions to form *o*- and *p*-alkylphenols. A picosecond time-resolved resonance Raman investigation of the photodeprotection reaction of *p*-hydroxyphenacyl diethyl phosphate led to the proposal of a short-lived ion pair, with phenonium ion characteristics.[119]

Nitrenium Ions

The 2-methoxyazepinium ion (**57**), a nitrogen analogue of the tropylium ion, reacts with benzene to afford three products of electrophilic aromatic substitution (see arrows for position of attachment of phenyl ring).[120] The result has been rationalized in terms of kinetic control based on the π_{LUMO} of the cation. Laser flash photolysis was employed to investigate the reaction of the *N*-methyl-*N*-(4-biphenylyl)nitrenium ion with amino acids and protein.[121] The electron-rich aromatic amino acids tryptophan and tyrosine, the sulfur-containing methionine and cysteine, and the basic lysine, histidine, and arginine all reacted, in competition with the solvent water, as did several representative proteins. Using laser flash photolysis, the kinetics of the reaction of the 2-fluorenylnitrenium ion with 2′-deoxyguanosine were determined as a function of solvent.[122] Significant decreases in rate constant with decreasing solvent basicity were interpreted in terms of the importance of a hydrogen bonding

interaction in the transition state of the reaction. 2-Oxo-substituted arylazides such as 2-azidobenzaldehyde and 2-azidoacetophenone react with benzene in the presence of BF_3 forming acridines.[123] The proposed mechanism involves an arylnitrenium intermediate.

Aminoflavone (**58**), an anticancer agent with potent growth inhibitory activity, was proposed to be metabolically activated to two arylnitrenium ions derived from the two NH_2 groups present in the drug.[124] The mutagenic potency of a series of heterocyclic amines found in cooked meat was evaluated and compared with structural features obtained by quantum chemical methods.[125] One of the principal determinants of mutagenicity is the stability of the nitrenium ion. Azide trapping experiments show that 4′-X-4-biphenylyloxenium ions (X = H, Br, Me, MeO) are intermediates in the hydrolysis of 4-aryl-4-acetoxycyclohexa-2,5-dienones or *O*-(4-aryl)phenyl-*N*-methanesulfonylhydroxylamines.[126] With the assumption of diffusion control for the reaction with azide ion, the lifetimes of the cations in water range from 12 ns (X = H) to 18 μs (X = MeO). Various criteria suggest that the cations are more accurately described as 4-aryl-1-oxocyclohexa-2,5-dienyl carbocations. Phenoxonium cation (**59**), a vitamin E model, was obtained by treatment of the phenol precursor with $NO^+SbF_6^-$ in acetonitrile.[127] The crystal structure of the SbF_6^- salt showed bond lengths consistent with structure (**60**) as the major resonance contributor, with structure (**59**) of relatively minor importance (as also concluded in ref. 126). In a related paper, an electrochemical investigation of the oxidation of α-tocopherol and trolox led to the proposal of a mechanism involving the formation of an aryloxenium ion: carbenium ion intermediate.[128]



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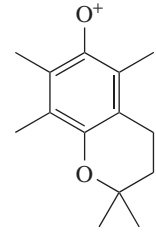
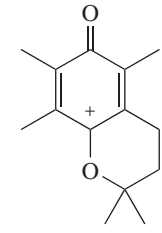


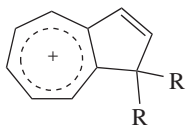
(**59**)



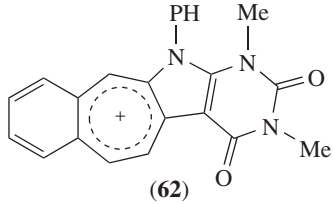
(**60**)

Aromatic Systems

Cations (**61**),[129] (**62**),[130] and (**63**)[131] were obtained as perchlorate or BF_4^- salts. The cations were characterized by NMR and X-ray methods; reduction potentials and pK_R^+ values were also determined. Density functional calculations were performed on the tropylium derivative (**64**), a number of substituted analogues, and a number of neutral systems.[132] The objective was to assess the utility of NICS (nuclear independent chemical shift) as a probe for detecting/sensing variation in aromaticity due to transannular $\pi-\pi$ interactions. A dicyanoheptafulvene has been prepared, with X-ray crystallographic analysis showing a significant contribution from the dipolar resonance contributor (**65**).[133] Addition of acid results in the tropylium



(**61**), R = Me, Et, Pr^n



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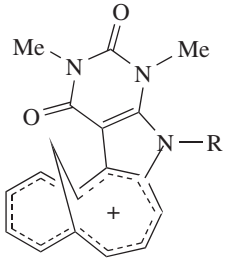
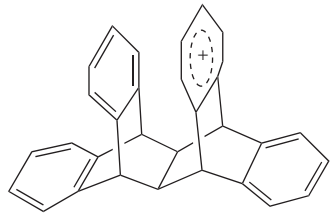
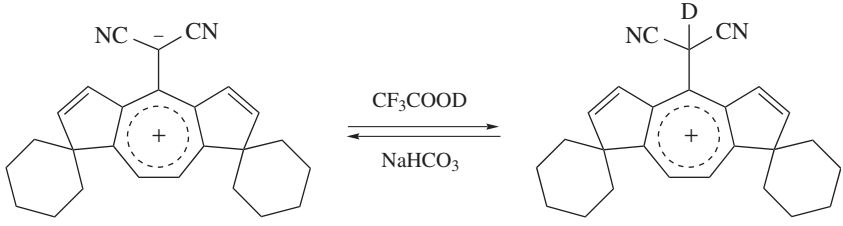


(**63**), R = Me, Ph



(**64**)

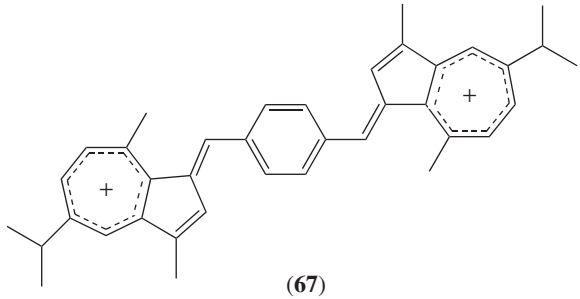


(**65**) (**66**)

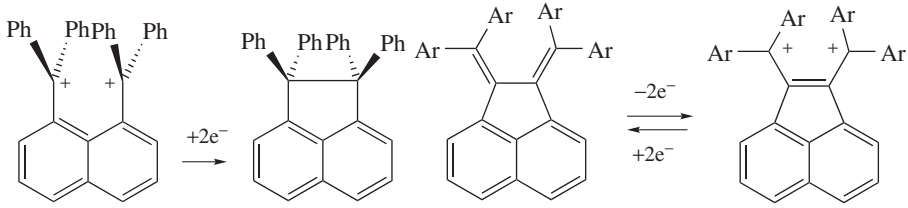
conjugate acid (**66**), which can be converted back to the zwitterionic form with base. The bis(diisopropylamino)cyclopropenium ion 2,3-$Pr^i_2C_3H^+$ undergoes an acid–base reaction with $KN(SiMe_3)_2$, whereby the hydrogen on the ring is lost.[134,135] The conjugate base is the bis(diisopropylamino)cyclopropenylidene carbene 2,3-$Pr^i_2C_3$:, and this can be isolated. Experimentally unknown monocyclic [11]annulenium ions were investigated by computational methods.[136] Six minima were located, four being aromatic, one non-aromatic, and the sixth a Mobius antiaromatic species. The antiaromatic properties of the cyclopentadienyl cation and its analogue with one silicon were addressed, along with a number of neutral and anionic analogues.[137] The objective was to evaluate the question of aromaticity through Pauling–Wheland resonance energies.

Dications

Isoprenoid acyclic polyene carbocations with 6, 14, and 18 π-electrons were synthesized.[138] Considering also previous data for carotenoid dications, an equation correlating λ_{max} (ranging from 400 to 1100 nm) and the number of sp^2 hybridized carbon atoms in the dication was developed. Dication (**67**) and an analogue with a different alkyl substitution pattern were prepared as PF_6^- salts.[139] These dications form

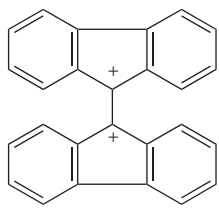


(**67**)

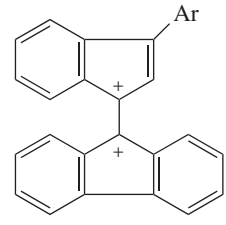


(**68**) (**69**) (**70**) (**71**)

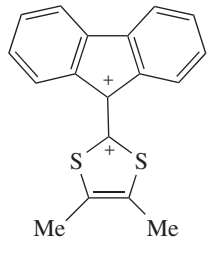
complexes with dibenzo-30-crown-10 and dibenzo-24-crown-8. The dication (**68**) exhibits an interesting two-electron reduction behaviour due to the close proximity of the two diarylmethyl cations, forming the acenaphthalene (**69**).[140] The dication is therefore an efficient two-electron oxidizing agent, for example, oxidatively coupling *N*,*N*-dialkylanilines at the *para*-position to form benzidines in excellent yield. In a related system, dienes (**70**), Ar = 4-Me_2N- and 4-$MeOC_6H_4$, were shown to undergo a reversible two-electron oxidation to give dications (**71**).[141] The antiaromaticity of the dication (**72**) was demonstrated through magnetic criteria, ^{1}H NMR shifts, nucleus-independent chemical shifts (NICS), and magnetic susceptibility exaltation.[142] Excellent agreement was seen in the calculated and experimental ^{1}H NMR shifts. Dications (**73**), with various Ar, were prepared to examine the response of the indenyl and fluorenyl cationic portions to magnetic measures of antiaromaticity.[143] All measures supported antiaromaticity, with the indenyl ring system (even in the absence of the aryl substituent) being less aromatic than the fluorenyl ring system. This stands in contrast to the situation with the isolated monocations. The reactions of maleimide and phthalimide with cyclohexane and benzene under superelectrophilic activation were reported.[144] For example, maleimide reacts with benzene in CF_3SO_3H to give predominantly a diphenyl derivative, with the proposed mechanism involving sequential Friedel–Crafts alkylation involving dications as the alkylating species. Dications such as (**74**)[145] and (**75**)[146] were obtained in the reversible two-electron electrochemical oxidation of alkene precursors. Superacid-promoted reactions of ammonium–carbocation dications show positive charge migration so as to separate the two positive charges in a predictable manner.[147] This charge migration chemistry is the basis of new synthetic reactions, for example to prepare aza-polycyclic aromatic compounds. The reactions of quinidine acetate, epiquinidine, and its acetate in superacids were studied. After



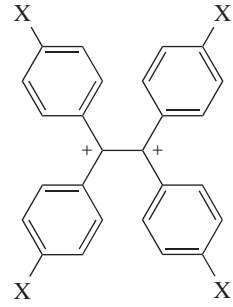
(**72**)



(**73**)



(**74**)

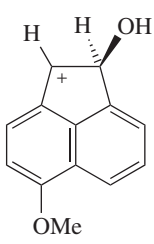


(**75**), X = OOCR, NHCOR, OAr

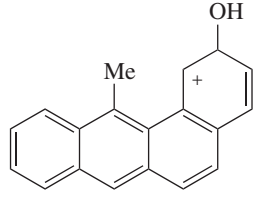
the two nitrogens have been protonated, alkene protonation leads to a trication that undergoes a series of relatively complex reactions, including rearrangements.[148]

Polycyclic Systems

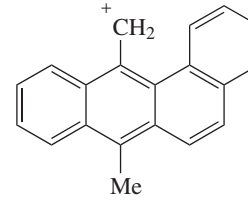
The acid-catalysed hydrolysis of 5-methoxyacenaphthylene 1,2-oxide was shown to proceed via the carbocation (**76**).[149] This cation reacted with water to give an approximately 3:2 ratio of *cis*:*trans* diols, despite the *trans*-diol being substantially more stable. Hence, transition state effects, and not thermodynamic stability, determine the products. A computational investigation examined carbocations derived from oxidized benzo[*a*]anthracenes.[150] Examples of cations considered are (**77**), derived by epoxidation and ring opening, and (**78**), derived by methyl oxidation and subsequent C−O bond heterolysis.



(**76**)



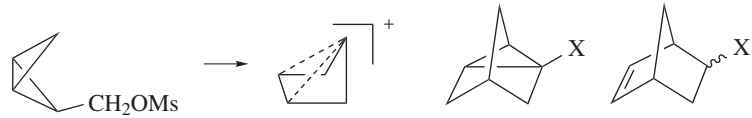
(**77**)



(**78**)

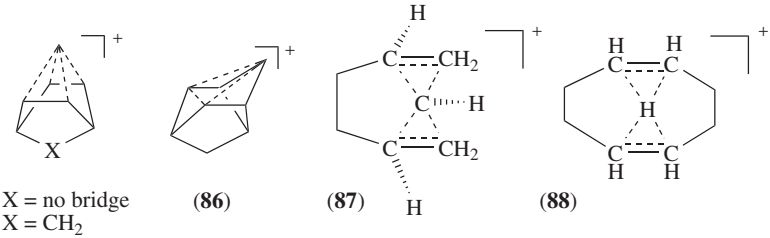
Carbonium (Bridged) Ions

A combined computational and experimental investigation of the protonation of adamantane was performed.[151] Computations showed four stable structures, a van der Waals complex between the 1-adamantyl cation and H(2), two isomeric complexes between the 2-adamantyl cation and H(2), and a *C*-adamantonium ion formed by protonation of the C(1)–C(2) bond. Computational studies examined various aspects of the CH_5^+ cation – potential energy surface, including the pathways leading to the fragments CH_3^+ and H_2,[152] fluxionality including the effect of deuteration,[153] and electron density charge topology as studied by Bader's theory of atoms in molecules.[154] Solvolysis of the mesylate (**79**) results in ring-opened products consistent with the bridged cation (**80**) as the intermediate.[155] The *exo*-isomer of (**79**) undergoes solvolysis with direct displacement of the leaving group and complete retention of the bicyclic structure. The products obtained on the fragmentation of the oxochlorocarbenes (X = OCCl), chlorocarbonates [X = OC(=O)Cl] and chlorosulfites (X = OSOCl) of (**81**), (**82**), and (**83**) were determined.[156] The fragmentation proceeds in polar solvents via a nortricyclyl cation:Z:chloride ion pair where the ions are separated by the spacer Z = CO, CO_2, or SO_2. For each of (**81**), (**82**), and (**83**), similar product distributions were observed with the three precursors. This indicates that similar ion pairs are formed.



(**79**) (**80**) (**81**) (**82**) *exo* (**83**) *endo*

Hypercoordinate square-pyramidal carbocations $C_7H_9^+$ and $C_8H_9^+$ were examined computationally.[157] For the former, (**84**) was found to be the minimum, and calculated ^{13}C NMR shifts were in good agreement with experimental values. For the latter, cations (**85**) and (**86**) were close in energy with a relative low barrier separating them. The calculated ^{13}C NMR shifts based on a weighted average of the two structures agreed with the experimental values. Quantum chemical calculations on carbonium ions containing hypercoordinated carbon atoms in distorted square-pyramidal geometries [e.g. (**87**)] were described.[158] In addition, transition structures for reactions involving the intramolecular attack of tetracoordinated carbon on carbenium carbons (i.e. where the tetracoordinate carbon centre acts as a nucleophile) were located. A similar study examined a set of nonclassical carbocations with tetracoordinated protons 'sandwiched' between two carbon–carbon double bonds [e.g. (**88**)].[159] The occurrence of five-centre, four-electron bonds was clearly demonstrated. Quantum chemical calculations have revealed an unusual rearrangement reaction of cyclopropylcarbinyl cations, a hybrid of a [1,2]-sigmatropic hydrogen shift and a two-electron electrocyclic ring opening.[160] The term 'hiscotropic' was coined to describe the reaction, which occurs over potential energy surfaces that are complicated, in some cases with flat plateaux and even bifurcations. A series of caged hydrocarbon cations containing



(**84**), X = no bridge
(**85**), X = CH_2

(**86**)

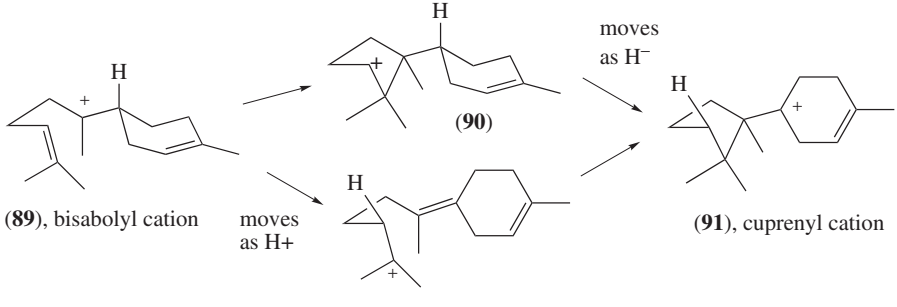
(**87**)

(**88**)

hexa- and octa-coordinate carbon centres were designed computationally.[161] For example, inserting C^{4+} into the centre of a caged system with four carbon–carbon double bonds held in close proximity is predicted to give an accessible tetracation where that central carbon is octacoordinate, being bonded to all eight of the alkene carbon atoms. Deamination of 1-alkyl-9-aminomethyltriptycenes was interpreted in terms of the loss of N_2 from a primary alkane diazonium ion concomitant with participation of a C–H bond of the neighbouring C–H group to form a non-classical carbonium ion with a three-centre, two-electron bond.[162] Non-classical carbonium ions such as corner-protonated cyclopropane were shown by computational methods to be excellent hydrogen bond donors to ammonia.[163] The relevance of such interactions in enzyme-catalysed terpenoid biosynthesis was discussed.

Carbocations in Biosynthesis

A quantum chemical investigation of the biosynthesis of farnesyl pyrophosphate through the condensation of isopentenyl pyrophosphate and dimethylallyl pyrophosphate suggests that the mechanism is concerted, although the transition state has carbocationic character.[164] Quantum chemical calculations were performed on the cyclization of the farnesyl cation to the sesquiterpene pentalenene.[165] Two distinct pathways with similar activation barriers were identified, each differing from previous proposed mechanisms, and each involving unusual carbocationic intermediates. Mechanisms previously proposed for enzyme-catalysed formation of the sesquiterpene trichodiene involve carbocation intermediates with a 1,4-hydride transfer as the key step, e.g. (**89**) → (**90**) → (**91**).[166] Quantum chemical calculations, however, show a



(**89**), bisabolyl cation

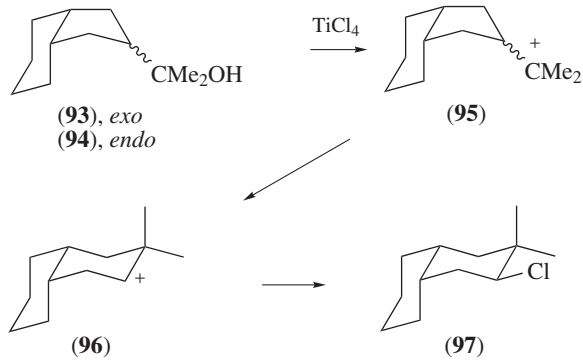
(**90**)

(**91**), cuprenyl cation

(**92**)

pathway (**89**) → (**92**) → (**91**) where hydrogen transfer as a proton is more favourable by over 10 kcal mol^{-1}. The energetics of a number of $C_{30}H_{51}O^+$ intermediates in the cationic cyclization of oxidosqualene to lanosterol, lupeol, and hopen-3β-ol were obtained by quantum mechanical methods.[167] The modest activation barriers so calculated combined with the exothermicity of the reactions led to the suggestion that the cationic intermediates do not require enzymatic stabilization. The reliability of quantum chemical methods for investigating such reactions was also addressed.

Stereoisomeric alcohols (**93**) and (**94**) yielded identical ring-expansion products [e.g. (**97**)] on formation of carbocations.[168] This is evidence of a stepwise reaction in sterol biosynthesis, whereby a tertiary cation [e.g. the model (**95**)] rearranges to a secondary cation (**96**)–an 'anti-Markovnikov rearrangement'. The synthetic aspects of biomimetic cyclizations of isoprenoid polyenes were reviewed.[169] Included was a detailed discussion of carbenium ion-initiated cyclizations, with a discussion of the different mechanisms that have been proposed. A novel biomimetic carbocation polyene cyclization of a daurichromenic ester was reported; an unusual 2 + 2-carbocation cyclization occurred as a side reaction.[170]



(**93**), *exo*
(**94**), *endo*

(**95**)

(**96**)

(**97**)

The diverse chemistry of the terpenoid cyclases was reviewed.[171] These enzymes catalyze cyclization reactions occurring by way of carbocations, where on average two-thirds of the carbon atoms of a linear polyisopropene undergo changes in bonding, hybridization, and/or configuration during the reaction. Type 2 isopentenyl diphosphate:dimethylallyl diphosphate isomerase, an enzyme that requires FMN for activity, was found to be irreversibly inhibited by an epoxide mechanism based inhibitor of the type 1 isomerase.[172] This led to the suggestion that the type 2 isomerase proceeds via a carbocation intermediate, with a proposal that a reduced flavin stabilizes this intermediate. A mechanistic study of the conversion of oxidosqualene to marneral by an oxidosqualene cyclase led to the proposal that the triterpene arises by Grob fragmentation of an intermediate carbocation.[173] A detailed mechanistic study was published employing deuterium isotope effects to examine the formation of the sesquiterpenes epiaristolochene and premnaspirodiene from farnesyl diphosphate catalysed by the appropriate enzymes.[174] Several carbocation intermediates are involved in the transformations, and the results of this study are explained through consideration of their

conformations and stereoelectronic requirements in the course of proton transfers, rearrangements, and eliminations. Molecular modelling and site-directed mutagenesis were combined to examine the mechanism of terpene syntheses catalysed by maize sesquiterpene synthases, enzymes that produce 14 different olefinic sesquiterpenes.[175] A bisabolyl cation is the key intermediate, and the study suggests that the steps in the reaction sequence are controlled by two active sites, with the conformation of this cation determining the pocket where the reaction occurs.

The initial steps in the biosynthesis of artemisin were investigated by isotopic labelling.[176] Three possible ring-closure mechanisms, two involving a bisabolyl carbocation and one involving a germacrenyl carbocation, were proposed and tested. Oxidosqualene–lanosterol cyclase mutants replacing a phenylalanine were described that generated different product profiles.[177] The study supports a model whereby there is stabilization of carbocationic intermediates by cation–π interactions. A polar amino acid side-chain can replace the π-stabilizing group, but with product differentiation. A detailed structural investigation was reported for prephenate dehydratase, an enzyme that catalyses the conversion of prephenate to phenylpyruvate in a two-step sequence of dehydration–decarboxylation, with a carbocation intermediate proposed for the first step.[178] The enzyme was proposed to function as an entropy trap, providing a highly pre-organized microenvironment that avoids the extensive solvent reorganization that accompanies carbocation formation. The stereochemistry in the acid-induced cyclization of a deuterium-labelled geranyl acetate was examined in solution and in zeolite Y.[179] Whereas the solution reaction showed negligible diastereoselectivity, the zeolite reaction showed considerable stereoselective disposition. This was explained by the proximity of the nucleophilic C=C to the intermediate carbocation, as a result of confinement within the zeolite. A carbocation mechanism for the antimalarial activity of artemisinin was probed by computational methods.[180] Although a number of cationic intermediates were shown to be possible, the conclusion was reached that the antimalarial activity is due to a radical pathway.

Carbocations in Synthesis

Recently published intramolecular Friedel–Crafts-type alkylations were reviewed, with an emphasis on chemo-, regio-, and enantio-selective examples.[181] Cyclopropanation reactions based on the γ-effect of tin on carbocationic intermediates were reviewed.[182] A novel approach for C(sp^3)–H bond functionalization was reported, whereby a tertiary benzylic C–H bond is activated by transfer of the hydrogen as hydride ion to a metal coordinated centre, followed by intramolecular reaction of the so-formed carbocation.[183] Benzyl, allyl, and propargyl cations can be formed and used in synthetically useful reactions by treatment of the appropriate alkoxide with BCl_3.[184] Based on knowledge of the electrophilicity of the cations and the nucleophilicity parameters of the target and the solvent, certain allyl and benzyl halides were predicted to allylate or benzylate indoles in 80% aqueous acetone (and not react with the solvent) via an S_N1 mechanism, without the aid of a catalyst to generate the carbocation.[185] This was borne out by experiment, where moderate to quantitative yields of products were obtained. Acid-catalysed reactions of 4,5-epoxy-9-trimethylsilyleudesmanes results in

rearrangement products determined by the stabilization of the rearranged carbocation by the silicon at its β-position.[186] With the aid of deuterium labelling, mechanisms of the reactions of methylenecyclopropanes with aldehydes in the presence of $BF_3.OEt_2$ were addressed, with several carbocations proposed as intermediates.[187]

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CHAPTER 8

Nucleophilic Aliphatic Substitution

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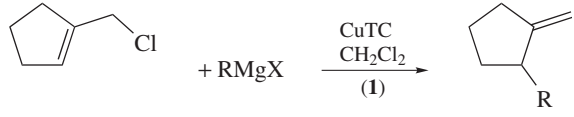
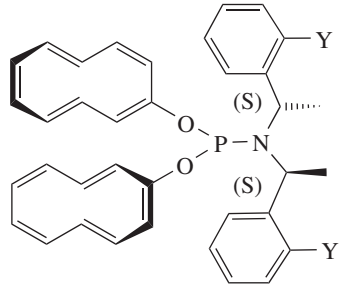
S_N Reactions Forming C–C Bonds

S_N2' products were obtained in good yield (83–99%) by highly regiospecific (79–98%) and enantiomeric specific (93–99.4% *ee*) reactions when variously substituted allylic (*ee*) chlorides were treated with a Grignard reagent in the presence of (**1**; Y = H) and ≤3 mol% of a copper thiophene carboxylate (CuTC) catalyst.[1]



The alkylation of γ-acetoxy or γ,γ-difluoro-α,β-unsaturated-δ-lactams (**2**) with Me_3CuLi_2.LiI.3LiBr and an alkyl halide[2] gave mainly the 3,6-*cis* isomer (**3**) when the alkyl halide was small (MeI), but mainly the 3,6-*trans* isomer (**4**) when a bulky (*de*) alkyl halide was used. Calculations at the B3LYP/6–31G(d) level of theory suggested the mechanism in Scheme 1 where the intermediate is stabilized by an interaction

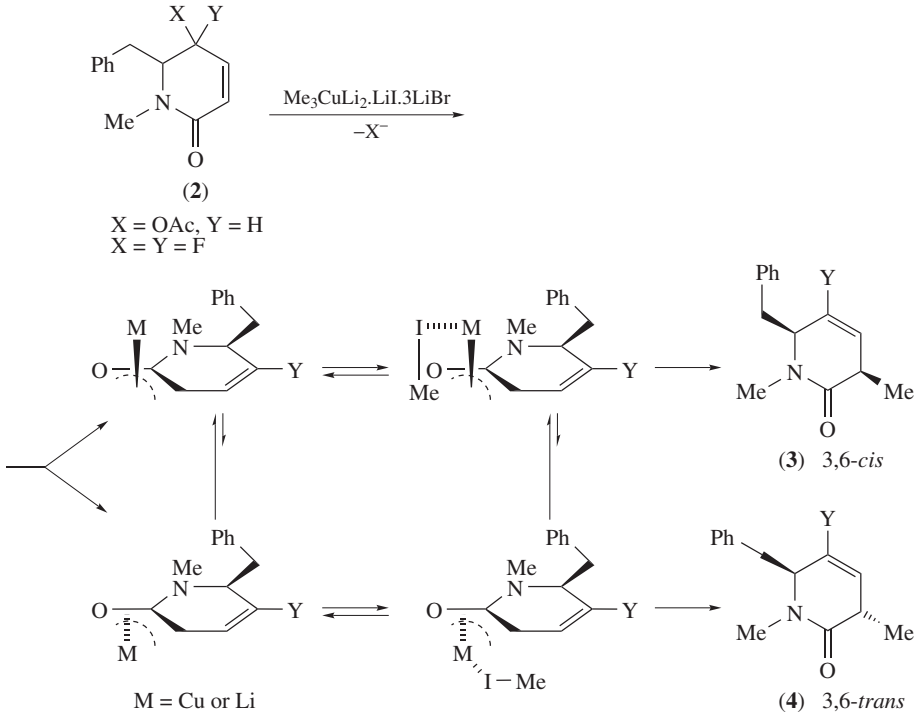
Organic Reaction Mechanisms 2006. Edited by A. C. Knipe



(**1**)

between a Cu or Li ion and the π-electrons of the benzene ring. Steric hindrance makes the transition state leading to the 3,6-*cis* product high energy when a bulky alkyl halide is used, so attack comes from the side opposite to the benzyl substituent. Total yields of 3,6-*cis* and 3,6-*trans* products ranged from 56 to 94%.

A highly regiospecific S_N2 alkylation occurs when allyl carbonates (**5**) are reacted with an iron catalyst (Fe^c) and PPh_3 in DMF at 80 °C.[3] It appears the product is formed with retention of configuration at C_α. A possible mechanism (Scheme 2), involves two regioselective S_N2' reactions.

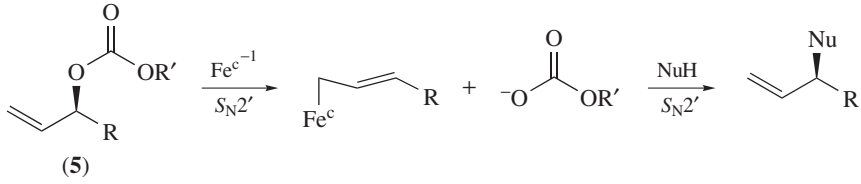


(**2**)

(**3**) 3,6-*cis*

(**4**) 3,6-*trans*

SCHEME 1



SCHEME 2

The formation of C–C bonds in S_N reactions using ketone enolates as nucleophiles has been reviewed.[4]

Allylic and Vinylic Substitutions

A wide range of substituted allyl carbonates have been found to undergo S_N2' reactions with potassium trialkylsilanoates in the presence of a chiral iridium catalyst regiospecificically (>99%) and with a very high (92–99%) enantioselectivity.[5] Hydrolysis of the resulting silyl ethers gives chiral secondary alcohols in high yields. (ee)

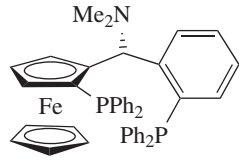
A new phosphoramidite ligand (**1**; Y = OMe), gives high enantioselectivities (92–99% *ee*) and regioselectivities (99% S_N2') in iridium-catalysed allylic substitution reactions of carbonates and acetates with carbanion or primary amine nucleophiles.[6] The new ligand also leads to a faster rate of reaction than other phosphoramidite ligands. (ee)

The use of the *o*-diphenylphosphanylbenzoyl leaving group in copper-catalysed allylic substitution reactions with a Grignard reagent has been studied extensively.[7] High S_N2' regiospecificity (≥95%) and complete stereospecificity are observed at room temperature when the solvent is a dichloromethane – diethyl ethyl mixture. A ^{31}P NMR study showed that there was a rapid ligand exchange on copper(I). This means that only 0.2 equiv. of catalyst is required for the reaction. The suggested mechanism, where two molecules of substrate become coordinated with the copper atom via their phosphorus atom, indicates that the reaction occurs via a *syn*-selective transfer to minimize A strain. (de)

The S_N1 hydrolysis of 5-methoxyacenaphthylene 1,2-oxide was found to occur preferentially via the 7.73 kcal mol^{-1} more stable carbenium ion,[8] as confirmed by B3LYP/6–31G* calculation. The predominant formation of the less stable *cis*-diol is a consequence of kinetic control and explained by calculations at the MP2/6–31G*// MP2/6–31G* level of theory, which reveal the stabilizing influence of the hydrogen bonding that occurs between the attacking water molecule and the β-OH group on the carbenium ion in the transition state.

The Taniaphos catalyst (**6**) has been found to give S_N2' products in excellent yields (90–98%) with a high enantioselectivity (90–98% *ee*) in the allylic substitution of several different leaving groups by Grignard reagents in the presence of $CuBr.SMe_2$ in *t*-BuOMe at −78 °C.[9] (ee)

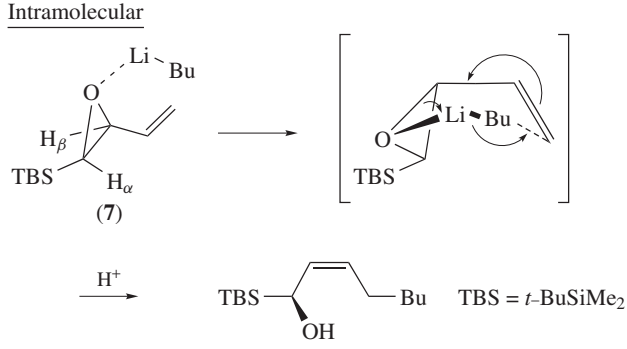
A detailed kinetic study[10] of a palladium-catalysed reversible *cis–trans* isomerization of cyclic allylic benzoates has shown how a change to a better leaving group



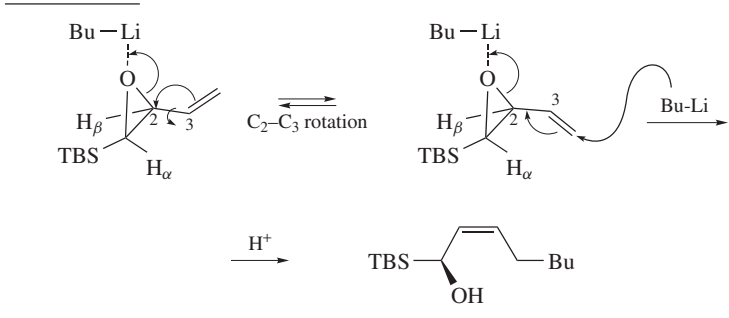
(**6**)

increases the rate of the reaction, which proceeds by S_N2 substitution of intermediate *cis* and *trans* palladium complexes, for which the best catalyst is $Pd^0(PPh_3)_4$. (ee)

The effect of added salts, the solvent, and the reaction temperature on the S_N2' reaction of silylated vinyloxiranes (**7**) with *n*-, *s*- and *t*-butyllithium has been investigated.[11] Higher yields of the favoured *Z*-isomer were obtained at a lower temperature and when the base was *t*-butyllithium. Both the *Z*:*E* ratio (*Z*:*E* = 5.3) and the yield (99%) were (de) slightly greater when the solvent was Et_2O rather than pentane. Adding LiCl, BF_3, or tetramethylethylenediamine to the solvent reversed the *Z*:*E* ratio, giving *Z*:*E* = 1:2.3 with LiCl, 1:3.4 with BF_3 and 1:3.5 with tetramethylethylenediamine, by changing the coordination with the oxirane oxygen. The results have been discussed with reference to alternative inter- and intra-molecular mechanisms, (Schemes 3 and 4, respectively)



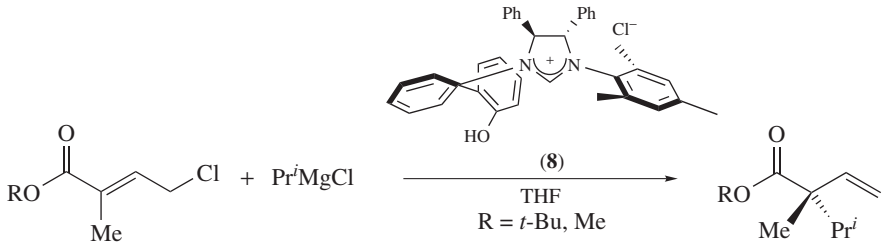
SCHEME 3



SCHEME 4

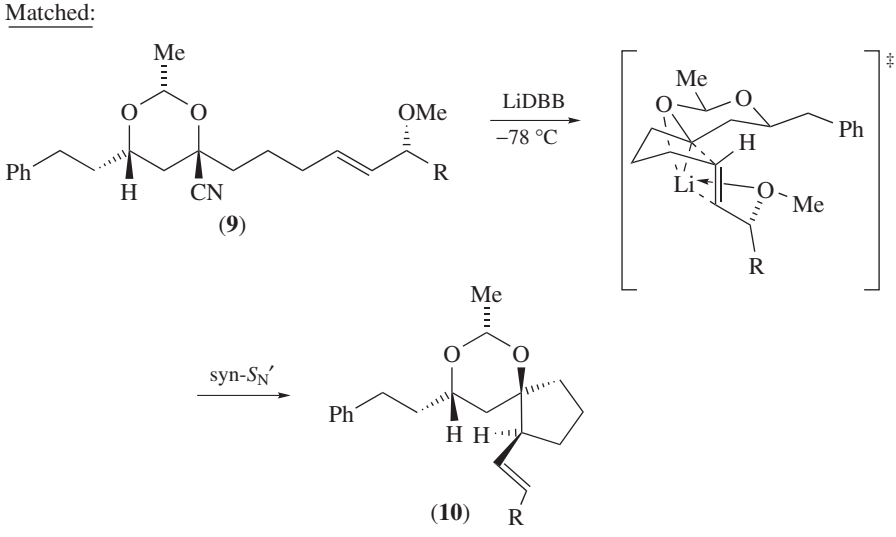
Allylic alcohols can be converted in high yield (74–94%) to the corresponding linear allylic trifluoroborate salts in two steps: by treatment with $[B(OH)_2]_2$, *p*-toluenesulfonic acid and a Pd–selenium complex catalyst, in DMSO–MeOH, and then by KHF_2.[12] The reaction is probably successful because the poor OH leaving group is converted to the excellent leaving group $OBOH(OH_2)B(OH)_2$ in the first step.

Allylic alkylations (Scheme 5) using Grignard reagents and the Lewis base imidazolinium chloride **(8)** have been found to give 82% of the S_N2' product with a 97% *ee*.[13] (*ee*)

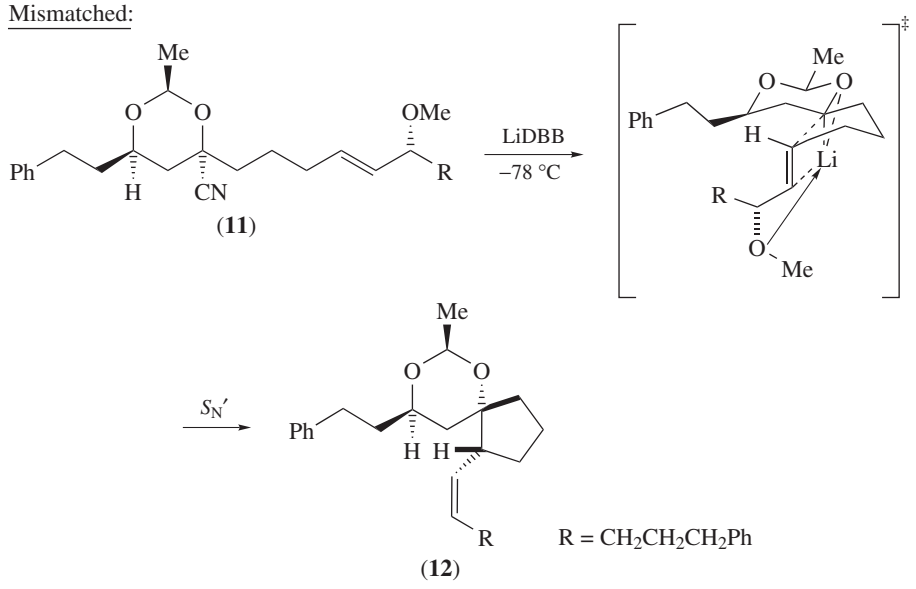


SCHEME 5

A mechanism has been proposed for the *syn*-S_N' allylic substitution of α-cyanoacetals with alkyllithium reagents.[14] The matched (**9**) and mismatched (**11**) substrates gave different products [98% (**10**) and 85% (**12**), respectively] when treated with lithium di-*t*-butyl biphenylide (LiDBB) in THF at −78 °C as shown in Schemes 6 and 7. The spiroether effect is the controlling factor in determining the products. (*de*)



SCHEME 6



SCHEME 7

The effect of leaving group, solvent, base, temperature, and ligands on the apparent S_N2' allylic arylation of *cis*-cyclopent-2-ene-1,4-diethylcarbonate with arylboronic acids [$ArB(OH)_2$] and a rhodium(I) catalyst has been reported.[15] The best conditions gave good to excellent yields with a high regiospecificity (>90%) and high enantioselectivity (84–92%). Two possible mechanisms, one requiring two substitution (ee) reactions and the other an addition – elimination mechanism, are discussed.

The regioselective and enantiospecific allylic substitution of alkyl-substituted allyl benzoates and carbamates with $(Me_2PhSi)_2Zn$ and CuI has been shown to occur by an (ee) oxidative addition – reduction elimination mechanism rather than an S_N2 mechanism.[16]

A natural bond orbital-based CI/MP through-space/bond interaction analysis of the S_N2 reaction between allyl bromide and ammonia[17] showed that allyl bromide reacted faster than propyl bromide because the $\sigma - \pi^*$ and $\pi - \sigma^*$ interactions stabilize the allyl bromide transition state equally.

Two reactions related to allylic substitution have used propargyl compounds as substrates. The S_N2' reaction between *gem*-difluoropropargyl bromide and a Grignard reagent is highly regiospecific if the reaction is carried out in the presence of a copper (I) halide catalyst.[18] Control experiments have shown that a magnesium organocuprate intermediate formed in the initial S_N2' reaction, undergoes a reductive elimination giving the difluoroallene. *Ab initio* calculations indicate the reaction occurs at C(3), the most positive site in the substrate, as revealed by the NBO (natural bond order) charge densities. The difluoroallene is often unstable and reacts further giving a monofluoride as the final product. The yields of difluoroallene range from 37 to 94%.

Finally, the S_N reaction of propargylic alcohols [$R^1R^2C(OH)C{\equiv}CR^3$] in refluxing acetonitrile has been found to occur in good (50–90%) yields when catalysed by

p-toluenesulfonic acid.[19] Nucleophiles, including alcohols, amines, thiols, sulfonamides, allyltrimethyl silane, and even aromatic and heteroaromatic compounds, can be used in this reaction. The product obtained using tertiary propargyl alcohol was racemic, indicating that at least this reaction occurred by an S_N1 mechanism.

Four reviews on allylic and vinyl substitution have been published.[20–23] The use of pentamethylcyclopentadienylruthenium catalysts for the S_N reactions of allyl substrates has been reviewed.[20] The S_N reactions of allyl substrates in the presence of ruthenium catalysts occur primarily at the most substituted position of the allylic group. All the catalysts involve formation of an intermediate where the allyl compound becomes associated with the Ru atom in the catalyst. The regiospecificity (50–98%) depends on the structure of the allylic substrate, the nucleophile, the solvent, the temperature, and the catalyst. These catalysts have also been used for protection of allylic alcohol and amino groups. Some of the reactions are stereospecific.

An excellent review[21] outlining the mechanism of diphenylphosphinobenzoic acid-based palladium-catalysed asymmetric substitution of allyl compounds with nucleophiles has been published. The mechanistic model developed for these reactions allows one to predict the stereochemistry of the product(s).

The use of C_2-symmetric chiral bis(oxazolines) in allylic substitutions has also been reviewed.[22]

The S_N2 reactions of vinylic compounds have been reviewed.[23] An $S_NV\sigma$ (an in-plane attack at the σ^* orbital giving inversion of configuration) and an $S_NV\pi$ mechanism (an out-of-plane attack on the π^* orbital giving retention of configuration) have been found with vinyl iodonium salts.

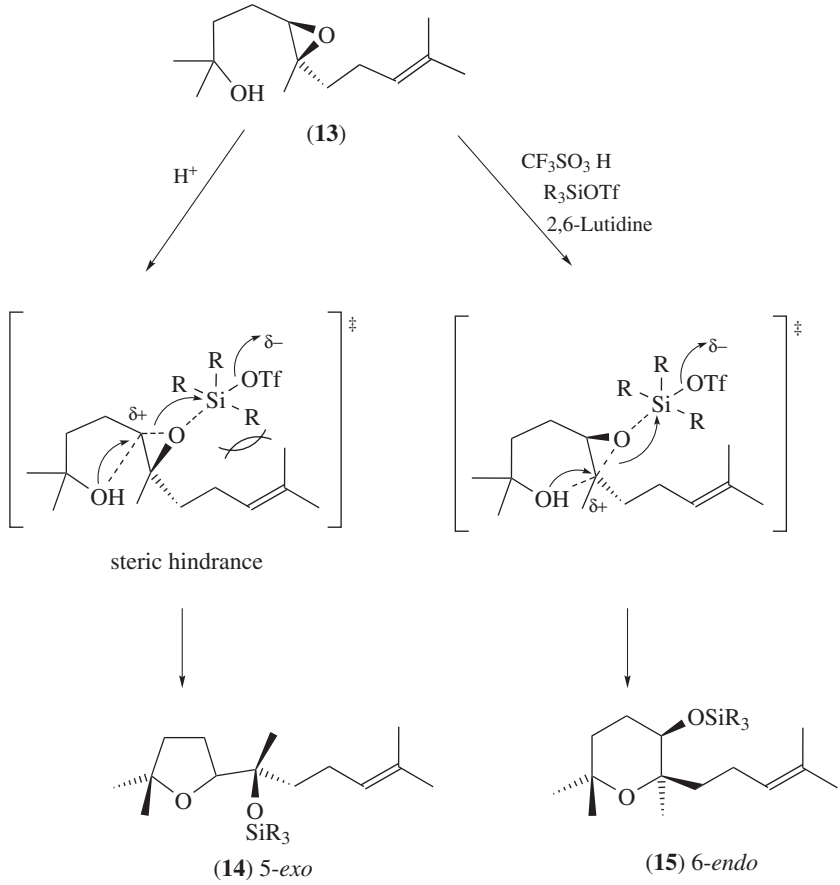
Finally, three other allylic substitution reactions[1–3] have been reported.

Reactions of Cyclic Ethers

Virtually all of the studies using cyclic ethers have been carried out on epoxides. For example, an investigation of the effect of changing the acid, the silyl triflate and the solvent showed that the bishomoepoxy alcohol (**13**) can be converted in high yield to the 6-*endo*-cyclic ether (**15**) rather than the normal 5-*exo*-cyclic ether (**14**) by reaction with trifluoromethanesulfonic acid, triisopropylsilyl triflate, and 2,6-lutidine in nitromethane (Scheme 8).[24] The regioselective production of the 6-*endo*-cyclic ether (**15**) is favoured when the partial positive charge is stabilized on a tertiary carbon and steric hindrance of the trialkyl silyl triflate leaving group in the transition state makes formation of the 5-*exo*-ether unfavourable.

Cyclic voltammetry, kinetic studies, and DFT calculations using a BP functional and the TZVP basis set showed that the major pathway of the non-regiospecific zinc-reduced titanocene-mediated ring opening of epoxides was initiated by a titanium dimer-epoxide compound that reacted in a rate-determining electron transfer mechanism.[25] The calculations showed that the transition state is early so the stereoselectivity is determined by steric effects rather than by the stability of intermediate radicals. This was confirmed by studies with more sterically crowded catalysts.

The ring opening of aryloxiranes with 3,5-dinitrobenzoic acid (HA) in acetonitrile has a Hammett $\rho^+ = -2.9$ and a transition state where C_α–O cleavage is greater than



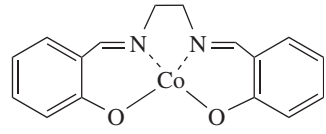
SCHEME 8

the formation of the new O–C_α bond.[26] Since the reaction is first order in the oxirane and second order in the acid, it has been suggested that pre-equilibrium association with HA is followed by attack of a second HA at the benzyl carbon. The much slower rate found when a more electron-withdrawing substituent is on the aryl ring was due to a large decrease in $\Delta S^{\neq}$ (i.e. much more negative) coupled with a small decrease in $\Delta H^{\neq}$ and suggests a later transition state.

Catalytic amounts of tin(II) chloride have been found to give good yields (72–86%) of the *trans*-amino alcohols when oxiranes have been treated with aromatic amines in (de) acetonitrile at room temperature.[27] Only the reaction with styrene oxide was regiospecific with the amine adding to the benzylic carbon of the epoxide ring.

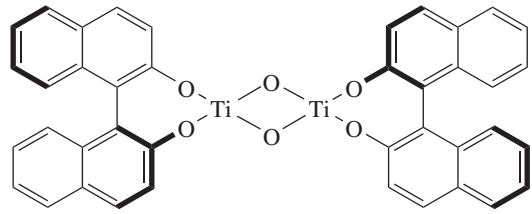
An investigation of the effect of various catalysts, the solvent, and alkyl groups on the oxirane ring[28] has shown that for ring opening with cyanide ion the best yields are obtained when the catalyst is (**16**) and the solvent is ethylene glycol. The reactions are regiospecific at the least substituted carbon and occur rapidly at room temperature,

giving the *trans*-β-hydroxynitrile in high yields (80–93%). The results imply that the reaction occurs by an S_N2 mechanism. (*de*)



(**16**)

An investigation of various catalysts, the solvent, and the additive used in the *meso*-stilbene oxide enantioselective ring opening with anilines at room temperature has been carried out.[29] The best catalyst, solvent, and additive proved to be (**17**), toluene and triphenylphosphane, respectively. The reaction gave 95% of the *syn*-β-amino alcohol with 78% *ee*. A single recrystallization increased the enantiomeric excess to 98%. The catalyst is recyclable. (*ee*)

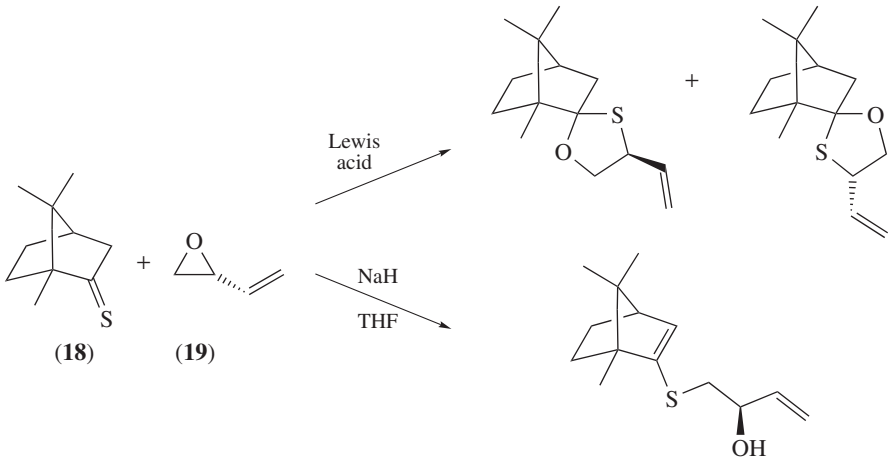


(**17**)

The major products of the S_N2 reaction between the sulfur of thiocamphor (**18**) and (*R*)-2-vinyloxirane (**19**) form regioselectively at the most hindered carbon when the reaction is carried out in the presence of the Lewis acids $ZnCl_2$, SiO_2, or $SnCl_4$.[30] When the reaction is carried out under basic conditions with NaH in anhydrous THF, however, the major product is formed when the sulfur of the enethiolate ion attacks the least substituted carbon in an S_N2 reaction (Scheme 9). The initial products from both reactions react further giving more complex products.

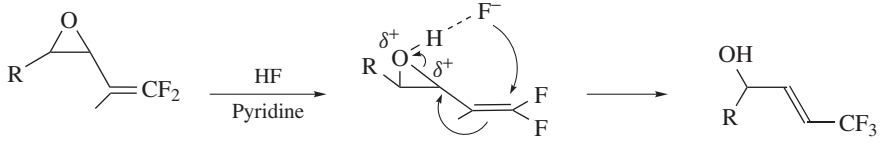
gem-Difluorinated vinyloxiranes (**20**) undergo S_N2' reactions when treated with HF–pyridine in CH_2Cl_2 at 0 °C.[31] Most of the reactions are stereoselective giving only the *E*-isomer (**21**). Treatment of the *gem*-difluorinated vinyloxiranes (**20**) with DIBAL-H or BH_3.THF (Scheme 11) gave the ring-opened allylic alcohol with high stereoselectivity. DIBAL-H gave mainly the *E*-isomer (**22**) and BH_3.THF gave only the *Z*-isomer (**23**) in most of the reactions. The *Z*-isomer is favoured when the reducing agent has small ligands (BH_3) while the *E*-product is found when the ligands are large, i.e. in DIBAL-H. Both the fluorination and the reduction reactions are feasible because the CF_2 carbon of the substrate has a significant positive charge. (*de*)

When treated with 3,5-dimethylpyrazole, epoxyvinyl sulfones (**24**) are converted to (**25**) by an S_N2' reaction that is both regiospecific and stereospecific.[32] The product



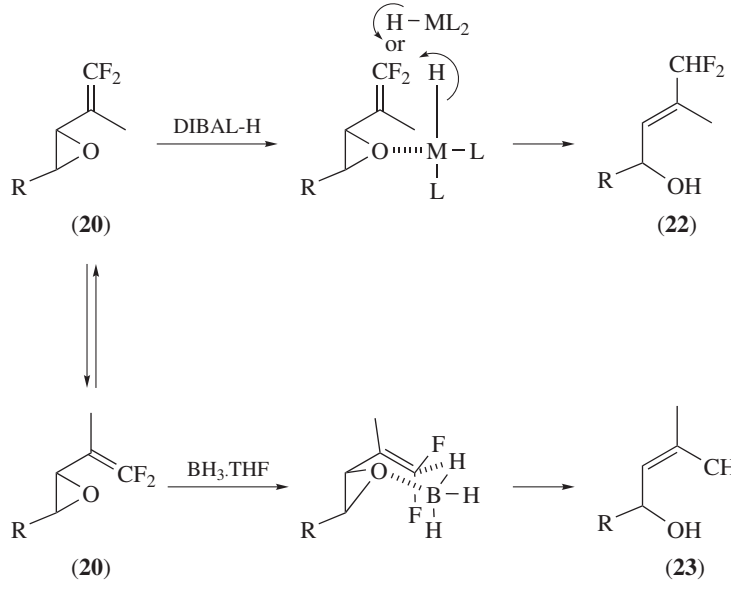
(**18**) (**19**)

SCHEME 9



(**20**) (**21**)

SCHEME 10

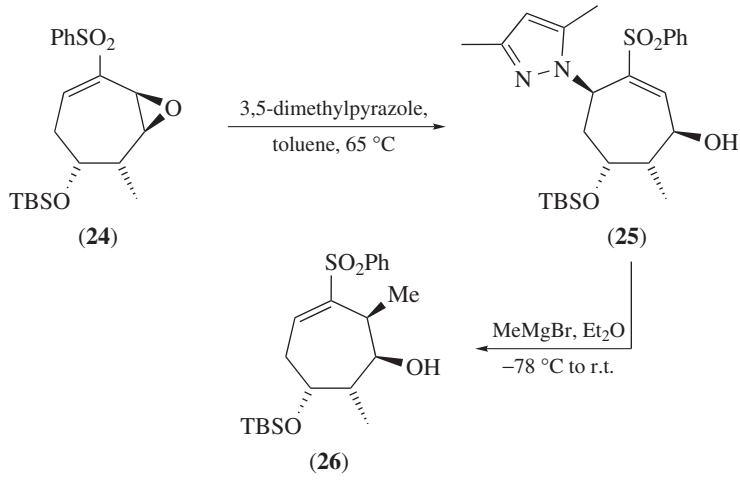


(**20**) (**22**)

(**20**) (**23**)

SCHEME 11

can be methylated in a second regio- and stereo-specific S_N2' reaction with MeMgBr (Scheme 12) to give >95% yield with 95% of (**26**) with the methyl group *syn* to the OH group. Surprisingly, when the temperature of the methylation was lowered to 0 °C, the *syn*:*anti* ratio decreased from 20:1 to 1:1 and it was reduced further to 1:4 at −45 °C. This temperature dependence was attributed to an equilibrium between two conformations of the magnesium alkoxide intermediates in the methylation reaction.



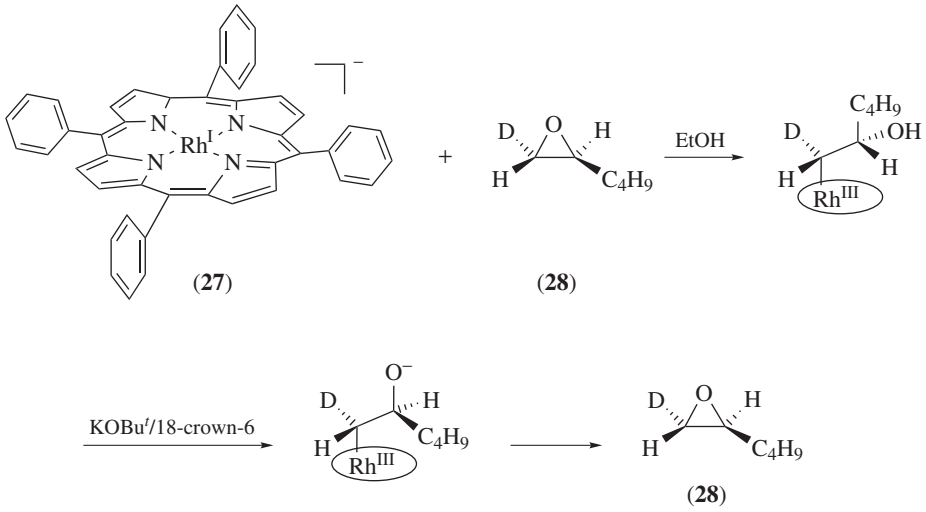
SCHEME 12

The ring opening of hindered 1,2-disubstituted epoxides by a copper-catalysed Grignard reagent generates two stereogenic centres with a high regiospecificity and in reasonable yields (60–85%).[33] When the *cis*-prop-1-enyl Grignard reagent was used, only the *cis*-product was obtained, whereas when the *trans*-prop-1-enyl Grignard reagent was used, some of the *cis*-product was obtained as a consequence of isomerization during the formation of the Grignard reagent.

Carbanions generated from fluorinated sulfones react regiospecifically and in high yield at the least hindered carbon of an epoxide.[34] The reactivity of the fluorinated nucleophile decreases from $(PhSO_2)_2CF^-$ to $PhSO_2CFH^-$ to $PhSO_2CF_2^-$ as expected considering the strong electron-withdrawing effect of the F. $PhSO_2CCl_2^-$ also reacted with epoxides regiospecifically in good yield. Only $(PhSO_2)_2CF^-$ reacted with a 2-substituted *N*-tosylaziridine.

An NMR study[35] using the labelled epoxide (**28**) has shown that both the ring-opening reaction by a rhodium tetraphenylporphyrin (**27**) and re-formation of the epoxide under basic conditions occur with inversion of configuration at the least substituted carbon (Scheme 13). This has been taken as evidence that both reactions occur by an S_N2-type mechanism.

Bromodimethylsulfonium bromide[36] reacts regiospecifically at the least substituted carbon of epoxides and aziridines in a few minutes at room temperature. The only exception is when a phenyl group is on one of the carbons of the epoxide or aziridine



SCHEME 13

ring. Since the nucleophile attacks the benzyl carbon of the ring in these reactions, it was suggested they occurred via the benzyl carbenium ion. The other reactions presumably occur via an S_N2 mechanism, since *trans*-products were obtained from bicyclic substrates.

The S_N2 reaction between ethylene oxide and guanine has been modelled using HF/6–311++G(2d,2p), B3LYP/6–311++G(2d,2p), and semiempirical AM1 and PM3 calculations.[37] The effect of adding water as the solvent was considered using the solvent reaction field (SCRF) and Langevine dipole (LD) methods. The HF and semiempirical methods gave similar values for the $\Delta G^{\neq}$, whereas the DFT calculations gave a significantly lower value. Adding solvent stabilized the transition state more than the reactants, thereby reducing $\Delta G^{\neq}$. Only the HF-LD method gave a value for $\Delta G^{\neq}$ close to the experimental value. The DFT calculations gave too small a value for $\Delta G^{\neq}$, and the semiempirical methods gave a value that was too large.

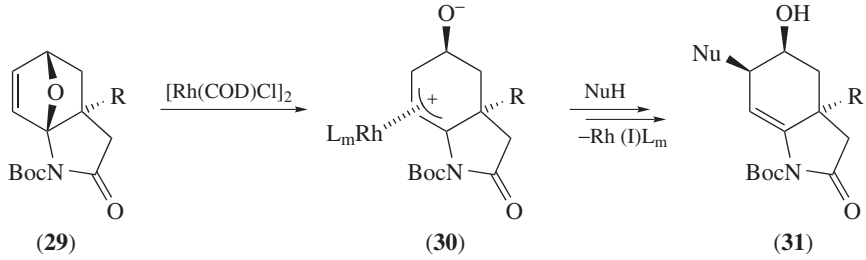
The geometries and energies of the complexes formed between BF_3 and MeOH, HOAc, dimethyl ether, diethyl ether, and ethylene oxide have been determined at the MP2/6–311++G(3df,2pd) and B3LYP/6–311++G(3df,2pd) levels of theory.[38] BF_3 forms bimolecular complexes with the lone pairs of electrons on the oxygen of dimethyl and diethyl ethers, MeOH, HOAc, and ethylene oxide. The tightest and loosest complexes are with diethyl ether and ethylene oxide, respectively. Higher levels of theory lead to shorter B–O distances in these complexes and the formation of F $\cdots$ H hydrogen bond(s) is primarily responsible for their stability. BF_3 also forms two trimolecular complexes: a $BF_3(MeOH)_2$ complex at high MeOH concentrations and a very stable $HOAc(BF_3)_2$ complex in HOAc. Because the complex formed between ethylene oxide and BF_3 is less stable than the complexes with the other reagents, it was concluded that BF_3 does not coordinate with the epoxide oxygen

in non-protogenic solvents, but activates the nucleophile, in the S_N2 ring opening of ethylene oxide.

The mechanisms and the regio- and stereo-selectivity of epoxide reactions have been reviewed.[39] The review also covers the role of epoxides in biologically important reactions. The achiral and chiral catalysts used in these reactions are discussed. A second review[40] discusses the ring-opening reactions of oxiranes with carbon nucleophiles. (de) (ee)

The reactions of larger cyclic ethers have also been investigated. A comparative study[41] of the ring-opening reaction between several *B*-bromoboranes and 2-methyltetrahydrofuran has established that the most regioselective reagent, $(MeO)_2BBr$, gave 91% of the primary bromide when it was mixed with the substrate at $-78\,^{\circ}C$ and warmed slowly to room temperature. The authors suggested that oxygen coordination with boron was followed by concerted intramolecular substitution by Br with C–O bond cleavage; the resulting $OB(OMe)_2$ group is then hydrolysed to OH.

The nucleophilic substitution reaction of 10-oxa-2-azatricyclo[5.2.1.$0^{1,5}$]decane (**29**) promoted by Rh(I) has been investigated.[42] The reactions, which occur with a high regiospecificity and stereoselectivity, give only or predominately (**31**) with the nucleophile *cis* to the OH group generated from the 10-oxa oxygen in the ring-opening reaction. A possible mechanism is shown in Scheme 14 for reactions using alcohols, amines, and phenylboronic acid as the nucleophile. 5,5-Dimethyl-2-phenyl-1,3,2-dioxaborinane was thought to react by a different mechanism. (de)



(**29**) (**30**) (**31**)

SCHEME 14

Aziridines and Other Small Ring Substitutions

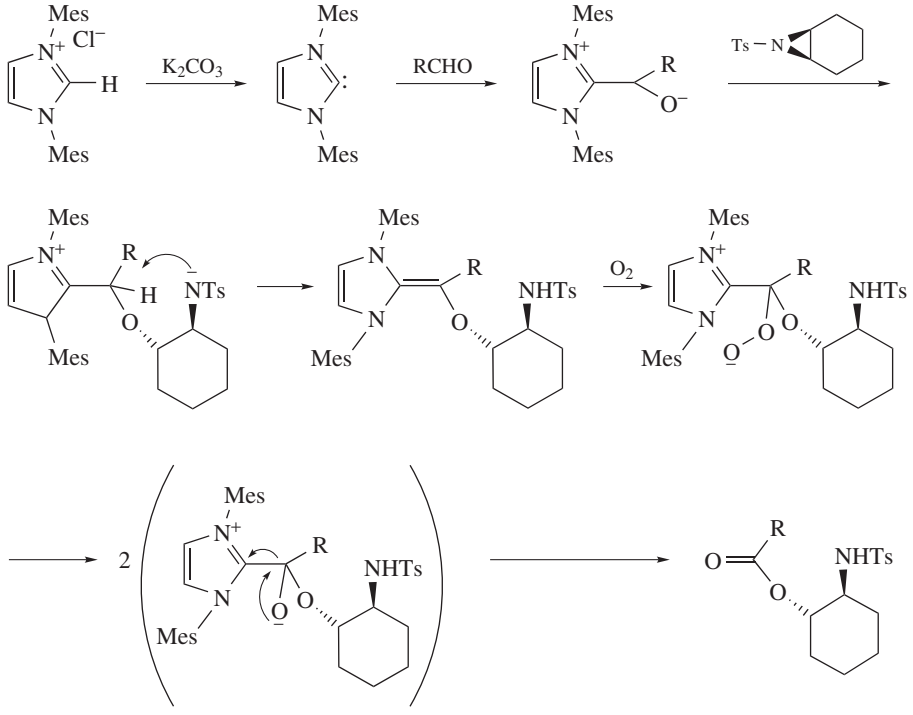
Several studies on the reactions and preparation of aziridines have been published. The ring opening of 2-substituted aziridines, accomplished by first converting them into aziridinium salts by reaction with a benzyl bromide and then attack of the bromide counter ion, gave only one bromide in a regio- and stereo-specific reaction.[43] Since attack by the bromide ion of the aziridinium salt *only* occurred at the most substituted carbon with an inversion of stereochemistry, it was concluded the reaction occurred by an S_N2 mechanism. This was supported by calculations at the MPWB1K/6–31+G(d) level of theory for reactions featuring two solvating acetonitrile molecules embedded in an acetonitrile matrix.

New ligands for a polymetallic Gd catalyst used in the ring opening of *meso*-aziridines with trimethylsilyl cyanide and 2,6-dimethylphenol have been developed.[44]

The new ligand–catalyst complex is huge with a metal:ligand ratio of 3:4 and two free OH groups. The yields of nitrile vary from 83 to 99% with an *ee* ≥95%.

An *N*-heterocyclic carbene (similar to that in Scheme 15) has proved to be an effective catalyst for the nucleophilic ring opening of *N*-tosylaziridines by silylated nucleophiles (Me_3SiX, X = N_3, Cl, I).[45] Yields range from 89 to 99% for reaction at the least substituted carbon, except when a phenyl group on one of the carbons of the aziridine ring induces predominant attack at the benzyl carbon. The stereochemistry is consistent with the S_N2 mechanism and THF was found to be the best solvent for the reaction.

Carbene-catalysed substitution of *N*-tosylaziridines with aldehydes[46] bearing both electron-withdrawing and electron-donating substituents has been reported to give good to excellent yields (50–90%) of β-amino esters by highly regiospecific reaction at the least substituted carbon of the aziridine (with one exception). A possible mechanism (Scheme 15) has been proposed. Intermediacy of the carboxylate anion has been ruled out.



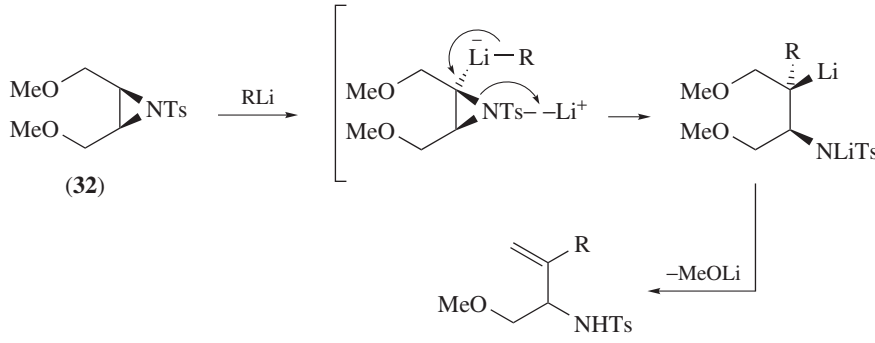
SCHEME 15

The unactivated aziridine-2-carboxylic acid methyl ester was found to react with two molecules of aromatic thiol.[47] Initial ring opening is followed by a faster reaction (since little mono substitution product is found), probably involving formation of an episulfonium ion which is then ring opened by the second ArSH. The same result

was found when aziridine-2,3-dicarboxylic acid diethyl ester was the substrate. No catalyst or solvent was required for these reactions.

DMSO has been found to catalyse the S_N reactions of aziridines with aromatic thiols and amines, and trimethylsilyl azide and chloride.[48] The reactions occur in good to excellent yields (73–97%) with high regiospecificity and stereoselectivity. Unless there is a phenyl substituent on the aziridine ring, the attack is completely (de) at the least substituted carbon giving only the *trans*-isomer as the product. Phenyl-substituted aziridines undergo nucleophilic attack at both ring carbons. DMSO does not cause reaction in the absence of the nucleophile, suggesting that the role of the solvent is to activate the nucleophile. Aliphatic amines and thiols react slowly.

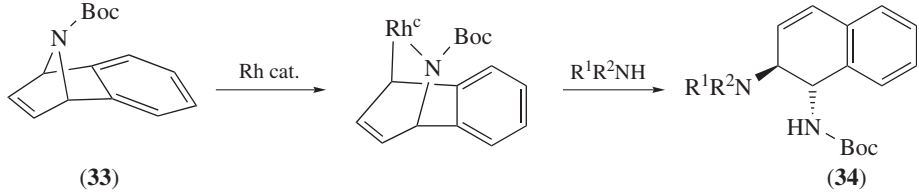
The products of alkylation of *N*-sulfonyl-protected aziridines (**32**) by alkyllithiums are unstable and undergo subsequent rapid elimination; a possible mechanism for the reaction is shown in Scheme 16.[49]



SCHEME 16

The ring-opening substitution of *N*-Boc-azabenznorbornadiene (**33**) with rhodium catalysts and aliphatic and aromatic amines gives chiral 1,2-diamino compounds (**34**), (ee) usually in high yields and enantioselectivities.[50] The effects of using different catalysts, additives, solvents, and substrate structures on the reaction have been investigated. A possible mechanism involves ring opening of the azanorbornadiene ring by the catalyst followed by an S_N2' reaction.

An S_N2 reaction with anchimeric assistance (via formation of a bicyclic aziridinium ion intermediate) has been proposed for the nucleophilic substitution of *trans*-2-substituted 3-piperidinol mesylates by nitrogen nucleophiles with retention of *trans*



SCHEME 17

stereochemistry.[51] The reaction is both stereospecific and regiospecific when the 2-substituent is phenyl but not when it is methyl. The *cis*-stereoisomer is thought to be formed in a direct S_N2 displacement of the mesylate group that competes with the formation of the aziridine ring intermediate. (de)

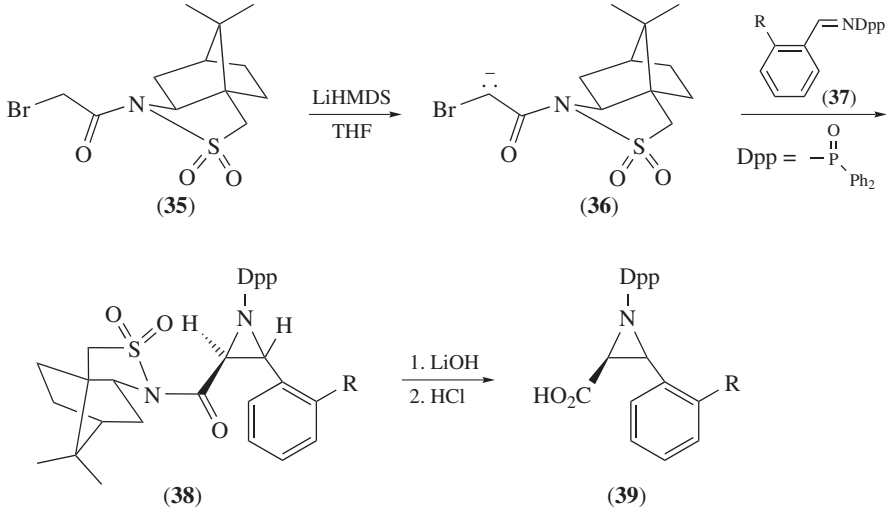
Two other reports of reactions involving aziridines[34,36] have been discussed above.

Calculations at the MP2(Full)/6–31++G(d,p)//MP2(Full)/6–31+G(d) level of theory were used to investigate the S_N reactions between ammonia and aziridine, azetidine, methylethylamine, and four fluorinated derivatives of aziridine.[52] The results show that aziridine and azetidine have strain energies of 27.3 and 25.2 kcal mol^{-1}, respectively, and that as a consequence they react 7.76×10^{23} and 2.30×10^{17} times faster with ammonia than does the methylene group of methylethylamine. However, even after subtracting the effect due to the release of ring strain, aziridine still reacts much faster than the other two substrates. This is because the electrostatic attraction of the charges in the product-like dipolar transition state are much greater for aziridine.

For fluoro-substituted aziridines, the strain energy in the ring increases from the *trans*-2,3- at 35.4 kcal mol^{-1}, to the monosubstititued, to the *cis*-2,3- to the 2,2-difluoroaziridine at 42.9 kcal mol^{-1}, all having a much higher strain energy than unsubstituted aziridine. The rate of the S_N2 reaction with NH_3 at C(3) increased from the *cis*-2,3-, to the monosubstituted, to the *trans*-2,3- to the 2,2-difluoroaziridine. The last compound reacted fastest due to the greater stabilization of the negative charge on the leaving group by the fluorines and to the electrostatic interaction between the fluorine and the NH_3 hydrogens in the transition state. *trans*-2,3-Difluoroaziridine reacts faster than the *cis*-isomer because the fluorine is closer to the imine hydrogen in the *trans*-transition state and because the encounter complex for the *trans*-substrate is higher energy. Adding an *N*-acetyl group to aziridine increases the rate 3×10^{18}-fold by equally decreasing the basicity of the leaving group (making a better leaving group) and increasing the ring strain in the substrate.

The substituent effects on the geometry of the *N*-substituted aziridine ring, the *N*-inversion energy barriers, and the transition states and activation energies for ring-opening reactions of aziridines by cyanide ion, have been calculated at the B3LYP/6–31+G* level of theory.[53] Electron-withdrawing groups on the ring nitrogen, especially those with a C=O or S=O or a phenyl group, stabilize incipient negative charge and thereby induce a faster reaction via an earlier, planar, transition state. Adding an electron-withdrawing C=OCH_3 group to one of the carbons of the aziridine ring switches the reaction from the least substituted carbon (CH_2) to the more substituted carbon (CHC=OCH_3).

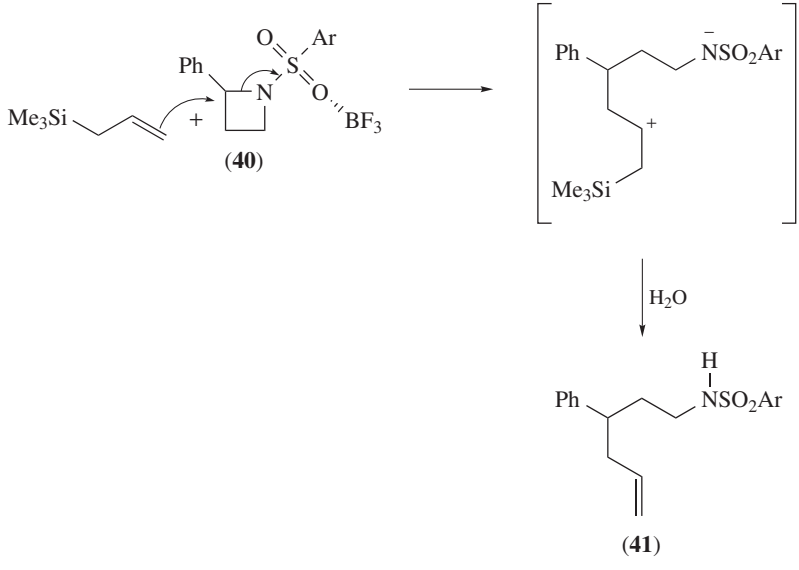
A method of preparing either *cis*- or *trans*-aziridine carboxylates (**39**) from *N*-diphenylphosphinylimines (**37**) and the chiral enolate (**36**) derived from *N*-bromoacetyl 2*S*-2,10-camphorsultam (**35**) has been reported.[54] When the arylimine is substituted in the *ortho*-position, the product is either a mixture of *cis*- and *trans*-aziridine or only the *trans*-isomer. When the *ortho*-substituent is H or NO_2, only a *cis*-aziridine is obtained. The suggested mechanism is partially shown in Scheme 18. Both steric and inductive effects of the *ortho*- substituent affect the stereochemistry of the addition complex (**38**) and the stereochemistry of the final aziridine.



SCHEME 18

Two reviews, one on the use of C_2-symmetric chiral bis(oxazolines) in the preparation of aziridines[55] and the other discussing the ring opening of aziridines with carbon nucleophiles,[40] have been published.

Two papers discussing the reactions of azetidines follow. *N*-Activated azetidines are converted into aminoalkenes in a regiospecific ring opening at the benzyl carbon when treated with allylsilanes and $BF_3{\cdot}OEt_2$ in dichloromethane (Scheme 19).[56]



SCHEME 19

The regiospecificity of the ring-opening S_N2 reactions of di- and tri-substituted azetidinium ions with azide ion, benzylamine, acetate ion, and alkoxide ions has also been investigated.[57] The products depend on the degree of substitution on the ring, the group on C(2), the nucleophilic atom and the configuration of the substituents on the ring. Epimerization at C(2) also affects the regiospecificity of these S_N2 reactions. Although the product composition is governed by several factors, 2,3-disubstituted azetidinium ions usually react exclusively at C(4) whereas trisubstituted isomers react at C(2). B3LYP/6–31G(d) calculations successfully predict the products of these reactions.

Finally, 1,1-dinitrocyclopropane reacts readily with C, N, O, and S nucleophiles opening the ring.[58] The yields of 1,1-dinitropropanes range from moderate (50%) to high (88%). When aliphatic amine nucleophiles are used, zwitterionic compounds are produced.

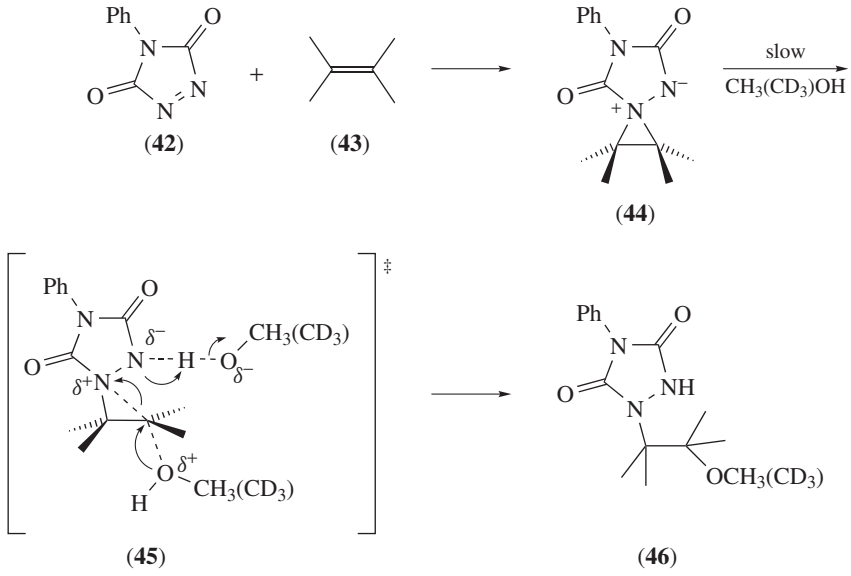
Studies Using Kinetic Isotope Effects

The perdeutero KIEs for the reactions between methyl, ethyl, isopropyl and *t*-butyl chlorides and ClO^-, measured in the gas phase using a tandem flowing afterglow-selected ion flow tube mass spectrometer, increased from 0.85 ± 0.01 to 0.99 ± 0.01 to 1.72 ± 0.05 to 2.31 ± 0.12, respectively.[59] The reactions with isopropyl and *t*-butyl chloride obviously occur mainly by the $E2$ pathway whereas methyl chloride obviously reacts by an S_N2 mechanism. The calculated reaction efficiencies for the S_N2 and $E2$ reactions between ethyl chloride and ClO^- have been found to be 2 and 26%, respectively, and the corresponding KIEs were 0.60 and 3.1, respectively, at the MP2/ADZP level of theory.[60] An overall KIE of 2.4 was predicted for the gas-phase reaction. The small experimental KIE of 0.99 for the perdeuteroethyl chloride reaction indicates that the S_N2 channel is much more important than the calculations suggest. The discrepancy between the experiment and the calculations was attributed to the difficulty in calculating the barrier height for the two reactions accurately.

Six different kinetic isotope effects for the S_N2 reaction between cyanide ion and ethyl chloride were measured in DMSO and in THF to learn how the change in solvent affected the structure of the transition state.[61] The secondary α- and β-deuterium, the α-carbon, the k^{11}/k^{14} nucleophile carbon, the nucleophile nitrogen, and the chlorine leaving group kinetic isotope effects for the reaction showed that the transition state in THF was only slightly tighter than that in DMSO, with very slightly shorter NC–C_α and C_α–Cl bonds. This change in transition-state structure supports the earlier contention that the transition states for S_N2 reactions where the nucleophile and the leaving group have the same charge would not be affected significantly by a change in solvent.[62] The results also suggest that the failure of theoretical calculations to reproduce the experimental KIEs in DMSO was not due to a lack of solvent modeling in the calculations.[63]

The large, inverse, solvent kinetic isotope effects, $k_{CH_3OD}/k_{CD_3OD} = 0.84$ and $k_{CH_3OH}/k_{CD_3OH} = 0.74$ found in the reaction (Scheme 20) of methanol with the intermediate aziridine (**44**) produced in the reaction between tetramethylethylene (**43**) and *N*-phenyltriazolinedione (**42**),[64] supported the existence of a tight S_N2-type transition state (**45**) with extensive O–C bond formation in the ring-opening step of the reaction,

i.e. these KIEs were attributed to the lesser steric hindrance with the smaller deuterated solvent. The KIEs of $k_{CH_3OD}/k_{CD_3OD} = 0.72$ and $k_{CH_3OH}/k_{CD_3OH} = 0.81$ found in the reaction with trimethylethylene were taken as evidence of a looser transition state.



SCHEME 20

The formation of organic fluorides has been a difficult undertaking. However, an investigation of the effect of the solvent, leaving group, and source of the fluoride ion has shown that using tetrabutylammonium fluoride or CsF in *t*-amyl alcohol is able to convert arene sulfonates into fluorides rapidly at 90 °C in excellent yields (>80%).[65] Since the half-life of ^{18}F is only 110 min, this is an important advance as it allows one to label compounds with ^{18}F for PET studies.

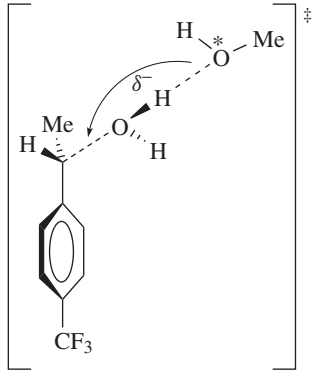
The transition structures and secondary α-deuterium and solvent KIEs were calculated for the S_N2 reactions of fluoride ion (solvated by water, MeOH, or HF) with methyl chloride, bromide, and iodide at the B3LYP/6–31++G(d,p) and MP2/6–31++G(d,p) levels of theory.[66] The rotational, vibrational, and translational contributions to the KIEs were also determined. One observation is that the KIEs calculated using the DFT method do not agree with the experimental KIEs. This is because the B3LYP/6–31++G(d,p) level of theory gives less inverse contributions from the out-of-plane bending vibrations. The solvent KIEs ($k_{CH_3OH}/k_{CD_3OD} \approx 0.6$) are substantially more inverse than the secondary α-deuterium KIEs ($k_{CH_3X}/k_{CD_3X} \approx 0.8$) and the KIEs found by deuterating the methyl group of MeOH (k_{CH_3OH}/k_{CD_3OH}) are also fairly large and inverse at approximately 0.8. The product of the translational, rotational, and low-frequency vibrational contributions to the total KIE is small and normal whereas the remaining vibrational contribution to the KIEs is large and inverse. It is interesting that the solvent molecule in these calculations increases the steric crowding in the transition state, making the out-of-plane bending

contribution to the KIE and the total KIE more inverse. The solvent KIE arises mainly from the change in the OH stretching vibration in water due to loss of the hydrogen bond to the F^- ion on going to the transition state. The important discovery however, is that transition-state theory cannot be used to predict either the solvent or the secondary α-deuterium KIEs for fast reactions having small or negative free energies of activation; thus, the calculated KIEs for the slow methyl chloride reaction agree with experiment very well whereas the calculated KIEs for the faster reactions with methyl bromide and especially methyl iodide are much more inverse than the experimental values. This is because the slow step of the fast reactions is the collision of the reactants and not passing over the transition state as transition-state theory requires.

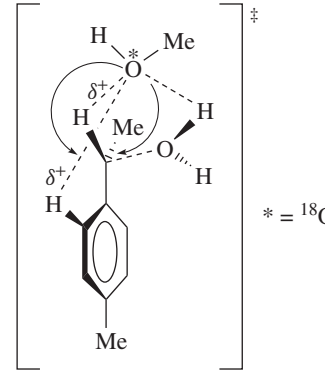
Finally, reviews discussing nucleophile carbon k^{11}/k^{14},[67] nitrogen k^{14}/k^{15},[68] and secondary α-deuterium[69] kinetic isotope effects in S_N2 reactions have been published.

Gas-phase Substitution Reactions

The substituent effect on the stereochemistry of the S_N1 methanolysis (using $Me^{18}OH_2^+$) of the pure stereoisomers of 1-arylethanols has been studied at different temperatures in the gas phase in the presence of triethylamine (to absorb the proton released in the S_N1 reaction) and methyl fluoride (to ensure complete thermalization).[70] The product with a retained stereochemistry is formed preferentially at or near room temperature in every case. Transition state (**47**) is favoured for carbenium ions with electron-withdrawing substituents where the greater positive charge on C_α increases the strength of the partial bond between the nucleophiles and C_α. The inverted product is believed to arise from transition state (**48**) that can form with more stable carbenium ions and those reacting at higher temperatures where the bonding to the nucleophiles is weaker. In fact, a racemic product is obtained at higher temperatures in the reaction where the *para*-substituent is H. The results are compared with those from similar reactions in solution.



(**47**)



(**48**)

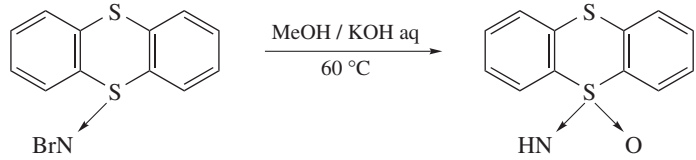
The S_N2 transition states and the encounter complexes for back- and front-side attack in the gas-phase reactions between $X:^-$ and CF_3X have been calculated at the

B3LYP/6–311+G(3df)//B3LYP/6–311+G(d) level of theory and determined experimentally using pulsed-ionization high-pressure mass spectrometry.[71] The front-side encounter complexes are more stable than the back-side complexes, probably due to the electrostatic repulsion between the nucleophile and the negatively charged fluorines in the back-side complexes. In spite of this, the reactions all occurred via back-side attack from the back-side $[X–CF_3–X]^-$ encounter complex because the back–side transition states were approximately 20 kcal mol^{-1} more stable than the front-side transition states. Where it could be checked, the theoretical and experimental values of ΔH° and ΔS° for formation of the encounter complexes agreed very well. Since the $Cl:^- + CF_3Br$ S_N2 reaction is described very well by Marcus theory, it is suggested the reaction is initiated by an electron transfer.

The perdeutero KIEs measured for the gas-phase reactions between methyl-, ethyl-, isopropyl- and *t*-butyl-chlorides and ClO^- [59] are discussed above.

Nucleophilic Substitution on Elements Other than Carbon

Possible mechanisms have been suggested for the alkaline hydrolysis of 5-(*N*-bromo) iminothianthrene (**49**) and its *cis*- and *trans*-10-oxide and 10,10-dioxide derivatives.[72] The base compound (**49**) and the *cis*-10 oxide undergo both changes shown in Scheme 21; i.e., formation of (**50**) by substitution at bromine and oxidation at sulfur. The *trans*-10-oxide and the 10,10-dioxide derivatives either react at bromine only or undergo both the reaction at bromine and at sulfur.

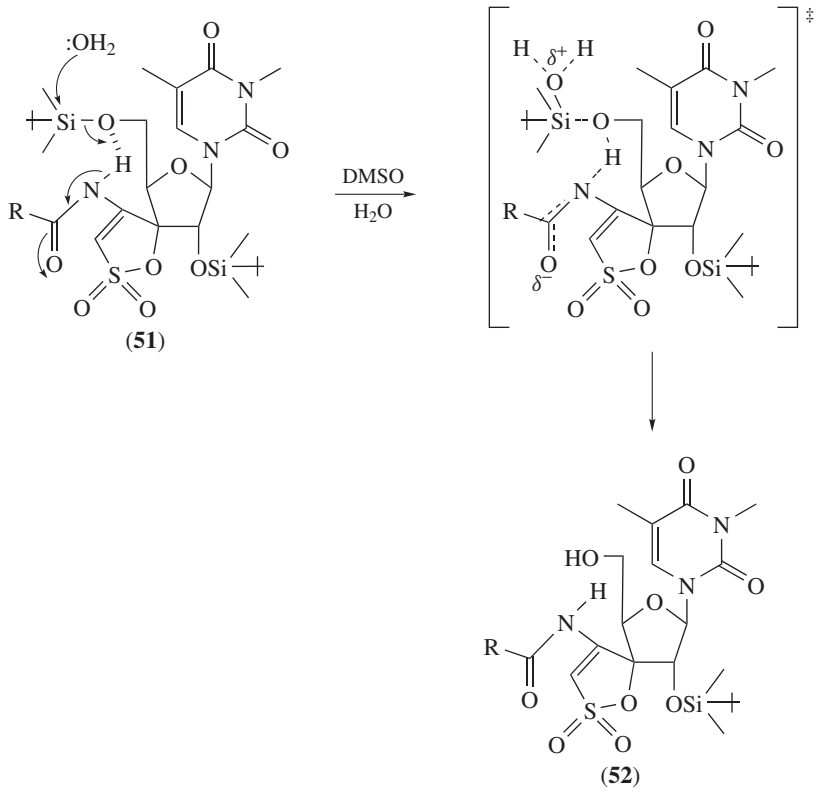


(**49**) (**50**)

SCHEME 21

The mechanism of the S_N hydrolysis reaction at silicon removing the 5′-*t*-butyldimethylsilyl group of 3-spiro-5″-(4″-acylamino-1″, 2″-oxathiole-2″, 2″-dioxide) nucleoside derivatives (**51**) involves neighbouring group participation by the N–H hydrogen of the 4″-acylamino group (Scheme 22).[73] Calculations at the B3LYP/6–31+(d) level of theory on modified substrates showed that the 4″-N–H bond was longer, the H–O distance from the 4″-N–H to the O of the 5′-silyloxy group was shorter, and the 5′-Si–O bond was longer in the substrates with a more electron-withdrawing group on the oxygen on the 4″-carbonyl group. All of these factors should increase the reactivity in agreement with experiment. Finally, the greater reactivity found in the most polar solvent tested, DMSO–water, is expected given the proposed mechanism.

The potential energy surfaces for the S_N2 reactions at carbon, silicon, and phosphorus have been calculated using the Amsterdam Density Functional method with the



SCHEME 22

OLYP/TZ2P functional.[74] The identity reactions where the leaving group was Cl^-, OH^- and OCH_3^- were investigated. Whereas the S_N2 reaction at carbon showed the expected two encounter complexes and one transition state, the reactions at silicon and phosphorus formed one stable encounter complex and no transition state. Although increasing either the steric crowding slightly or the coordination number on phosphorus does not change the mechanism, increasing both the coordination number *and* the steric crowding markedly causes the energy of the transition complex to increase and leads to a triple-well potential energy surface. However, adding a more electronegative atom to the phosphorus, i.e. changing a Cl to F, or changing to a better nucleophile, led to a reaction with the formation of a stable encounter complex and no central barrier. An activation strain model was used to illustrate how steric strain and electronic effects affect the central barrier for these reactions.

A review[75] of the S_N reactions at neutral nitrogen, oxygen, and sulfur has been published. The substitution reactions at nitrogen and oxygen predicted by theory and found experimentally occur by an S_N2 mechanism and are faster than the corresponding reactions at carbon. The S_N reactions at sulfur, on the other hand, mostly occur by an addition–elimination mechanism, although some S_N2 mechanisms have been

suggested. The stereochemistry and mechanisms of the S_N reactions at carbon and nitrogen that occur when the nucleophile is an ion pair rather than a free ion, are also included.

Medium Effects/Solvent Effects

The effect of high concentrations of $MClO_4$, $M(ClO_4)_2$, and R_4NX salts on S_N1 and S_N2 hydrolyses in aqueous sulfolane has been investigated.[76] In the S_N1 reaction of 1-adamantyl chloride and 2-adamantyl bromide, increasing the concentration of either $MClO_4$ or $M(ClO_4)_2$ causes a large increase in rate. In fact, the order of rate increase with concentration was $Na^+ < Li^+ < Mg^{2+} = Ba^{2+}$. The cation was thought to provide electrophilic catalysis in the removal of the leaving group (carbenium ion formation) and by changing the bulk properties of the solvent into those of a non-aqueous solvent. The addition of R_4NX salts decreased the rate of reaction of both adamantyl substrates with the order $ClO_4^- < Br^- < Cl^- < TsO^-$ by decreasing the activity of the water acting as a nucleophile. Increasing the length of the carbon chains in the ammonium ion also decreased the rate of the S_N1 reaction. Cobalt and particularly nickel salts were effective in accelerating the S_N1 reaction of 1-adamantyl chloride. The rates of the S_N2 reactions of *n*-hexyl halides and tosylate decreased slightly on addition of high concentrations of metal and ammonium perchlorates. The effect was attributed to a decrease in the activity of the water nucleophile. However, adding ammonium halides can either increase (by converting R–Cl into R–Br) or decrease (by converting R–Br into R–Cl) the rates of reaction by introducing a competing S_N2 halide exchange reaction. Raman spectroscopy was used to show that adding salts or organic solvents or increasing the temperature broke up the hydrogen-bonding network in the bulk water solvent.

The energy barriers and solvent effects for the S_N2 identity reactions of methyl halides have been calculated in the gas phase and in aqueous solution using several valence bond PCM methods.[77] The breathing orbital valence bond (BOVB) and the valence bond-polarized continuum (VBPCM//BOVB) model reproduced the experimental reaction barriers, ($F > Cl > Br > I$) the solvation energies of X^- ($F^- > Cl^- > Br^- > I^-$) and the theoretical quantum mechanical results very well. The triple-ion VB structure makes the most important contribution to the transition-state wavefunction in the gas phase and this contribution is even greater in solution. The results shed light on the origin of the barrier heights and the solvent effects on these reactions.

The nucleophilicity of chloride ion in the S_N2 reaction with methyl benzenesulfonate was found to decrease as the solvent was changed from cyclohexane to acetone to butan-2-one to DMF to acetonitrile to methanol.[78] Activation parameters in each solvent are reported.

The effect of solvent on the S_N2 reaction between methyl iodide and 2-amino-1-methylbenzimidazole has been investigated experimentally in acetonitrile and in the gas phase at two different levels of theory, B3LYP/[6–311++G(3df,3pd)/LanL2DZ]//B3LYP/[6–31G(d)/LanL2DZ] and B3LYP/[6–311++G(3df,3pd)/LanL2DZ]//B3LYP/[6–31+G(d)/LanL2DZ].[79] The effect of the acetonitrile was determined using the

PCM model. AIM calculations were also used to investigate hydrogen bonding in each intermediate. The experimental and theoretical results are in excellent agreement. The calculations also indicate the reaction will be much faster in acetonitrile than in the gas phase, as one would expect for a process forming ionic products.

The energies and structures of the transition states and the activation parameters for the S_N2 reactions between *para*-substituted benzyl bromides and bromide ion or pyridine have been calculated at the B3LYP/6–31G(d) level of theory in the gas phase and in acetone using the PCM model.[80] The charges, bond lengths, and bond angles for the transition states for reaction in the gas phase and in acetone correlated with the Hammett σ and σ^+ constants, respectively. An electron-withdrawing *para*-substitutent leads to a tighter transition state in the gas phase. The substituent effects are larger and the transition states looser in acetone. In the gas phase, both $\Delta G^{\neq}$ and $\Delta H^{\neq}$ correlated with σ whereas in solution both the calculated and experimental $\Delta G^{\neq}$ and $\Delta H^{\neq}$ were a maximum when the *para*-substituent was H, i.e. both electron-donating and electron-withdrawing substituents increased the rate of reaction with bromide ion. The calculated $\Delta G^{\neq}$ and $\Delta H^{\neq}$ are smaller than the experimental values. This was attributed to the form of the bromide ion, i.e. a free ion in the calculations and an ion pair in acetone.

The reactions with pyridine have different transition states in the gas phase and in solution, i.e. the transition states are central in acetone and methanol but product-like in the gas phase. This is attributed to the attraction of the developing positive and negative charges on these transition states in the gas phase. The calculated changes in geometry of the transition states and in $\Delta G^{\neq}$ and $\Delta H^{\neq}$ correlate with σ in the gas phase but σ^+ in solution. As in the reaction with bromide ion, however, the $\Delta G^{\neq}$ and $\Delta H^{\neq}$ values in acetone are maximum when the *para*-substituent is H. Also, the substituent effect is again greater in solution than in the gas phase. Finally, the failure of the calculations, even at higher levels of theory, to calculate the breaks in the $\Delta G^{\neq}$ and $\Delta H^{\neq}$ versus Hammett substituent constants in solution suggests that solvation effects play an important role in these reactions.

Finally, the substituent effects on the pyridine nucleophile are smaller than those on the substrate and both the calculated and experimental $\Delta G^{\neq}$ and $\Delta H^{\neq}$ correlate with the corresponding σ values. A better nucleophile leads to a later transition state.

The rate of the S_N2 reaction between benzyl bromide and benzimidazole in 11 solvents was found to vary with two properties of the solvent: the polarizability and the hydrogen bond acceptor (basicity), with a slightly stronger correlation with the polarizability of the solvent.[81] The importance of the polarizability is due to the need to solvate the developing positive charge on the nitrogen nucleophile in the transition state. The hydrogen bond acceptor ability is required for solvating the developing negative charge on the bromide ion in the transition state. The $\Delta G^{\neq}$ values become smaller and the $\Delta S^{\neq}$ values more negative when the solvent is changed from methanol to most other solvents. This behaviour is found because of the developing charges in the transition state. The usual V-shaped Hammett ρ plot with the slowest reaction for the unsubstituted benzyl bromide was observed for the reaction. Finally, the reaction is less affected by substituents at higher temperatures.

The rate of the S_N2 reaction between *p*-nitrobenzyl bromide and 2-mercaptobenzoxazole has been measured in 14 protic and dipolar aprotic solvents.[82] The rates correlated strongly with the electron pair accepting ability and the hydrogen bond accepting ability of the solvent, with the former being almost twice as important as the latter. The transition state is more highly solvated than the reactants. The solvent hydrogen bond accepting ability is important because it solvates the developing chloride ion and the electron pair accepting ability is important because it solvates the developing positive charge on the sulfur nucleophile. The $\Delta G^{\neq}$ values are effectively independent of the solvent.

The solvolysis of trimethylsilyl trifluoromethanesulfonate has been determined in several solvents and solvent mixtures.[83] The two-term Grunwald–Winstein equation indicated that the rates were strongly dependent on the nucleophilicity and only slightly dependent on the ionizing power of the solvent. This, and the large negative $\Delta S^{\neq}$ found in four solvents, suggest the reactions occur by an S_N2 mechanism. The trimethylsilyl group does not affect the rate appreciably, probably because the steric and electronic effects of the trimethylsilyl group are almost equal.

The rate of the solvolysis reaction between 3-methyl-3-chlorobut-1-ene and 13 different alcohols correlated ($r = 0.977$) with the solvent's E_T value.[84] The weak negative correlation with solvent nucleophilicity and the first-order kinetics was taken as evidence that the reaction occurs via an S_N1 mechanism.

A detailed reassessment of several multi-parameter correlations describing the solvent effects on the rates of four solvolytic S_N reactions has shown that great caution should be exercised when using these relationships.[85] The conclusions based on the multi-parameter correlations are not reliable because (i) both random and systematic errors have been underestimated, (ii) mechanisms may change when different substrates are involved, (iii) data extrapolated from different temperatures, and (iv) only small numbers of samples have been used in establishing these relationships.

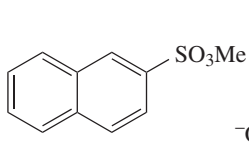
The N/s values [where $\log k = s(E + N)$] for several carbanion (nitronate and malonic acid derivatives) nucleophiles have been determined using benzhydrilium ions in MeOH–acetonitrile (9:91 v/v) and compared with the corresponding values in H_2O and in DMSO.[86] With one exception, $^{-}CH(CN)_2$, the nucleophilicity increases from water to MeOH to DMSO by varying amounts. The difference in behaviour is attributed to solvation rather than to the basicity of the anions.

Finally, a study in which six different kinetic isotope effects for the S_N2 reaction between cyanide ion and ethyl chloride were measured in DMSO and in THF has shown that the transition state in THF was only slightly tighter than that in DMSO with very slightly shorter NC–C_α and C_α–Cl bonds,[61] and another on the effect of the solvent, leaving group, and source of the fluoride ion in synthesizing organic fluorides is discussed above.[65]

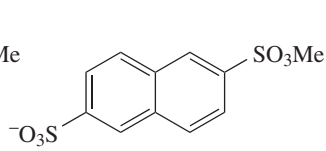
Micelles and Phase-transfer Catalysis in Substitution Reactions

Several studies have examined the effect of micelles on the rates of S_N reactions. The S_N2 reactions of (**53**), (**54**), and (**55**) with bromide ion have been studied in wet CH_2Cl_2

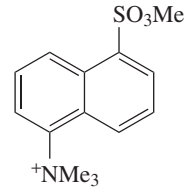
in the presence of the reversed micelles formed from cetyltrimethylammonium bromide (CTA), cetyltripropylammonium bromide (CTPA), and tetra-*n*-butylammonium bromide (TBA).[87] The rates of (**53**) and (**54**) increase markedly in the presence of the micelles whereas the rate of (**55**) does not, presumably because the positive (**55**) does not interact with the cationic micelle. It is suggested that (**55**) reacts fastest because of the ionic attraction between the charges on the substrate and the bromide ion; (**53**) reacts the slowest. The rate of reaction of (**55**) decreases as the micelles change from TBA to CTPA to CTA. This occurs because the bromide ion interacts more strongly with the ammonium ion when the head group is smaller. Adding more water to the reaction mixture reduces the rate of all three reactions until the ratio $\{[H_2O]/[CTA]\} = w_0 \approx 6$, where 'water pool' reverse micelles form. The initial decrease in rate on adding water presumably occurs because water solvates the bromide ion by hydrogen bonding. Adding water does not change the relative reactivity of (**53**)–(**55**).



(**53**)



(**54**)



(**55**)

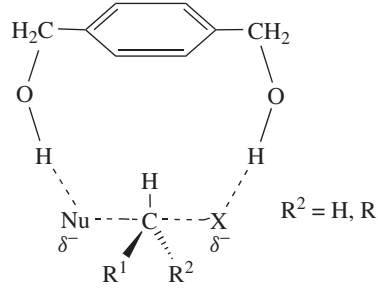
The effect of different cationic micelles on the S_N2 reaction between methyl 4-nitrobenzenesulfonate and bromide ion has been studied.[88] The micelle systems were hexadecyltributylammonium bromide and four alkyltriphenylphosphonium bromides featuring C_{10}-, C_{12}-, C_{14}-, and C_{16}-alkyltriphenylphosphonium groups, respectively. As expected, the rate of reaction increases with increase in the surfactant concentration and the hydrophobic chain length of the surfactant for all of the surfactants tested. However, the rate increases are greater with the alkyltriphenylphosphonium bromides. Reasons for this are suggested. Two mixed micelle systems investigated had slower rates and showed non-ideal behaviour. Only a mixed micelle system of two triphenylphosphonium salts showed ideal behaviour. Molecular modeling at the HF/6–31+G* level of theory using a single surfactant molecule suggested that the superior catalysis of the alkyltriphenylphosphonium bromides was due to (i) the phosphorus being positively charged whereas the nitrogen is negatively charged in the ammonium salt surfactants because its positive charge is distributed over its substituent groups and/or (ii) the bromide ion interacting less strongly with the alkyltriphenylphosphonium head group due to steric hindrance with the phenyl substituents; this allows more room for substrate binding.

Adding more tetradecyltrimethylamonium bromide micelles to the S_N2 reaction between methyl naphthalene-2-sulfonate in aqueous DMSO increases the rate by (i) increasing the amount of substrate in the micelle where the bromide ion concentration is high, (ii) increasing the electrophilic interaction of the ammonium head groups with the developing naphthalene-2-sulfonate ion, and (iii) disrupting the hydration shell around the bromide ion nucleophile. However, increasing the proportion of DMSO

decreases the catalytic effect of the micelles.[89] This occurs because (i) the substrate does not bind to the micelles as well at higher [DMSO], where the bulk phase becomes a better solvent for the substrate, and (ii) the micelles become smaller, i.e. they ionize more, so less substrate is bound in the micelles, thereby reducing the amount of reaction catalysed by the micelle. The rate constant for the S_N2 reaction in the micelle is not affected significantly by the amount of DMSO in the solvent.

Three papers have reported on phase-transfer types of catalysis. The ionic liquid butylmethylimidazolium tetrachloroferrate catalyses the biphasic S_N reaction between primary and secondary alkyl halides with β-hydrogens and the Grignard reagent *p*-FC_6H_4MgBr.[90] The yields ranged from 60 to 89%.

The other two papers have investigated the catalytic effect of 1,4-benzenedimethanol on the S_N2 reaction between acetate ion and ethyl chloride in DMSO.[91,92] Calculations using the ONIOM[CCSD(T)/6–311+G(2df,2p):MP2/6–31+G(d)] level of theory and the PCM solvent continuum model suggest that the overall effect of the catalyst is to reduce $\Delta G^{\neq}$ by 5.9 kcal mol^{-1} by stabilizing the transition state (**56**), even though the catalyst also stabilizes the acetate ion. Another advantage of this type of catalysis is that it should reduce the amount of any competing $E2$ reaction. These calculations also suggest that the catalysis of the S_N2 reaction between alkyl chlorides and acetate ion by 1,4-benzenedimethanol will be more effective for primary alkyl chlorides than for secondary alkyl chlorides.[92] The catalytic effect in DMSO is smaller for secondary chlorides, i.e. the catalyst reduces $\Delta G^{\neq}$ by 4.7 kcal mol^{-1} for the propyl chloride reaction whereas it reduces $\Delta G^{\neq}$ by only 0.6 kcal mol^{-1} for the isopropyl chloride reaction. The catalytic effect is smaller for isopropyl chloride because (i) the transition state is looser and solvation of the nucleophiles in the transition state is greater making catalysis less important and (ii) increasing steric hindrance between the substrate and the catalyst makes catalyst binding weaker.



(**56**)

Structural Effects

The effect of changing the nucleophile in an S_N reaction continues to attract considerable interest. A study of the rates of the S_N2 reactions between *S*-methyldibenzothiophenium ion or methyl iodide and many nucleophiles[93] has shown that the

nucleophilicity towards C_{sp^2} and C_{sp^3} are closely related. This has led to the suggestion of a new equation, $\log k = s_E s_N(E + N)$, where s_E is the electrophile specific slope, s_N is the nucleophile specific slope, E is the electrophilicity parameter and N is the nucleophilicity parameter, relating nucleophilicity to reactivity. It is important to note that this equation encompasses the familiar $\log k = s_N(E + N)$ used for the S_N1 reactions of benzyhydryl substrates, etc., when $s_E = 1.0$, the familiar Swain–Scott equation when $s_N = 0.6$, and the Ritchie equation when $s_E = 1.0$ and $s_N = 0.6$. Some possible limitations for the new equation are suggested.

A $\log k_s = s_f(E_f + N_f)$ equation relating the rate of solvolyses to the nucleofugality (the leaving group ability) of a leaving group in a specific solvent and from a specific substrate has been proposed,[94] where N_f and s_f are nucleofuge-specific parameters and E_f is an electrofuge-specific parameter. The nucleofugality, N_f, which varies with the substrate, leaving group, and solvent, is found from k_s by setting $s_f = 1.00$ and $E_f = 0.00$ for the 4, 4′-diansylcarbenium ion and the leaving group Cl^- in ethanol at 25 °C. N_f values were reported for TsO^-, Br^-, Cl^-, $CF_3CO_2^-$, 3,5-dinitrobenzoate and *p*-nitrobenzoate in EtOH, 80% EtOH–water, MeOH, TFE, and 80 and 90% acetone–water. E_f values were also found for several substituted benzhydryl carbenium ions. The solvent effect on the ionization rates k_s for benzhydryl-LG correlates with the negative charge density on the leaving group (LG) and falls in the order R-Cl > R-Br ≈ R-OTs > R-CF_3CO_2 > R-3,5-dinitrobenzoate. The E_f value correlates very well ($r^2 = 0.992$) with the Hammett σ value and inversely with the electrophilicity parameter ($r^2 = 0.996$) E from the $\log k = s(N + E)$ equation.

In a second publication, E_f and N_f values for the $\log k_s = s_f(E_f + N_f)$ equation have been determined for many new carbenium ions and leaving groups in different solvents.[95] An analysis of the data indicated that s_f was equal to or near 1.0 for most S_N1 reactions and that compounds having $(E_f + N_f) > -2$ solvolyse with half-lives of <1 min whereas those with $(E_f + N_f) > -6.5$ solvolyse with half-lives of >1 month. Substrates with intermediate values of $(E_f + N_f)$ react at measureable rates at 25 °C. Hence, one can use the N_f and E_f values to determine if a substrate will be stable during purification and or a synthetic transformation or whether it will undergo solvolyses too fast to be purified or reacted.

A critical analysis of the $\log k_s = s_f(E_f + N_f)$ equation has been published[96] and new equations that provide more reliable E_f and N_f values have been suggested. The proposed E_f and N_f values are $E_f = \log k_{RCl/EtOH/25\,^\circ C} - 1.87$ and $N_f = 6.14 + \log k_{BX/any\ solvent/25\,^\circ C}$, where RCl and BX are chlorides and benzhydryl substrates, respectively. A new equation, $\log k_{t\text{-alkylX/any solvent}} - E_f + N'_f$ where $N'_f = 3.90 + Y_{any\ solvent} + \log k(X/Cl)$ is proposed for the solvolysis of *t*-butyl chloride and similar substrates.

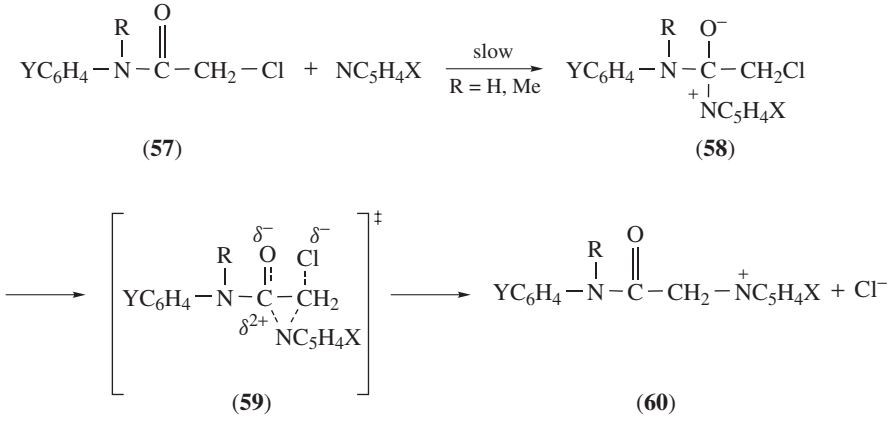
The nucleophilicity scale based on the stretching frequency of the hydrogen bond between a nucleophile and an acid (Nu–HX) [97] was tested against experiment using the hard acids HF, HCN, and BF_3 and the soft acid BH_3.[98] The correlation with the hard acids is excellent but fails when a soft acid is used. A new nucleophilicity index, $\omega^- = \frac{1}{2}[(\mu_A - \mu_B)^2/(\eta_A + \eta_B)^2]\eta_A$, where μ_A, and μ_B, are the chemical potentials of the nucleophilic and electrophilic molecules, respectively, and η_A and η_B are their respective hardnesses, has been proposed. This gives the relative nucleophilicity that is

based on the electrophile used. The μ and η values are found using the frozen orbital and finite difference approximation, respectively. The new nucleophilicity scale has been tested using gas-phase S_N2 reactions of MeCl, MeBr and $MeOCOCF_3$. The reaction efficiency, the rate of reaction/rate of collision, correlated with ω^- for the MeCl and MeBr reactions ($r = 0.980$ and 0.923, respectively) but less well for the $MeOCOCF_3$ reactions where $r = 0.851$.

The potential energy profiles of 18 identity S_N2 reactions of methyl substrates where the nucleophile is NH_2^-, OH^-, F^-, PH_2^-, SH^-, Cl^-, AsH_2^-, SeH^-, or Br^- and their protonated (neutral) form, have been estimated in the gas phase using G2 quantum-chemical calculations.[99] The barrier heights, which are calculated to within 10 kJ mol^{-1}, and the geometry of the transition states, are very similar for anionic and neutral nucleophiles. The width and height of the central barrier and the imaginary frequency vary significantly with the nucleophile. The barrier height decreases from left to right in the periodic table and is related inversely to the ionization energy of the nucleophile. Reactions where the substrate has a greater charge separation have lower central barriers due to decreased electron repulsion in the transition state. Where they form, the front-side encounter complexes (CH_3–X–X) are more stable than the back-side encounter complexes. However, PH_2^-, SH^-, AsH_2^- and SeH^- do not form an encounter complex. The S_N2 transition states, however, display the normal Walden inversion. The C–X bond length in both the reactants and transition states decreases as the nucleophilic atom moves from right to left and up a column in the periodic table. The C–X transition state bond length increases with the height of the central barrier for both the neutral and negative nucleophiles. Finally, it is suggested that nucleophilicity is determined by two factors, exothermicity of the reaction (basicity of the nucleophile) and the intrinsic reactivity (barrier height) of the nucleophile. Intrinsic nucleophilicity will dominate for thermal neutral and slightly exothermic reactions while nucleophilicity will be related to basicity in very exothermic reactions.

A kinetic study showed the S_N reactions between *meta*- and *para*-substituted pyridines and *para*-substituted α-chloroacetanilides (**57**; R = H) were faster than those with *para*-substituted *N*-methyl-α-chloroacetanilides (**57**; R = Me).[100] Also, the small and negative cross-interaction constants ($\rho_{XY} = -0.06$ and -0.10, respectively) and the small Brønsted β_X coefficients (0.30 and 0.32, respectively) for the two sets of substrates and the failure of the reactivity–selectivity principle suggest the mechanism involves a slow nucleophilic attack on the carbonyl carbon followed by a rapid concerted transfer of the nucleophile and expulsion of the leaving group from intermediate (**58**) (Scheme 23). The *N*-methyl substrate reacts slower because the methyl group reduces the positive charge on the carbonyl carbon in the rate-determining step of the reaction.

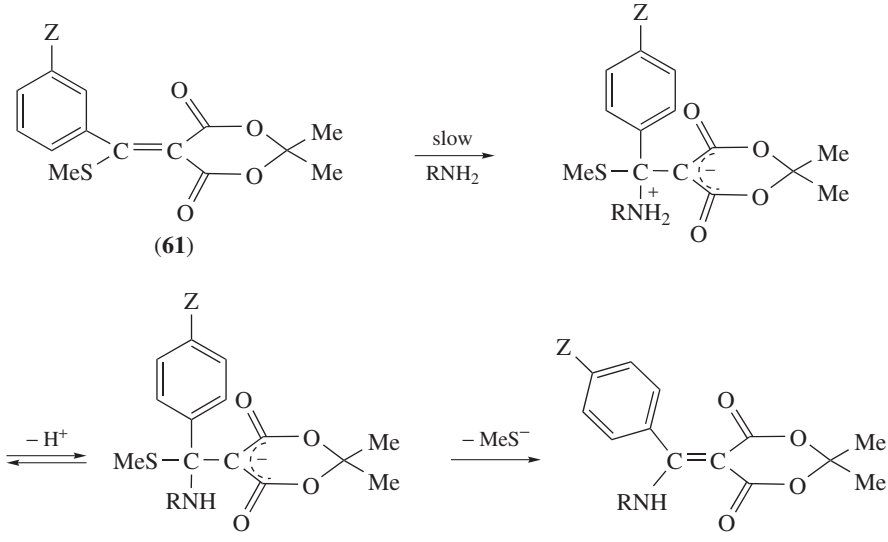
A kinetic study in 50% aqueous DMSO has shown that the first step in the three-step mechanism (Scheme 24) proposed for the S_NV reaction between *para*-substituted (methylthio)benzylidene Meldrum's acids (**61**) and four aliphatic primary amines is rate determining.[101] The evidence supporting this mechanism is that the reactions are second order kinetically and show no base catalysis. A value of $\beta_{nuc} = 0.32$ for the reaction with primary amines is smaller than the $\beta_{nuc} = 0.41$ found for the reaction with the less reactive secondary amines, indicating that N–C_α bond formation is more



SCHEME 23

advanced in the transition state of the latter reaction. This is a Hammond–Leffler effect. Hammett plots found by changing the Z substituent gave $\rho = 0.40$ for the reaction with butylamine. Larger Hammett ρ values were found for the reaction with piperidine and oxygen and sulfur nucleophiles, confirming an earlier transition state with less N–C_α bond formation and less positive charge on nitrogen in the butylamine (the primary amine) reaction.

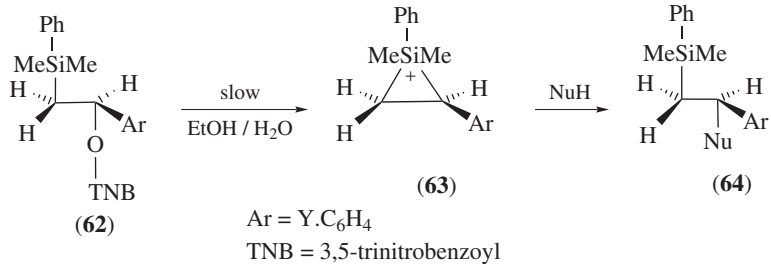
The Hammett ρ values for the S_N2 reaction between diphenylamine and *para*-substituted benzyl bromides in methanol decrease from 0.64 to 0.10 as the reaction



SCHEME 24

temperature increases from 298 to 313 K.[102] This suggests that the isokinetic temperature (where the substituent effect = 0.0) is 315 K. The $\Delta H^{\neq}$ values vary directly with the $\Delta S^{\neq}$ values for these reactions.

The solvolysis rates of 2-(dimethylphenylsilyl)-1-(Y-phenyl)ethyl 3,5-dinitrobenzoates (**62**) in 60% aqueous ethanol were analysed using using the Yukawa–Tsuno equation.[103] The ρ value of -2.95 with $r \approx 1.04$ found by changing the α-aryl substituent was much smaller than the ρ value of -5.45 found for the corresponding non-silylated system. This, the fact that the rate constant for the silylated substrate was $>10^5$-fold faster than the rate of the non-silylated compound, and the small α value of 0.52 found from the $\log(k_Y/k_H)_{Si} = \alpha \log(k_Y/k_H)_{non\text{-}Si}$ plot was taken as evidence that the reaction of the silyl compound occurred via a tight transition state with significant neighbouring silyl participation (Scheme 25).



(**62**) (**63**) (**64**)

Ar = Y.C_6H_4

TNB = 3,5-trinitrobenzoyl

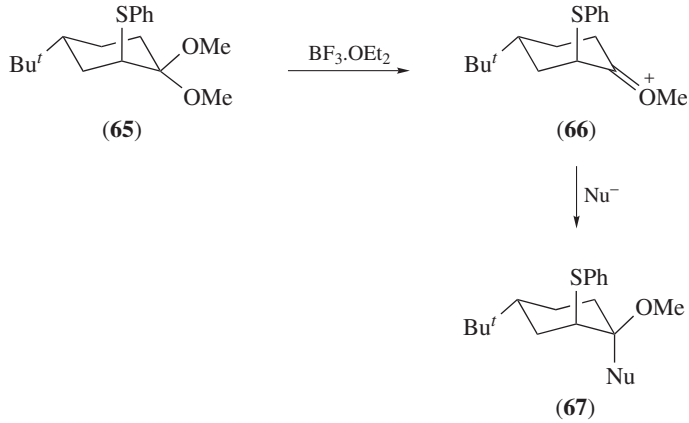
SCHEME 25

The S_N reactions of cyclohexanone acetals substituted at C(2) with sulfur, iodine, or chlorine are thought to occur when the nucleophile attacks the oxocarbenium ion intermediate with the substituent on C(2) in an axial conformation.[104] The most stereospecific reactions (i.e. $\geq$92% *trans*), were when the substituent at C(2) was sulfur. This mechanism (Scheme 26) is supported by HF/6–31G* calculations that show the oxocarbenium ion (**66**) with the sulfur at C(2) in the axial position to be the most stable, and by the high yield of the *trans*-isomer (**67**) in the products.

Finally, the substituent effects on the geometry of the *N*-substituted aziridine ring, the *N*-inversion energy barriers, and the ring opening reactions of aziridines by cyanide ion[53] have been discussed

Theoretical Studies

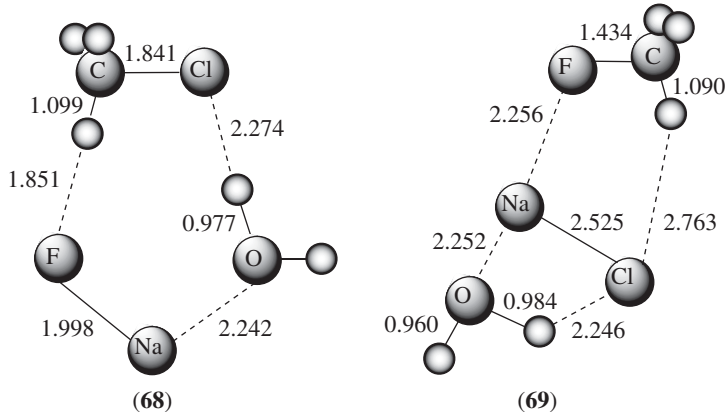
Most of these theoretical investigations have been carried out using methyl compounds as the substrate. For example, the S_N2 reaction between OH^- and methyl chloride has been investigated for non-linear and linear collisions using *ab initio* molecular dynamics calculations.[105] The potential energy surface was calculated at the MP2/6–311++G(2df,2pd) level of theory and the collision energy was set at 25 kcal mol^{-1}. The results for 495 trajectories indicated that the reactants pass from the initial encounter complex to the transition state in 0.02 ps and to the product encounter



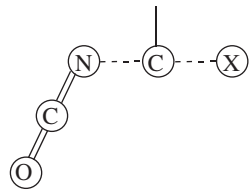
SCHEME 26

complex in another 0.04 ps. The total reaction is over in 0.30 ps. Some of the energy is transferred into the internal modes of the product while 72% goes to translational motion of the products. The populations of the translational energies are different for the linear and non-linear collisions, being broader for the non-linear collisions. Although the maximum translational energy is normally found for a collinear reaction, the maximum translational energy in this reaction occurs when the incoming nucleophile is ~1.2 Å from the straight line defined by the linear transition state geometry. This is because the transition state is slightly bent with an O–C–Cl angle of 183.1°.

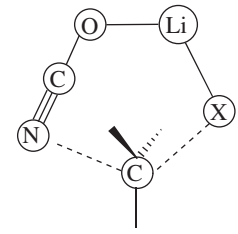
B3LYP/6–311++G**-level calculations have been used to predict the structure of the encounter complex (**68**) for the S_N2 reaction between F^- and methyl chloride in the presence of one molecule of water.[106] Structure (**68**) was chosen as the encounter complex even though it does not have the lowest energy, but because it has the greatest negative charge on fluorine. Structure (**69**) is the encounter complex for the reverse reaction.



The S_N2 reactions of a free cyanate ion or a lithium isocyanate ion pair with methyl halides have been investigated at the MP2/6–311+G(d,p) level of theory.[107] Although the ion-pair reactions are slower than the free-ion reactions, the calculated $\Delta H^{\neq}$ decreases in the order MeF > MeCl > MeBr > MeI as expected for both the free-ion and ion-pair reactions. The calculations also show that both the free-ion and ion-pair reactions occur with inversion, rather than with retention of configuration, via the transition states (**70**) and (**71**), respectively. In both the free-ion and ion-pair reactions, the percentage extension of the C–X bond in the transition state decreases when a better leaving group is used, i.e. the transition state is earlier for leaving groups having a smaller C–X bond dissociation energy. Finally, including the solvent DMSO in calculations using the PCM approach leads to a much slower reaction with a looser transition state but does not change the mechanism of either the free ion or the ion pair reaction. In agreement with experiment, the calculations predict that the only product in the gas phase and in solution will be methyl isocyanate.

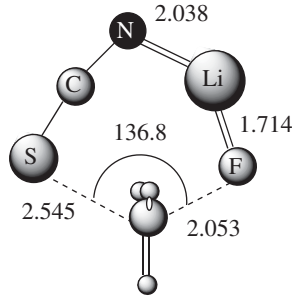


(**70**)

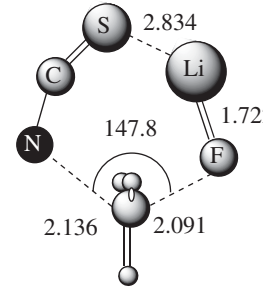


(**71**)

The S_N2 reaction between lithium isothiocyanate ion pair and methyl fluoride has been calculated at the MP2(full)/6–311+G**//HF/6–311+G** level of theory in the gas phase and in acetone using the PCM model.[108] Both the gas phase and acetone reactions occur with inversion, rather than retention, of configuration. However, the transition states and products are different in the gas phase and in solution; methyl thiocyanate is formed in the gas phase by transition state (**72**) whereas methyl isothiocyanate is formed much more slowly in acetone via the looser transition state (**73**).

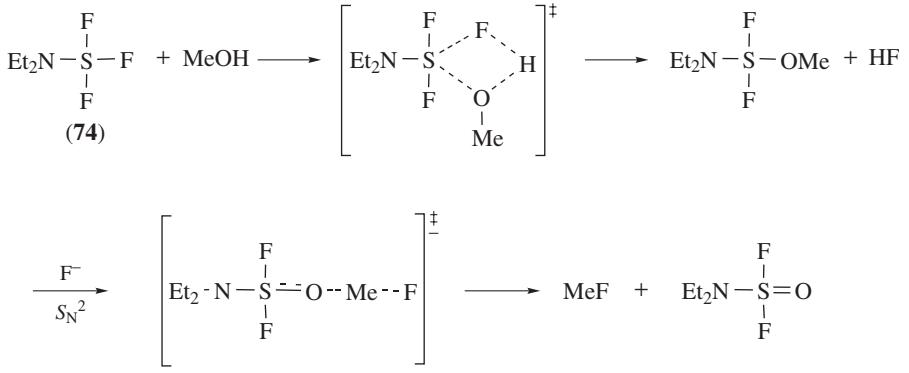


(**72**)



(**73**)

The mechanism for the fluorination of methanol by diethylaminosulfur triflouride (**74**) has been investigated in the gas phase and in dichloromethane using the RHF and B3LYP methods with the 6–31G+** basis set and truncated structures for the reactants.[109] Solvent effects were calculated using the PCM approach. Truncating the reactant did not affect the results significantly. The results suggest that fluorination occurs via an S_N2 mechanism in both the gas phase and dichloromethane, (Scheme 27).



SCHEME 27

A direct dynamics simulation of the S_N2 identity reaction of CD_3Cl at the MP2/6–31G* level of theory[110] found that the dynamics of the trajectories from the transition state were inconsistent with both RRKM and transition state theory.

The reaction force, the negative derivative of the potential energy along the intrinsic reaction coordinate, for the gas-phase S_N2 reaction between water and methyl chloride has been calculated at the B3LYP/6–31G* level of theory.[111] The calculations show that there are four different regions for the reaction force of an S_N2 reaction (Fig. 1). These are: (1) a preparation region leading to a minimum value of the reaction force where the reactants become orientated for reaction, which requires an expenditure of force, (2) an increasing reaction force to a value of zero at the transition state as the driving force for the reaction begins to be realized, (3) an increase in the reaction force as the structural changes for the reaction are completed and the driving force for the reaction is maximized, and (4) a relaxation region to a reaction force of zero as the molecules relax to their equilibrium state. In region 1–2, the C–Cl bond lengthens, the carbon approaches planarity, and hydrogen bonds between the Cl and a H on water and between the O and a methyl H begin to form. In region 2–3, to C–O bond begins to form, the C–Cl bond continues to lengthen, and the hydrogen bond between Cl and a H on water strengthens. In region 3–4, the new O–C bond formation, the C–Cl bond rupture, and the Cl–H bond formation are completed. In region 4, the molecules relax to their equilibrium energies. The changes in charge density of the atoms, the charge separation during the reaction, the electrostatic potential, and the average ionization energy of the system all reach their maximum values at the end

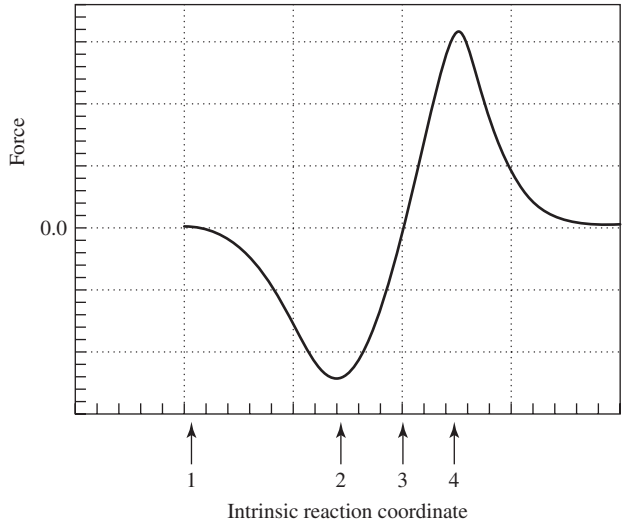


FIGURE 8.1

of region 3. It is worth noting that the maximum rate of change in these properties occurs at the transition state.

MP2/6–31++G(d,p) and $G3_m$ calculations of the identity reactions between protonated methyl, ethyl, isopropyl, and *t*-butyl amines, alcohols, and fluorides led the author to suggest that the S_N1–S_N2 model needs to be rethought.[112,113] Two problems have been identified. First, while simple theory predicts the reactivity decreases from methyl to ethyl to isopropyl to *t*-butyl for steric reasons, the calculations indicated this order was only found for the reactions with NH_3. The order when water is the nucleophile was *t*-butyl > isopropyl > methyl > ethyl and the fluoride ion reactions all occurred at nearly the same rate. Another problem was that the preference for back-side attack decreases in the order methyl > ethyl > secondary > tertiary for the reaction with NH_3 and water, whereas even the protonated methyl fluoride reacts by a front-side attack. In fact, front-side attack becomes more favourable as the size of the alkyl group increases and a better leaving group is used. This suggests that the S_N reactions of secondary and particularly tertiary substrates with very good leaving groups may occur by front-side attack. Front-side attack has also been observed for other S_N2 processes with special structural properties.

The S_N reactions between HF and protonated methyl, ethyl, isopropyl, and *t*-butyl fluorides in the gas phase have been examined at the MP2/6–31++G(d,p) level of theory.[112,113] The reaction of CH_3FH^+ clearly occurs via back-side attack as the transition state for this process is of lower energy than the transition state for front-side attack. The $EtFH^+$ can react via a more stable back-side S_N2 reaction or an S_N1 reaction via front-side attack since the S_N1 pathway is 4.4 kJ mol^{-1} lower in energy. No S_N2 path could be found for *i*-$PrFH^+$ and the front- and back-side pathways had equal activation energies for *t*-$BuFH^+$, which effectively reacts by an S_N1 mechanism. The conclusion is that the preference for back-side attack is reduced as the size of

the alkyl group and the leaving group ability increase. Again, it is concluded that the results of S_N reactions should be understood by a competition between front- and back-side attack rather than from competing S_N1 and S_N2 mechanisms.

A comparative static (time-independent) and dynamic (time-dependent) conversion of the transition state for the gas-phase methyl chloride identity S_N2 reaction into the product ion–molecule complex has been carried out using the hybrid PBE0 functional and the 6–31+G(d,p) basis set.[114] The static approach follows the intrinsic reaction coordinate while the dynamic approach is based on the atom-centred density matrix propagation (ADMP) model and quantum chemical topology (QCT) analyses. A three step-electron charge-transfer mechanism has been proposed for the static process whereas a five-step electron charge-transfer mechanism is required for the dynamic pathway where there is a stronger electron exchange leading to a maximization of both covalent and non-covalent interactions during the formation of the product ion–molecule complex. The QCT approach reveals the crucial role of the electron charge transfers during the reaction.

Other calculations using more complex substrates have been undertaken. Two of these deal with the reactions of polyfluorosulfonate esters. The S_N reaction between $CF_3CH_2OSO_2R$ and F^- could occur at either the $C_\alpha H_2$ carbon or at the more positive S.[115] DFT calculations at three different levels of theory up to B3LYP/6–311++G** have confirmed the experimental observations that the reaction only gives the product resulting from F^- attack at C_α. Although the energies of the transition states for C_α and S attack are virtually identical, the energy from the encounter complex to the transition state for attack at C_α is 2.2 kcal mol^{-1} less than that for attack at S. More important, however, is that attack by F^- at S is reversible whereas that at C_α is not. Therefore, the product will only be that from attack at C_α. It is worth noting that interaction between the attacking fluoride ion and the $C_\beta F_3$ carbon stabilizes the transition state for reaction at C_α. Calculations using the PCM approach show that the reaction is at C_α in both cyclohexane and DMSO and is faster in DMSO.

Finally, the calculations suggest that the S_N2 reaction between fluoride ion and perfluoro isomer ($CF_3CF_2OSO_2CF_3$) occurs via a front-side S_N2 reaction at S displacing a $CF_3CF_2O^-$ anion.[115,116] The transition state for attack at S is of lower energy than that for attack at C_α because the attacking fluoride ion can still be stabilized by an interaction with the carbon of the terminal CF_3 group and because of the better leaving group. The S_N2 reaction at S is irreversible because the $CF_3CF_2O^-$ anion undergoes a rapid decomposition to $CF_3COF + F^-$.

The S_N2 portion of the substitution reaction converting chlorosuccinate dianion into malic acid involves the formation of either an α- or a β-lactone intermediate.[117] PCM/B3LYP/6–31+G* calculations have shown that the reaction in water goes via the β-lactone with a central transition state where the C–Cl and C–O bond orders are 0.37 and 0.43, respectively. The transition state for the formation of the α-lactone is product-like with C–Cl and C–O bond orders of 0.1 and 0.7, respectively. The β-lactone route is favoured because (i) the O–C–Cl bond angle of 174° in the transition state forming the β-lactone is much greater than the 139° required for forming the α-lactone, (ii) there is less ring strain in the earlier transition state in the β-lactone reaction, and (iii) the coulombic repulsion between the negative charges in the substrate

are relieved on going to the transition state. The α-lactone route is favoured in the gas phase because the unfavourable electronic interaction between the negative chlorine and carboxylate oxygens on the adjacent carbon is reduced as the α-lactone is formed. The different mechanisms in the gas phase and in solution show that solvent plays a very important role in this reaction.

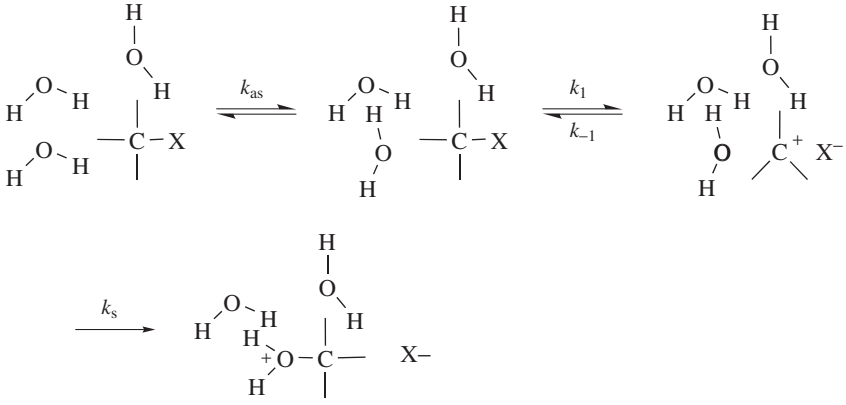
Calculations at the B3LYP and MP2 levels of theory with the 6–31+G* basis set were used to model the S_N2 reactions of the intermediates formed when alkyllithiums were reacted with several 1,1-dibromo- and 1,1-dichloro-alkenes.[118] The calculations showed, correctly, that the most sterically constrained halogen was attacked in the first step of the reaction and that the intramolecular substitution reaction in the second step of the reaction occurred by an S_N2 mechanism.

Other theoretical studies discussed above include investigations of the potential energy profiles of 18 gas-phase identity S_N2 reactions of methyl substrates using G2 quantum-chemical calculations,[99] the transition structures, and secondary α-deuterium and solvent KIEs for the S_N2 reaction between microsolvated fluoride ion and methyl halides,[66] the S_N2 reaction between ethylene oxide and guanine,[37] the complexes formed between BF_3 and MeOH, HOAc, dimethyl ether, diethyl ether, and ethylene oxide,[38] the testing of a new nucleophilicity scale,[98] the potential energy surfaces for the S_N2 reactions at carbon, silicon, and phosphorus,[74] and a natural bond orbital-based CI/MP through-space/bond interaction analysis of the S_N2 reaction between allyl bromide and ammonia.[17]

Miscellaneous Kinetic Studies

The solvolysis of (*S*)-1-(3-nitrophenyl)ethyl tosylate, ^{18}O-labelled in the sulfonyl oxygens of the tosylate group, in 50% v/v aqueous trifluoroethanol has been investigated.[119] The rate constants k_{isom}, k_{rac}, and k_{solv} (where k_{isom} is the rate constant for the exchange of the ^{16}O oxygen bonded to the carbon in the substrate with an ^{18}O oxygen on the sulfur of the leaving tosylate group, k_{rac} is the rate constant for conversion of the *S* to the *R* stereoisomer, and k_{solv} is the rate constant for the formation of the solvolysis product) were determined for the reaction. It was concluded that the reaction cannot go via a carbenium ion pair intermediate, for two reasons. First, the ratio $k_{isom}/k_{rac} \approx 80$ and the maximum k_{isom}/k_{rac} was estimated to be ~ 7 for a reaction going via an ion-pair intermediate. The carbenium ion-pair mechanism was also eliminated as a possibility because $k_{solv}/k_{isom} \approx 260$. Since $k_{isom} = 1.5 \times 10^{10}\ s^{-1}$ and $k_{solv}/k_{isom} \approx 260$, k_{solv} would be greater than the diffusion controlled limit. Since this is not possible, a new mechanism (Scheme 28) in which solvent reorganization occurs before the ionization step has been proposed for this reaction. Finally, it is suggested the ^{16}O–^{18}O isomerization occurs on a flat energy surface, i.e. with no activation energy, via a $[C_\alpha^{+\cdot}{}^{-}OSO_2Ar]$ intermediate that forms by stretching the C_α–O bond in the substrate.

The rate constants and equilibrium constants for the formation of THF from butane-1,4-diol in water have been measured at temperatures between 200 and 350 °C.[120] Although the reaction is reversible, the yield of THF at 350 °C is 94%. The reaction rate increased with decreasing pH at all temperatures, although the change in rate with



SCHEME 28

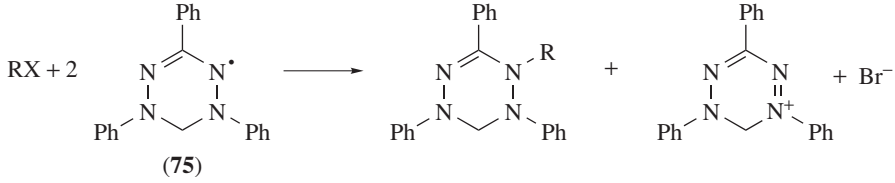
decreasing pH at near-neutral conditions was very small. Adding CO_2 to the reaction increased the rate two and three times at 250 and 300 °C, respectively, by forming H_2CO_3 and decreasing the pH. However, the effect of adding CO_2 was smaller than expected because the kinetic order with respect to H^+ was only ~0.4. This indicates that water can be the source of the proton needed for the reaction. The mechanism involves three steps: (1) protonation of the diol by water or H^+, (2) a rate-determining cyclization to form the protonated THF, and (3) deprotonation to give THF. Kinetic equations and the rate constant and activation energy for each step of the reaction are given.

The effect on the solvolysis rate of replacing a methyl group of cumyl chloride with an ethyl, isopropyl, or *t*-butyl group has been determined in 90% aqueous acetone and 90% aqueous acetonitrile.[121] The greater reduction in the rate of reaction with increasing size of the replacing group (by 3.5 with ethyl to 625 times with *t*-butyl) in 90% aqueous acetone correlates ($r = 0.991$) with Charlton's steric factor. This reduction in rate has been attributed to a steric effect that reduces the planarity and the resonance stabilization of the developing carbenium ion in the transition state rather than to a small electronic effect. Although the reaction is 10 times faster in the more polar solvent (90% aqueous acetonitrile), as one would expect, the reduction in rate with increasing size of the substituting group is effectively identical with that found in 90% aqueous acetone and the correlation with Charlton's steric factors is even higher at 0.995. Changing one of the methyl groups on the substrate to ethyl does not change the Hammett ρ^+ value significantly. This shows that adding the ethyl group does not affect the stabilization of the developing carbenium ion by the benzene ring significantly.

The rates for the S_N2 reactions of seven different anionic nucleophiles (Cl^-, Br^-, I^-, OAc^-, CN^-, SCN^- and trifluoromethylacetate$^-$) with methyl *p*-nitrobenzenesulfonate have been determined in CH_2Cl_2, MeOH, DMSO, and three ionic liquid solvents.[122] The reactivity was not correlated with the dielectric constant for the solvents as predicted by the Hughes–Ingold rules and a different nucleophilic order was found in

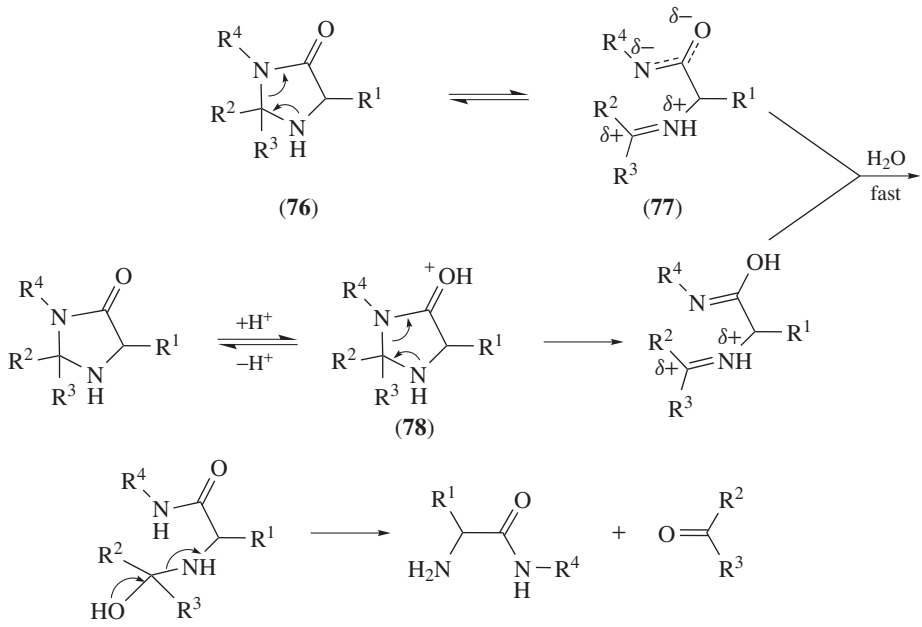
each solvent. Moreover, the change in rate from MeOH (the slowest) to DMSO (the fastest) varied with the nucleophile, e.g. the rate for SCN^- increased only 13-fold whereas that for acetate ion increased 6471-fold. The rates for each nucleophile were examined using the three-parameter Kamlet–Taft equation that is based on the ability of the solvent to form hydrogen bonds (α), the ability of the solvent to accept a hydrogen bond (β) and the polarizability of the solvent (π^*). There was a strong negative correlation with α for all the nucleophiles, i.e. the rate decreases as the solvent becomes more able to hydrogen bond to the negative nucleophile. Also, as expected, the dependence on α increases with the hardness of the nucleophile. Large positive correlations with π^* were found for three nucleophiles (CN^-, OAc^-, and TFA^-), whereas I^- and OAc^- had weak positive correlations with β. Neither $\Delta H^{\neq}$ nor $\Delta S^{\neq}$ correlated with the parameters in the Kamlet–Taft equation. However, the $\Delta S^{\neq}$ values were generally more negative for the ionic liquid reactions, suggesting that the anionic nucleophiles were maximally solvated by the corresponding cations in the ionic liquids.

Triphenylverdazyl (**75**) has been proposed as a trapping reagent for solvent-separated ion pairs.[123] The results obtained in a study of the S_N reaction of benzhydryl bromide in anhydrous acetonitrile[124] showed that alkylation of (**75**) rarely occurs; rather, it reacts with HBr formed when traces of water in the solvent react with the alkyl halide or its carbenium ion. Other arguments against the hypothesis that triphenylverdazyl is a trapping agent for solvent-separated ion pairs are given.



An extensive review with many examples[125] shows that the reactivity–selectivity principle cannot be used to predict the selectivity of a reaction except in unique systems where one reaction is close to or diffusion controlled. The relative importance of the Hammond effect and the frontier-orbital effects determines the reactivity–selectivity relationship that will be found in a particular system. The review also concludes that the Hammond–Leffler α-value cannot be used as an indicator of transition-state structure.

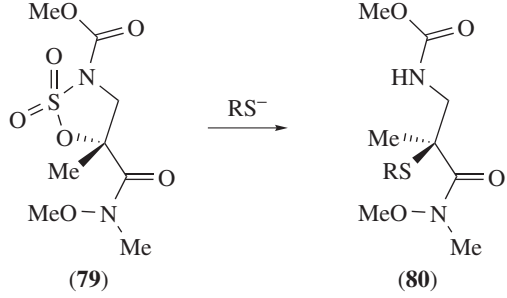
A kinetic study[126] has shown that the rate constants for S_N1 hydrolysis of imidazolidin-4-ones (**76**) via the neutral substrate *and* after protonation at either the N(1) or the carbonyl oxygen (**78**) (Scheme 29) are similar. Theoretical calculations at the AM1 and B3LYP/6–31G* levels of theory have shown that the barrier to reaction is much smaller for both the O and N protonated pathways in the gas phase. This is due to the high energy of the ionic intermediate (**77**) formed in the reaction of the neutral substrate, i.e. the doubly charged intermediate would be solvated and therefore of lower energy in solution where the rate constants for the neutral and protonated reactions are similar. Although the calculations were unable to indicate whether the



SCHEME 29

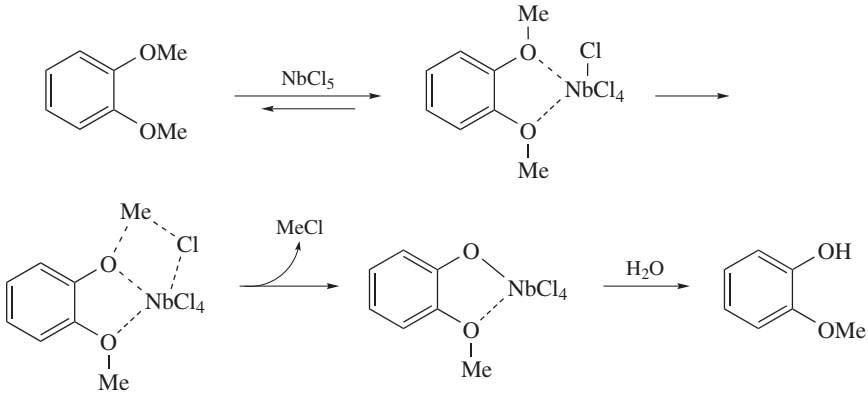
O or N protonation mechanism was the lowest energy pathway, the authors preferred the O protonation mechanism, via (**78**). Steric effects at N(1) and C(2) were found to have a significant effect on the rate of reaction.

The cyclic sulfamidate (**79**) reacts with a host of neutral and anionic sulfur nucleophiles to give an excellent yield (84–99%) of product (**80**).[127] 1,8-Diazabicyclo[5.4.0] undec-7-ene (DBU) was added to ionize the neutral nucleophiles. All the reactions proceed with an inversion of configuration at the *quaternary* carbon even when tertiary alkanethiols are used. Therefore, since a kinetic study showed that the reaction is first order in both the nucleophile and (**79**), an S_N2 mechanism applies.



The strong Lewis acid niobium(V) pentachloride has been found to be an effective reagent for the monodealkylation of diethers with two alkyl–aryl linkages.[128]

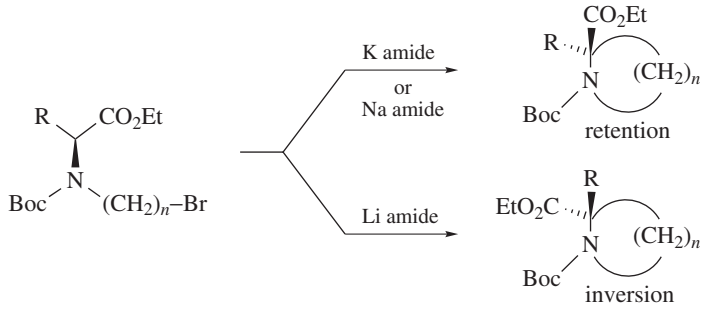
The reaction always occurs at the most sterically crowded alkyl group and the alkyl group reactivity decreases in the order benzyl > ethyl > methyl. This suggests that the reaction proceeds via an S_N1 mechanism. Also, the reaction occurs in high yield ($\geq$84%) only when the ether groups are in close proximity or when another group that can coordinate with niobium, e.g. a $-CO_2Me$ group, is close to the ether group. The reaction occurs in high yield whether electron-withdrawing or -donating groups are adjacent to the ether groups. The proposed mechanism is illustrated in Scheme 30 for reaction of 1,2-dimethoxybenzene, for which proposed intermediates have been detected using NMR spectroscopy.



SCHEME 30

The best solvent, temperature, and Lewis acid conditions for the S_N reactions of (*RS*)-1-(2-nitrobenzenesulfonyl)- and (*RS*)-1-(4-nitrobenzenesulfonyl)-3-methoxy-1,2,3,5-tetrahydro-4,1-benzoxazepines with silylated 5-fluorouracil and uracil[129] proved to be $SnCl_4$ at 50 °C in MeCN. The more nucleophilic silylated uracil reacts faster at its N(3) atom giving mainly the cyclic *O*,*N*-acetal (by C–OMe cleavage). The silylated 5-fluorouracil, on the other hand, reacts at its less sterically hindered N(1) atom and gives mainly an acyclic product (by ring C–O cleavage). Calculations at the HF/6–31G** level of theory support the experimental observations.

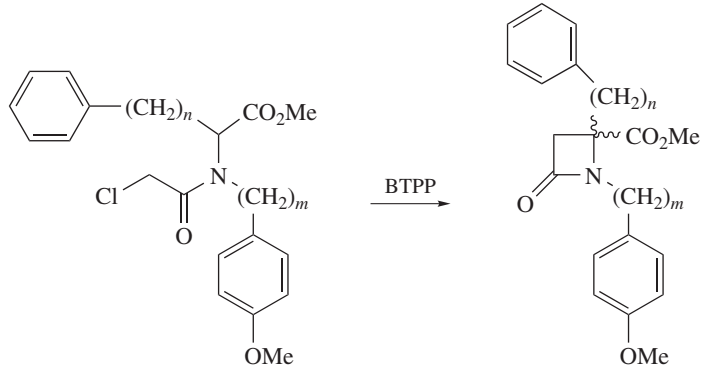
A highly enantioselective dehydrobrominative cyclization of α-amino acid derivatives (**81**) that can occur with either retention or inversion of configuration[130] has been reported. Simply changing the counterion of the amide ion base and the solvent from sodium or potassium amide in DMF or THF to lithium amide in THF or toluene changes the reaction from one with retention of configuration to one with inversion of configuration (Scheme 31). Both reactions are highly enantioselective (most give >90% *ee*) and in high yield (usually >90%). The commonly used bases were (ee) potassium hexamethyldisilazide and lithium 2,2,6,6-tetramethylpiperidide. By varying the number of carbons in the $(CH_2)_nBr$ group, one can obtain four-, five-, or six-membered ring products. The products from these reactions can be easily converted into α,α-disubstituted α-amino acids.



SCHEME 31

The mechanism of the N^6-acyladenine and silylating method for the ribosylation of adenine has been determined.[131] The kinetic product formed by ribosylation at N(1) has been isolated. The reaction occurs here because the N(7) position is sterically hindered.

The effect of (i) the distance between the side-chain phenyl and the α-chiral reaction centre, (ii) the distance between the 4-methoxyphenyl ring and the nitrogen atom, and (iii) the effect of adding TADDOL in the BTPP base-catalysed formation of the β-lactam (**83**) from (**82**) was investigated.[132] The most enantioselective reaction (74% *ee*) occurred when $n = 0$ and $m = 1$. TADDOL had a variable effect on the enantioselectivity but had a negative effect on the enantioselectivity in the reaction with $n = 0$ and $m = 1$. Reasons for the observed enantioselectivities are presented.



(**82**) (**83**)

Recent advances in the scope and mechanisms of Pummerer-type reactions have been reviewed.[133]

S_N Reactions Producing Polymers

Polyetherols are formed by reaction of hydroxymethyl derivatives of uric acid and ethylene oxide or propylene oxide. A kinetic study of the simple model reaction[134]

between the tetrakis(hydroxymethyl)uric acid and oxirane indicated that the reaction occurred by a four step mechanism. This mechanism involves (i) release of formaldehyde from a nitrogen in the substrate forming an NH (imide) group on the uric acid derivative, (ii) a proton transfer from the imide group to the oxirane forming an imide ion–protonated oxirane ion pair, (iii) the rate-determining attack of an oxygen of a hydroxymethyl group on the substrate on the carbon of the protonated oxirane (an S_N2 reaction) adding the oxirane to the hydroxymethyl group of the substrate and (iv) transfer of the proton from the protonated product to the $N:^-$ group of the imide ion re-forming the imide.

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CHAPTER 9

Carbanions and Electrophilic Aliphatic Substitution

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Carbanion Structure and Stability

The linear correlation between the $\Delta E\pi$ values for *meta*- and *para*-substituted benzylic anions and the Hammett σ constants has suggested that π conjugation may be used to explain the influence of substituents which have π orbitals.[1]

The structure of *n*-butyllithium in mixtures of ethers and 1,2-diamines has been investigated.[2] Solutions in TMEDA–THF (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) are not amenable to detailed investigation because of rapid ligand exchange. TMCDA–THF mixtures (TMCDA = *trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclohexanediamine) afford clean assignments for a mixture of homo- and hetero-solvated dimers but demonstrate poor control over structure. TMCDA–tetrahydropyran (THP) mixtures and TMEDA–Et_2O mixtures afford clean structural assignments and also excellent structural control. Rate studies of the 1,2-addition of *n*-BuLi using TMCDA–THP mixtures revealed cooperative solvation in which both THP and TMCDA coordinate to lithium at the monomer- and dimer-based transition structures.

The molecular geometries of nitrogen squaric acid and its dimeric derivatives have been optimized at RHF/6–311+G** and RB3LYP/6–311+G** levels of theory.[3] The

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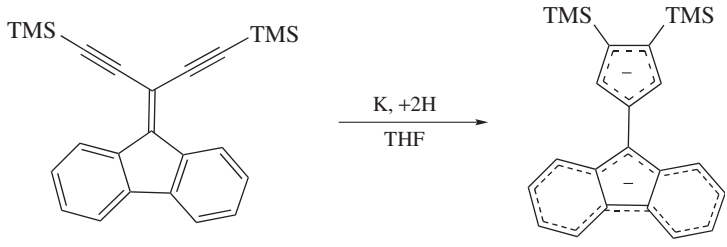
geometric, energetic, and magnetic criteria have indicated that nitrogen squaric acid is aromatic, and the dimer should be considered as only partly aromatic.

The IR spectra and structures of the free tricyanomethanide carbanion and its potassium ion pair have been studied by both spectroscopic experiment and DFT B3LYP force field computations.[4] According to the computations, the conversion of the free tricyanomethanide carbanion into an ion pair results in essential changes in the lower-frequency vibration. The experimental geometry agrees with an ion-pair structure with K^+ along the C–C≡N axis.

The basicity of the anion CH_2X^-, as a function of X, has been found to decrease in groups 16 (from OH to SH), 15 (from NH_2 to PH_2), and 14 (from CH_3 to SiH_3), because the α-stabilization of CH_2X^- increases.[5] In contrast, the basicity of CH_2X^- along the series X = F, Cl, Br, I does not decrease, as commonly assumed. Fluorine has been found more effective than the heavier halogens for α-stabilization of carbanions.

Various cross-conjugated enediynes undergo 'Bergman-type' cycloaromatizations upon reduction with potassium metal, generating anions of fulvenes and fulvalene derivatives (Scheme 1).[6] Not all cross-conjugated enediynes yield cyclized dianions upon reduction; some give uncyclized, Y-shaped, cross-conjugated dianions, whereas others apparently yield radical anions that either dimerize or persist as monomers.



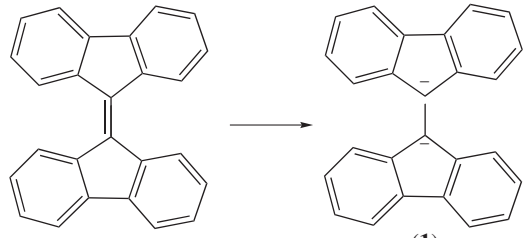
SCHEME 1

The reduction of several annelated corannulene derivatives has been performed using lithium and potassium metals.[7] It has been found that annelation affects the annulenic character of corannulene by changing its charge distribution; the dianions of derivatives that are annelated with six-membered rings have less annulenic character and are less paratropic than corannulene dianion.

A systematic density functional theory level investigation of differently substituted pyridinium methylides has been carried out to determine the role of C_{ylidic} lone-pair-associated hyperconjugative and negative hyperconjugative interactions in deciding conformational preferences.[8] Deviation from the coplanar orientation of the carbanionic centre with the pyridine ring and its substituent dependence have been found to correlate well with the relative opportunities for conjugative and negative hyperconjugative interactions of an ylidic moiety with different substituent groups present at the ylidic carbon.

The aromaticity of the dianion (**1**) and the antiaromaticity of the correponding dication of tetrabenzo[5.5]fulvalene have been evaluated through magnetic criteria, ^1H

NMR shifts, nucleus-independent chemical shifts, NICS, and magnetic susceptibility exaltation, Λ.[9] It has been found that counterions play a more important role in the behavior of dianions than dications, as shown by the improvement in the agreement of experimental and calculated shifts for dianions with the inclusion of counterions.



(**1**)

Carbanion Reactions

Enolates and Related Species

The preparation of α-lithio aldehydes, α-lithio ketones, and related compounds and their applications to organic synthesis has been reviewed.[10] The Tsuji–Trost allylic alkylation with ketone enolates has been highlighted.[11]

Alkali metal counterion has been found to control the enolate protonation stereoselectivity.[12] This remarkable phenomenon has been reported for lithium and potassium enolates of a norborneol derivative.

The molecular mechanisms for the nucleophilic addition of lithium enolates and silyl ketene acetals to nitrones in the absence and in the presence of a Lewis acid catalyst to give isoxazolidin-5-ones or hydroxylamines have been investigated by DFT methods at the B3LYP/6–31G* level.[13] An analysis of the global electrophilicity of the reagents accounts for the strong electrophile activation of the Lewis acid-coordinated nitrone, (*ee*) and the analysis of the local indices leads to an explanation for the experimentally observed regioselectivity.

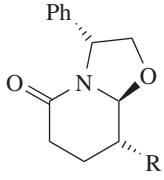
A density functional study of enantioselectivity in the 2-methylproline-catalysed α-alkylation of aldehydes has been reported.[14] On the basis of the computed barriers and transition states, an explanation has been provided for the remarkable and unexpected increase in enantioselectivity that is observed when using 2-methylproline instead of proline as the catalyst.

The independent generation and reactivity of allenic enolates has been investigated.[15] Under kinetic conditions, these highly reactive species are protonated in the $\alpha,\beta-\pi$ plane with preference (E) to the larger β group. Under thermodynamic con- (*de*) ditions, addition/elimination equilibrates the two product stereoisomers. The kinetic protonation stereochemistry has been found a function of solvent, proton donor, and donor concentration.

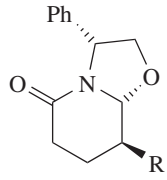
The alkylation of *cis*- and *trans*-4-fluoro-*N*-Boc-L-proline methyl esters has been examined by exposing their lithium enolates to a range of alkylating agents.[16] The process showed a high degree of facial diastereoselectivity, invariably giving rise to (*de*) products bearing the alkyl group *anti* with respect to the fluorine atom.

The mechanism of the Perkin condensation involving benzal acetate has been revised.[17] It has been demonstrated that the enolate of the *gem*-diacetate derived from the aromatic aldehyde and acetic anhydride–rather than the enolate of acetic anhydride itself–adds to the aldehyde in the key step. The deprotonation of the diacetate to the enolate appeared to be assisted electrophilically by the neighbouring acetate group.

The origin of the diastereoselective alkylation of enolates of oxazolopiperidones (**2**) and (**3**) has been studied by means of theoretical calculations and experimental assays.[18] For the unsubstituted oxazolopiperidone, the alkylation with methyl chloride is predicted to afford mainly the *exo* product, a finding further corroborated from the analysis of the experimental outcome obtained in the reaction of the racemic oxazolopiperidone. However, such a preference can be drastically altered by the presence of substituents attached to the fused ring.

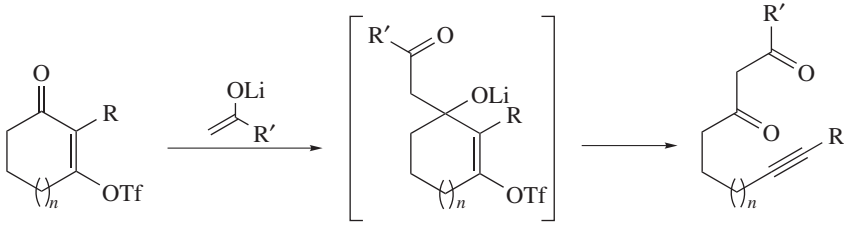


(**2**)



(**3**)

The Claisen-type condensation reaction of cyclic vinylogous carboxylic acid triflates with lithium enolates and their analogues has provided acyclic alkynes bearing a 1,3-diketone-type moiety.[19] The reaction mechanism has been proposed to proceed via a 1,2-addition of the enolate to the vinylogous acyl triflate, followed by fragmentation of the aldolate intermediate (Scheme 2).



$n = 1, 2$

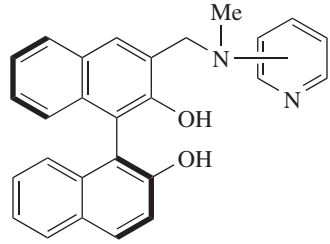
SCHEME 2

A kinetic and mechanistic study of substituent effects in the nucleophilic acyl group has been performed for the Claisen-like condensation of a series of 1-arylacetyl-6-acetyl-3,4,7,8-tetramethylglycolurils.[20] The reactions proceeded in virtually quantitative yield and are highly regioselective. The results have been explained by a mechanism in which deprotonation of the substrates is rate limiting; thus, deprotonation of the arylacetyl groups is favoured.

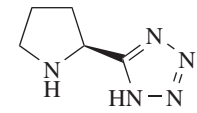
The first *E*-selective Knoevenagel condensation of acetoacetic derivatives has been developed by using TEMPO for the acylated substituent.[21] Alternatively, *Z*-selective Knoevenagel condensation was achieved by use of amide analogues including the Weinreb amide. (*de*)

The mechanism of Morita–Baylis–Hillman (MBH) alkylation has been investigated.[22] An MBH intermediate exhibiting unprecedented *trans* geometry of the phosphonium salt and acyl group has been isolated for the first time. (*de*)

(*S*)-3-(*N*-Isopropyl-*N*-3-pyridinylaminomethyl)BINOL (**4**) has been established as an efficient asymmetric bifunctional organocatalyst for the aza-MBH reaction.[23] The acid–base functionalities cooperate in substrate activation and fixing of the organocatalyst conformation to promote the reaction with high enantiocontrol. (*ee*)



(**4**)



(**5**)

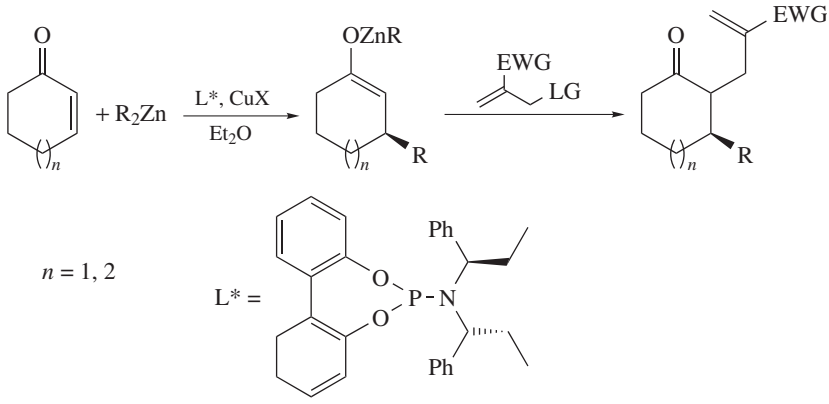
Asymmetric organocatalytic conjugate addition of malonates to enones has been performed using a proline tetrazole catalyst (**5**).[24] The reaction has provided good results for a range of substrates, furnishing the products in good yield with good to high enantioselectivities. (*ee*)

The regio- and stereo-selective rhodium-catalysed allylic alkylations of chelated enolates have been investigated.[25] It has been found that the Rh-catalysed allylic alkylation is as efficient and versatile as the Pd-catalysed version. In reactions of chelated enolates with suitable protecting groups, high yields and selectivities were obtained, and the regioselectivity can be directed by the reaction parameters. (*de*)

A simple method for the direct catalytic allylic alkylation of aldehydes and cyclic ketones has been developed.[26] The direct catalytic highly chemo- and regio-selective intermolecular α-allylic alkylation reaction has been mediated by an unprecedented combination of palladium and enamine catalysis which furnishes α-allylic alkylated aldehydes and cyclic ketones in high yield.

Mixed aggregates of chiral lithium amide and lithium ester enolate have been employed in the enantioselective conjugate addition on α,β-unsaturated esters.[27] Michael adducts have been obtained in *ee*s up to 76% combining a lithium enolate and a chiral 3-aminopyrrolidine lithium amide. The sense of the induction has been found to be determined by both the relative configuration of the stereogenic centres borne by the amide and the solvent. (*ee*)

The copper-catalysed asymmetric conjugate addition of dialkylzinc leads to homochiral zinc enolates.[28] These intermediates have been trapped *in situ* with activated allylic electrophiles, without the need for additional palladium catalysis (Scheme 3). (*ee*)

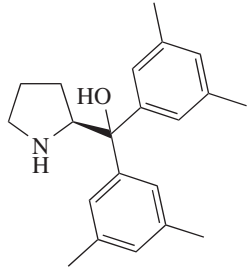


SCHEME 3

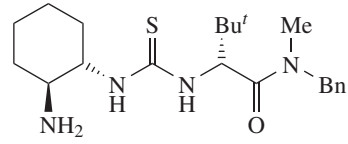
High *trans* selectivity (85:15 to 100:0) and excellent enantioselectivities (up to 99%) (*de*) have been reported.

The synthesis of chiral *syn*-β-amino esters has been performed by the addition of titanium ester enolates to aldimines containing a chiral α-methylbenzylamine moiety.[29] (*de*) The reactions take place in high yields and diastereomeric ratios (up to 96:4).

A series of diaryl-2-pyrrolidinemethanols have been tested as catalysts for the enantioselective Michael addition of malonate esters to nitroalkenes.[30] Bis-(3,5-dimethylphenyl)[(*S*)-pyrrolidin-2-yl]methanol (**6**), easily prepared from L-proline, has been found the most efficient bifunctional organocatalyst, providing up to 56% *ee*. (*ee*)



(**6**)



(**7**)

The highly enantioselective direct conjugate addition of ketones to nitroalkenes has been promoted by a chiral primary amine–thiourea catalyst (**7**).[31] The observed *anti* diastereoselectivity has suggested participation of a (*Z*)-enamine intermediate, given (*de*) the complementary diastereoselectivity obtained in analogous reactions involving (*E*)-enamines generated from secondary amine catalysts.

Asymmetric 1,4-addition of various malonates to enones has been carried out using tetrabutylammonium tetrahydroborate (TBATB) in the presence of a chiral ligand.[32] ^{11}B NMR spectroscopic studies have explained the unexpected reactivity through the

predominant formation of an aminodiol-modified borate complex in the presence of a hydride acceptor.

Significant mechanistic insights into the DABCO-catalysed isomerization of γ-hydroxy-α,β-alkynyl esters to γ-oxo-α,β-*trans*-alkenyl esters have been reported.[33] The reaction mechanism involves cumulene formation, protonation with the conjugate acid of the amine, and protonation of the resulting allenol with water.

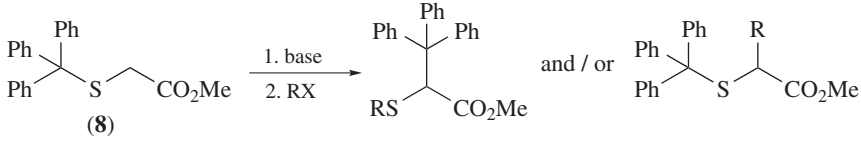
Heteroatom-stabilized Species

The epoxy-Ramberg–Bäcklund reaction (ERBR) has been used for the conversion of α,β-epoxy sulfones into a range of mono-, di-, and tri-substituted allylic alcohols.[34] Modification of this method has permitted the preparation of enantio-enriched allylic alcohols following the diastereoselective epoxidation of enantio-enriched vinyl sulfones that were accessed efficiently from the chiral pool.

Vicarious nucleophilic substitution reactions of azolopyridazines have been found to be controlled by methyl substituents.[35] On treatment with bromomethyl phenyl sulfone in DMSO–*t*-BuOK, azolopyridazines yield mainly typical reaction products, whereas 7-methylazolopyridazines under the same conditions undergo annulation. These competitive reactions illustrate the role of charge distribution and steric hindrance for the course of the nucleophilic substitution.

The stereocontrolled synthesis of functionalized lactams has been achieved via sulfur-stabilized enolates.[36] Thio-substituted enolates were the reagents of choice as these proved to be more generally applicable than the corresponding sulfoxide-substituted enolates.

The lithium enolate formed from methyl *S*-trityl mercaptoacetate (**8**) has been *C*-alkylated in high yield at or below $-40\,^{\circ}C$ (Scheme 4).[37] At higher temperatures, the [1,2]-thio-Wittig rearrangement of the enolate was the predominant process. ESR evidence has indicated that the rearrangement occurred by a radical mechanism.



(**8**)

RX = DOAc, MeI, BnBr, MeO_2CCH_2Br

Scheme 4

Stabilized sulfonium ylides react with cyclopentenone to give the corresponding cyclopropane with high diastereoselectivity as a result of base- or ylide-mediated (*de*) equilibration of the intermediate betaine.[38] When using chiral sulfonium ylides, betaine equilibration compromises enantioselectivity, because whereas one diastereomer ring closes rapidly, the other diastereomer undergoes epimerization at the ester stereocentre, ultimately leading to the opposite enantiomer of the cyclopropane.

The salt-free Wittig reaction of non-, semi-, and stabilized ylides has been investigated on realistic systems using density functional theory (DFT) calculations, including

continuum solvation.[39] The results provided unequivocal support for the generally accepted mechanism and are in very good agreement with experimental selectivities. (de) The *E*/*Z* selectivity of non- and semi-stabilized ylides cannot be fully understood without considering the energy of the elimination TS.

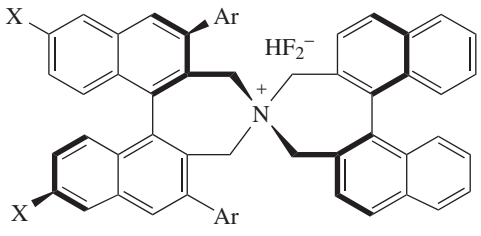
The existence of oxaarsetanes during an arsa-Wittig reaction has been proved by ^{1}H and ^{17}O NMR spectroscopy.[40] ^{75}As NMR spectra were obtained from the corresponding arsonium salts and arsane oxides. It has been shown that the reaction mechanism of the arsa-Wittig reaction is identical with that of the phospha-Wittig reaction.

The regioselective functionalization of nitrobenzene and benzonitrile derivatives has been performed via nucleophilic aromatic substitution of hydrogen by phosphorus-stabilized carbanions.[41] Lithium phosphazenes have been found to be the most suitable nucleophiles for the substitution of hydrogen in nitrobenzene. This method represents a convenient alternative to the vicarious nucleophilic substitution for the synthesis of benzylic phosphorus derivatives using phosphorus-stabilized anions that do not bear a leaving group at the carbanionic centre.

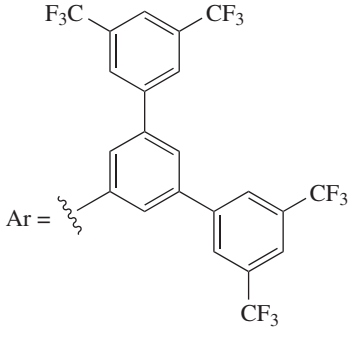
The catalytic asymmetric Henry reaction has been reviewed.[42] Mild and efficient enantioselective nitroaldol reactions of nitromethane with various aldehydes have been (ee) catalysed by chiral copper Schiff-base complexes yielding the corresponding adducts with high yields and good enantiometric excess.[43,44]

5-Pyrrolidin-2-yltetrazole has been found to be a versatile organocatalyst for the asymmetric conjugate addition of nitroalkanes to enones.[45] Using this catalyst, this transformation requires short reaction times, tolerates a broad substrate scope, and possibly proceeds via generation of an iminium species.

A highly diastereo- and enantio-selective formal conjugate addition of nitroalkanes (de) to nitroalkenes has been achieved using a chiral ammonium bifluoride catalyst (**9**).[46] (ee) This strategy provides a reliable route to optically active 1,3-dinitro compounds.

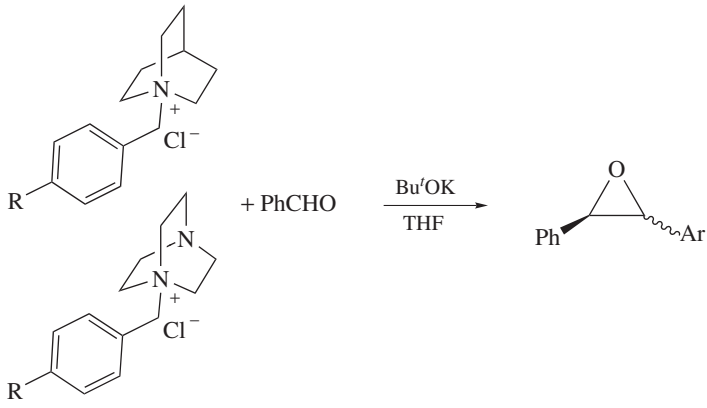


(**9**) X = H, CF_3



An enantioselective aza-Henry reaction has been performed in the presence of zinc (ee) triflate and *N*-methylephedrine.[47] This method features tolerance to imines that bear aryl groups of diverse electronic nature and substitution patterns.

It has been reported that yield and diastereoselectivity in reactions of aryl-stabilized (de) ammonium ylides with aldehydes are strongly influenced by the nature of the amine and the ylide substituent (Scheme 5).[48] Electron-deficient aromatics, which are able to



SCHEME 5

stabilize the ylide, give good yields, whereas electron-rich aromatics, which destabilize the ylide, give poor yields. DFT calculations are consistent with a mechanism in which reversibility in betaine formation is finely balanced due to the high barrier to ring closure.

Organometallic Species

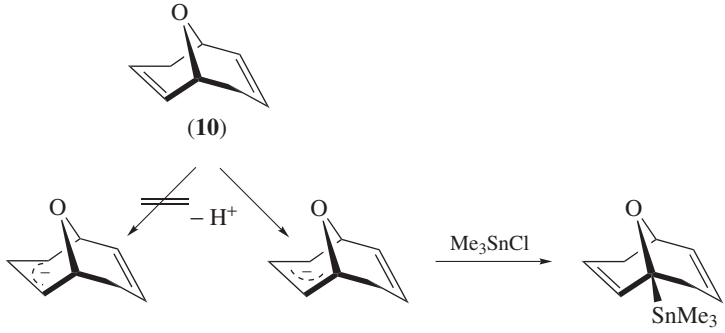
Organolithium species

Volume 8a of the *Science of Synthesis* series has reviewed the synthesis and applications in organic synthesis of the following organolithium compounds: alkyl- and cycloalkyl-lithium,[49] alkenyllithium,[50] allyllithium,[51] benzyllithium and (lithiomethyl) hetarenes,[52] β-lithiocarboxylic acids and related compounds,[53] and bis(organosulfanyl)- and bis(organoselanyl)-methyllithium compounds.[54]

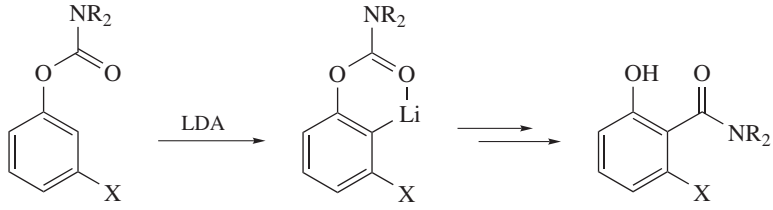
Directed lithiation A new route to bridgehead alkenes based on a deprotonation reaction has been established.[55] The deprotonation of 9-oxabicyclo[3.3.1]nonadiene (**10**) with *t*-BuLi–TMEDA occurs selectively in the allylic position. While (**10**) has four allyl positions, only one bridgehead proton is removed, as demonstrated by quenching with Me_3SnCl, Me_3SiOTf, and Me_3PbCl (Scheme 6).

The lithiation/boronation of 1,4-dihalobenzenes (Hal = F, Cl, Br) bearing various functional groups in the 2-position has been investigated using lithium diisopropylamide as the metalating agent and trialkyl borate $B(OR)_3$ as the electrophile.[56] It has been demonstrated that sufficient steric hindrance precludes effective *ortho*-lithiation at the 3-position. In such cases, a strong *meta*-directing effect of an oxygen- or sulfur-based substituent (OMe, $OSiMe_3$, SMe), resulting in the preferred formation of 2,6-disubstituted 1,4-dihalobenzenes has been observed.

The role of aggregates and mixed aggregates on the lithium diisopropylamide-mediated anionic Fries rearrangements of aryl carbamates (Scheme 7) has been described.[57] Substituents at the *meta*-position of the arene (X = H, OMe, F) and the



SCHEME 6



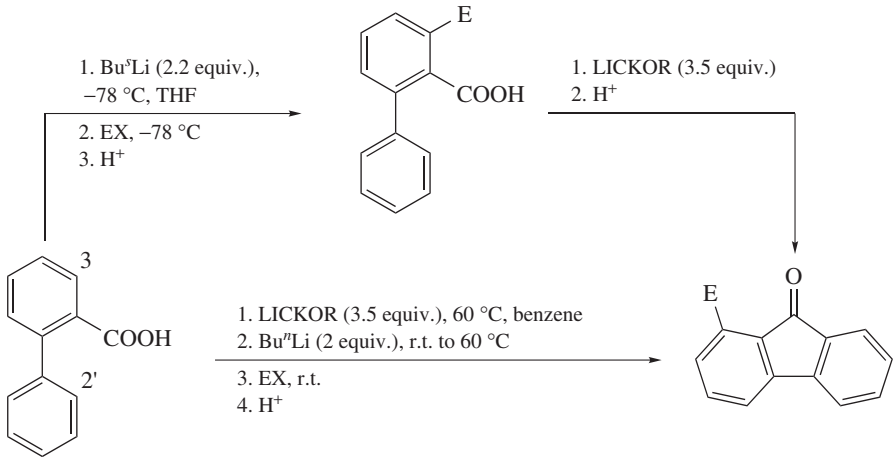
SCHEME 7

dialkylamino moiety of the carbamate (Me_2N, Et_2N, and i-Pr_2N) markedly influence the relative rates of *ortho*-lithiation and subsequent Fries rearrangement.

By treatment with *s*-BuLi–TMEDA at −78 °C, unprotected 2-methoxybenzoic acid has been deprotonated exclusively in the position *ortho* to the carboxylate.[58] A reversal of regioselectivity is observed when the acid has been treated with *n*-BuLi–*t*-BuOK. These results are of general utility for the one-pot preparation of a variety of very simple 3- and 6-substituted 2-methoxybenzoic acids that are not easily accessible by conventional means.

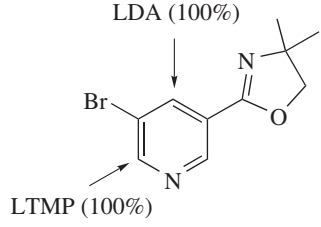
The expedient and regioselective metalation of unprotected biphenyl-2-, -3-, and -4-carboxylic acids has been reported.[59] Unprotected biphenyl-2-carboxylic acid has been cleanly metalated with *sec*-butyllithium at the position adjacent to the carboxylate and can then be subjected to site-selective electrophilic substitution (Scheme 8). The remote C(2′)-position has been attacked by the superbasic mixture of *n*-BuLi and *t*-BuOK (LICKOR) in THF or benzene. The resulting dianion cyclizes to give the fluorenone skeleton. The mechanism of the metalation of homologous compounds, 2-(pyridin-3-yl)benzoic acid derivatives, with strong bases has also been discussed.[60]

The regioselectivity in lithiation of 1-methylpyrazole has been investigated by experimental, DFT and multinuclear NMR studies.[61] In THF, 1-methylpyrazole reacts initially at the exocyclic α-position, to give an α-lithiated species which forms the thermodynamic product C(5)-Li in an intermolecular reaction. A coordination from N(2) to lithium apparently favours formation of the kinetic product α-Li.



SCHEME 8

Lithiation of 5-bromonicotinic acid protected as a secondary or tertiary amide and also (4,4′-dimethyl)oxazoline (**11**) with lithium amides has been reported.[62] The unusual C(2) and C(4) regioselective lithiation of 3-bromo-5-(4,4′-dimethyl)oxazolinylpyridine using LTMP versus LDA has been observed, providing a new route to substituted nicotinic acid scaffolds.



(**11**)

The synthesis of new 4,6-disubstituted dihydrodipyridopyrazines has been performed starting from corresponding carboxaldehydes via lithiation directed by α-aminoalkoxides.[63] *N*,*N*,*N*′-trimethylethylenediamine has been used as the amine component for *in situ* formation of the α-aminoalkoxides.

ortho-Metalation of enantiopure sulfoxides has been described for aromatic and ferrocenyl derivatives.[64,65] New aminosulfoxides have been obtained with complete (*de*) diastereocontrol when Dpp or Boc groups were used ($dr > 98{:}2$).

Addition and other reactions The relative basicities of solutions of *n*-BuLi in cyclohexane as a function of the addition of increasing increments of THF or TMEDA have been assessed.[66] By measuring the rates of loss of chlorobenzene in the varied media

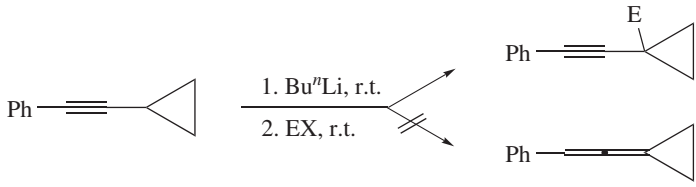
and also by certain ^{7}Li NMR studies, a gradual, controlled increase in the basicity of *n*-BuLi in cyclohexane with increasing increments of THF or TMEDA has been observed.

Transition structures for the lithium–bromine exchange reaction of 1,1-dibromoalkenes with methyllithium have been located by both the B3LYP and the MP2 levels of theory with the 6–31+G* basis set.[67] The reaction with methyllithium dimer gave similar results with lower activation energies. These calculations predict both the kinetic and the thermodynamic stereoselectivity correctly. It has been found that predominantly the sterically more constrained bromine atom of 1,1-dibromoalkenes reacted with alkyllithium (dimer) in the kinetic condition.

It has been demonstrated that lithium–bromine exchange of a representative aryl bromide, 1-bromo-4-*t*-butylbenzene, may be accomplished in high yield at 0 °C, a temperature significantly higher than that normally used for the process.[68] The reaction has been performed with 2 equiv. of *t*-BuLi in heptane in a predominantly hydrocarbon medium containing a small (1% v/v) to modest (10% v/v) quantity of any of a variety of ethers (Et_2O, THF, THP, or MTBE). The exchange reaction between 1-bromo-4-*t*-butylbenzene and *n*-BuLi, which is slow in pure diethyl ether, proceeds in high yield in a hydrocarbon medium containing a small amount (1% v/v) of THF.

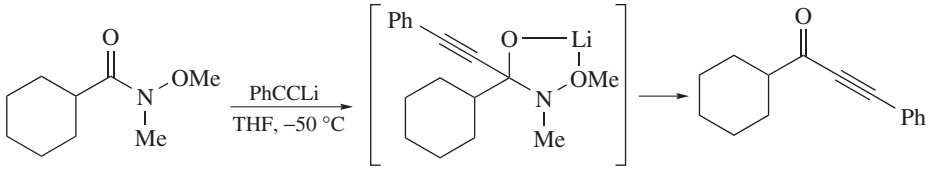
The carbolithiation of six- to nine-membered 3-methylenecycloalka-1,4-dienes has been investigated and shown to be an exceptionally facile and general process.[69] Primary, secondary, and tertiary organolithium reagents may be employed for carbolithiation of cyclic trienes with uniform efficiency, generating cyclic pentadienyl carbanions. The six-electron pentadienyl systems display unique reactivity as a function of ring size.

The cyclopropyl effect has controlled the regioselectivity of the cross-coupling reactions of propargylic/allenylic metallic species with electrophiles afford alkynic cyclopropanes (Scheme 9).[70] Cyclopropyl ring strain, which makes the formation of vinylidenecyclopropanes unfavourable, is believed to control the regioselectivity.



SCHEME 9

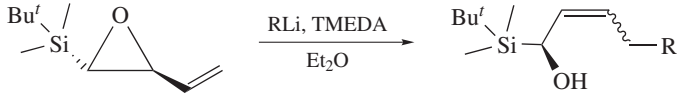
The mechanism of acylation of lithium phenylacetylide with a Weinreb amide has been investigated (Scheme 10).[71] Dimeric lithium acetylide has reacted via a monosolvated monomer-based transition structure. The robust tetrahedral intermediate (**12**) forms sequentially a C(1) 2:2 mixed tetramer with the excess lithium acetylide and a 1:3 (alkoxide-rich) mixed tetramer. The stabilities of the mixed tetramers are consistent with a pronounced autoinhibition.



(**12**)

SCHEME 10

The regioselective reaction of *trans*-2-(*t*-butyldimethylsilyl)-3-vinyloxirane (**13**) with primary, secondary, and tertiary butyllithium has proceeded in a S_N2' fashion and allowed the formation of α-silylated allylic alcohols with diastereomeric ratios of over 7:1 in favour of the (*Z*)-alkenes (Scheme 11).[72] A study of the effect of temperature, time, addition of salt, and polarity of the solvent on the diastereoselectivity of the reaction has been described. (*de*)



(**13**) R = Bu^n, Bu^s, Bu^t

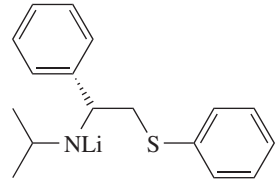
SCHEME 11

A mechanistic study of the Wittig rearrangement of lithiated allyl aryl ethers has been reported.[73] At −75 °C, α-lithiated allyl phenyl ether undergoes mainly the [1,2]-Wittig rearrangement to afford, after acidic hydrolysis, 1-phenylprop-2-en-1-ol as the main product. A second metalation taking place at one of the *ortho* positions is the sole competing side reaction. Both the significant decrease of the isomerization rate upon the introduction of a *t*-butyl substituent in the *para* position of the aromatic ring and the complete absence of [1,4] rearrangement products suggest an intramolecular addition/elimination process bringing about the aryl migration.

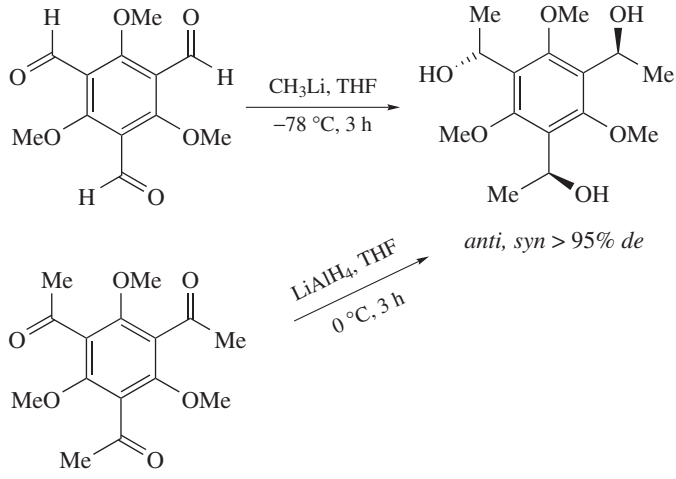
Studies on the deprotonation and subsequent [1,4]-Wittig rearrangement of α-benzyloxyallylsilanes have shown that the two processes are separate rather than concerted events.[74] The presence of anion-stabilizing groups on the migrating substituent could be detrimental to the success of the reaction.

Several asymmetric 1,2-additions of various organolithium reagents (methyllithium, *n*-butyllithium, phenyllithium, lithioacetonitrile, lithium *n*-propylacetylide, and lithium phenylacetylide) to aldehydes result in decent to excellent *ee*s (65–98%) when performed in the presence of a chiral lithium amido sulfide [e.g. (**14**)].[75] The chiral lithium amido sulfides invariably have exhibited higher levels of enantioselectivity compared to the structurally similar chiral lithium amido ethers and the chiral lithium amide without a chelating group. (*de*) (*ee*)

The first highly diastereoselective, one-pot organometallic addition and hydride reduction reactions (>95% *de*) involving three symmetry-equivalent carbonyl centres (*de*)



(**14**)



SCHEME 12

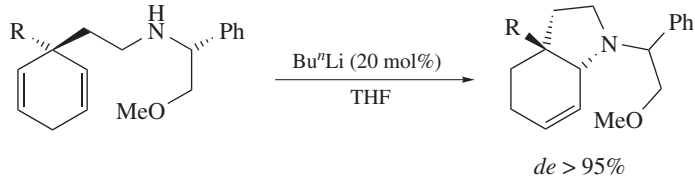
have been described (Scheme 12).[76] Three-fold methyllithium addition to 2,4,6-trimethoxybenzene-1,3,5-tricarbaldehyde gives the *anti,syn*-triol exclusively; addition of HMPA to the reaction or replacement of the substrate's methoxy groups with ethyl groups affords a statistical 3:1 (*anti,syn*:*syn,syn*) diastereomeric product ratio. Analogous asymmetric induction has been found upon hydride reduction of the complementary triketone, 2,4,6-trimethoxybenzene-1,3,5-triethanone (Scheme 12). Chelation and steric (gearing) effects about the crowded aromatic core contributed to the observed stereoselectivity.

The reactions of ketone dilithio α,β-dianions with imines and hydrazones have been investigated.[77] The nucleophilic addition reaction to C−N double bonds took place selectively at the β-position of dianions to form lithium (Z)-enolates containing a lithium amide portion, which is then transformed into γ-amino ketones and related compounds by the subsequent reaction with electrophiles.

The effect of donor ligands on the addition of PhLi to (E)-cinnamaldehyde in THF, under conditions that lead the reaction towards the production of 1,3-diphenylpropanone, has been studied.[78] It has been observed that in the presence of TMEDA and HMPT, the rate of that reaction becomes slower than in the absence of ligands; the effect of HMPA was even more spectacular: at concentration ratios [HMPA]:[PhLi] $\geq$ 4 the reaction becomes almost completely inhibited. As an extension of the above

study, *in situ* addition of an organolithium reagent into the N=O bond leads to an almost quantitative conversion into the corresponding hydrazone.[79]

Intramolecular hydroamination of cyclohexa-2,5-dienes has afforded the corresponding bicyclic allylic amines with high selectivity (Scheme 13).[80] The reaction does not proceed through a direct hydroamination of one of the diastereotopic alkenes but more likely involves a diastereoselective protonation of a pentadienyl anion, followed by addition of a lithium amide across the double bond of the resulting 1,3-diene and a highly regioselective protonation of the final allylic anion.

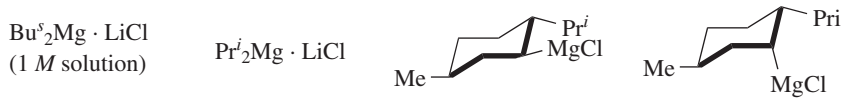


SCHEME 13

It has been demonstrated that α-alkyl-α-amino-*N*-[(silyl)methyl]-β-lactams can be regarded as new *N*-methyl-β-lactam cryptocarbanion sources.[81] Compared with previously reported nonenolate *N*-benzyl-β-lactams, the α-lithiated derivatives of *N*-[(silyl)methyl]-β-lactams are remarkably stable, with no apparent tendency to nucleophilic ring opening or ring cycloexpansion side-reactions. According to MO calculations and experimental observations, the origin of such stability seems to lie primarily on the coordination of the lithium cation by the β-lactam carbonyl and, to a lesser extent, on the 'α-effect' of the trimethylsilyl groups.

Organomagnesium species

Efficient procedures for the shifting of alkyl magnesiate–dialkyl magnesiate equilibria by additives or the alternative direct preparations of dialkyl magnesiates have been developed.[82] Compounds (**15**) and (**16**) has displayed exceptional reactivities for otherwise challenging Br–Mg exchange reactions, thus giving dialkyl magnesiates general synthetic value.



(**15**) (**16**) (**17**) (**18**)

The direct synthesis of Grignard reagents from enantiomerically pure alkyl halides has always resulted in a 1:1 ratio of the two possible epimers.[83] Once formed, the two components of the reagent are configurationally stable. If the reactivity of the two epimers differs significantly, as in the case of MenMgCl (**17**) and NeomMgCl

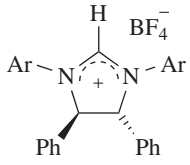
(**18**), it is possible to use each component selectively in reactions with electrophiles. This can be achieved by using thermodynamic/kinetic control of the reaction, altering temperature, solvent polarity, and stoichiometry.

Grignard reagents have been generated from magnesium and organic iodides in the ionic liquid *n*-butylpyridinium tetrafluoroborate, [bpy][BF_4], and they showed different reactivity from classical Grignard reagents in organic solvents.[84]

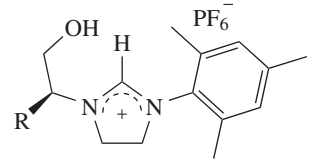
Readily available THF solutions of $LnCl_3.2LiCl$ (Ln = La, Ce, Nd) have been found to be superior promoters for the addition of various organometallic reagents to ketones.[85] They also catalyse efficiently the addition of organomagnesium compounds to imines.

The mechanism of the enantioselective 1,4-addition of Grignard reagents to α,β-unsaturated carbonyl compounds promoted by copper complexes of chiral ferrocenyl diphosphines has been explored through kinetic, spectroscopic, and electrochemical analysis.[86] On the basis of these studies, a structure of the active catalyst is proposed. The roles of the solvent, copper halide, and the Grignard reagent have been examined. (*ee*)

An efficient way to create, enantioselectively, all-carbon quaternary centres, by the unprecedented asymmetric conjugate addition of Grignard reagents to enones has been developed using a copper catalyst and a chiral diaminocarbene ligand of the corresponding salt (**19**) or (**20**).[87] (*ee*)



(**19**)

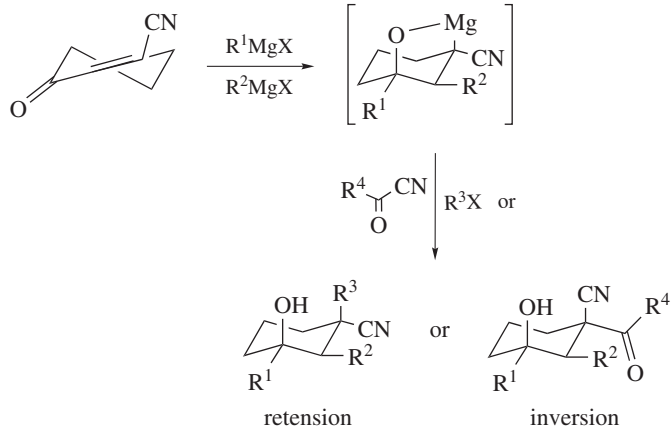


(**20**)

Sequential carbonyl addition–conjugate addition of Grignard reagents to 3-oxocyclohex-1-ene-1-carbonitrile has generated *C*-magnesiated nitriles whose alkylation stereoselectivities intimately depend on the nature of the electrophile.[88] The alkylation of these *C*-magnesiated nitriles with alkyl halides, sulfonates, and unstrained ketones occurs with the retention of the C–Mg configuration, whereas aldehyde and acyl cyanide acylations proceed with inversion of the stereochemistry (Scheme 14). Mechanistic probes indicated that the stereoselectivity is controlled by stereoelectronic effects for most electrophiles, except allylic, benzylic, and cyclopropyl halides, where single electron transfer processes intervene.

A ferrocenyl catalyst system able to perform highly enantioselective Cu-catalysed allylic alkylations with Grignard reagents has been described.[89] The alkylated products have been obtained in high yields with good to excellent enantioselectivities (*ee* up to 98%). (*ee*)

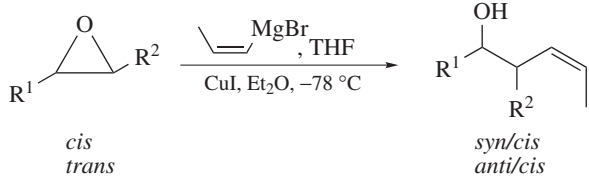
The *o*-diphenylphosphanylbenzoyl (*o*-DPPB) group has been explored as a directing leaving group in copper-mediated and copper-catalysed allylic substitution with Grignard reagents.[90] Complete control of chemo-, regio- and stereo-selectivity with complete *syn*-1,3-chirality transfer has been observed as a result of the directed nature



SCHEME 14

of the reaction. No excess of organometallic reagent is required and the directing group can be recovered quantitatively.

Hindered protected and unprotected epoxy alcohols have been regioselectively cleaved using copper-catalysed *cis*- and *trans*-prop-1-enylmagnesium bromide (Scheme 15).[91] The reactions exhibited good yield and excellent regioselectivity in systems where organocuprates and organoalanes failed. The *cis* Grignard reagent displayed no double-bond isomerization, whereas the *trans* isomer showed partial *trans*-to-*cis* equilibration, which has been minimized by controlling the reagent formation conditions.



SCHEME 15

A copper-free catalytic enantioselective addition to γ-chloro-α,β-unsaturated esters has been developed in the presence of *N*-heterocyclic carbenes.[92] The activation of Grignard reagents has been achieved using a Lewis base. (ee)

The ionic liquid butylmethylimidazolium tetrachloroferrate (bmim-$FeCl_4$) has been found to be a very effective and completely air-stable catalyst for the biphasic Grignard cross-coupling with primary and secondary alkyl halides bearing β-hydrogens.[93] The ionic liquid catalyst has been successfully recycled four times.

The addition of Grignard reagents to chiral trifluoromethyl *t*-butyl sulfinimine–ethanol adducts has afforded protected trifluoromethylamines in high yields with good (de)

to excellent diastereoselectivities.[94] The stereochemical outcome of the addition has been opposite to that expected via a chelation controlled transition state.

Organozinc species

Recent trends in enantioselective diorganozinc additions to aldehydes and developments in the use of dialkylzincs in radical reactions have been reviewed.[95,96] (ee)

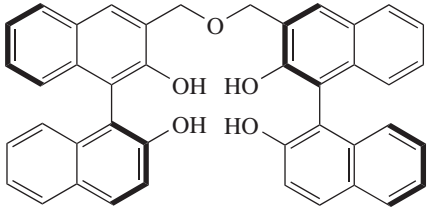
Grid-based QSSR methods have been used to predict catalyst enantioselectivities with a high degree of accuracy and precision.[97] The empirical models are easily assembled from a small set of ligands and their experimentally measured selectivities such as might be determined in preliminary screening. Relatively quick theoretical calculations provide models that allow a researcher to readily distinguish poorly, moderately, and highly selective catalysts, e.g. for asymmetric addition of Et_2Zn to PhCHO. (ee)

The first enantioselective one-pot, three-component imino Reformatsky reactions have been reviewed.[98] (ee) (−)-*N*,*N*-Dimethylaminoisoborneol has been found to be an excellent ligand for the enantioselective addition of Reformatsky reagents to aromatic and aliphatic aldehydes.[99] Enantioselectivities up to 93% *ee* have been obtained with sulfur-containing aldehydes. (ee)

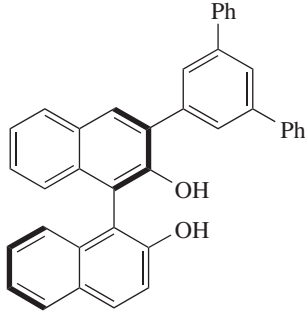
Directed metalation using alkali metal-mediated zincation has been developed for mono- and poly-cyclic aromatic derivatives.[100,101]

Asymmetric 1,4-addition of arylzinc chlorides to (*E*)-3-arylpropenals has proceeded with high enantioselectivity in the presence of a rhodium–(*R*)-binap catalyst and chlorotrimethylsilane.[102] The corresponding 3,3-diarylpropanals were obtained in high yields and excellent enantiomeric excess (98–99% *ee*). (ee)

A Et_2Zn–(*S*, *S*)-linked-BINOL (**21**) complex has been found suitable for chemoselective enolate formation from a hydroxy ketone in the presence of isomerizable aliphatic *N*-diphenylphosphinoylimines.[103] The reaction proceeded smoothly and β-alkyl-β-amino-α-hydroxy ketones were obtained in good yield and high enantioselectivity (up to 99% *ee*). (ee) A titanium complex derived from 3-(3,5-diphenylphenyl)-BINOL (**22**) has exhibited an enhanced catalytic activity in the asymmetric alkylation of aldehydes, allowing the reduction of the catalyst amount to less than 1 mol% without deterioration in enantioselectivity.[104] (ee)

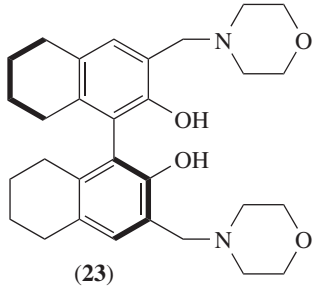


(**21**)



(**22**)

A binol derivative (**23**) has allowed high enantioselectivities in the reaction of diphenylzinc with both aliphatic and aromatic aldehydes.[105] Unlike other catalysts developed for the addition of diphenylzinc, the use of (**23**) avoids the need for additive and gives excellent results at room temperature. (*ee*)



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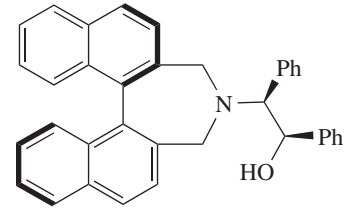
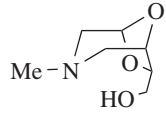


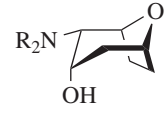
(**24**)

The direct addition of *in situ*-prepared arylzinc to aldehydes with chiral binaphthyl-derived amino alcohols (**24**) as catalysts has afforded optically active diarylmethanols in high yields and with excellent enantioselectivities (up to 99% *ee*).[106] By using a single catalyst, both enantiomers of many pharmaceutically interesting diarylmethanols can be obtained by the proper combination of various arylzinc reagents with different aldehydes. (*ee*)

The synthesis of a new enantiopure, conformationally constrained 1,4-amino alcohol (**25**) has been reported, starting from commercially available reagents from the chiral pool.[107] This 1,4-amino alcohol has been used as a chiral ligand in the addition of Et_2Zn to aldehydes (best *ee* 98%) and in the synthesis of chiral propargylic alcohols (best *ee* 70%) by alkynylzinc species. (*ee*)



(**25**)

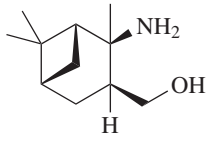


(**26**)

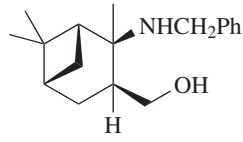
NR_2 = pyrrolidine, piperidine, morpholine

A *de novo* structural class of chiral amino alcohol catalysts has been identified through a synergistic effort combining novel architectures from 4 + 3-cycloadditions and quantum mechanical interaction field predictions that closely match subsequent experimental measurements.[108] On the basis of the assignment of absolute configuration of the resulting alcohol, a stereochemical model using ligand (**26**) has been proposed.

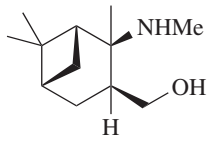
Primary, secondary, and tertiary γ-amino alcohols (**27**–**30**) have been used as chiral catalysts in the enantioselective addition of diethylzinc to aromatic aldehydes.[109] The first evidence of the substituent-dependent enantioselectivity of 1,3-amino alcohol catalysts has been observed, and the phenomenon interpreted by using molecular modeling at the *ab initio* level. (*ee*)



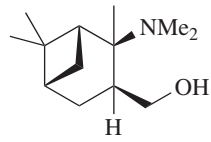
(**27**)



(**28**)

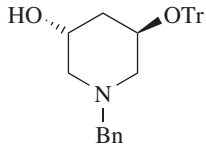


(**29**)

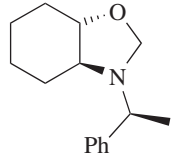


(**30**)

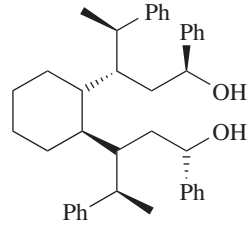
A series of chiral (3*R*,5*R*)-dihydroxypiperidine derivatives have been conveniently prepared from *trans*-4-hydroxy-L-proline and applied to the catalytic enantioselective addition of diethylzinc to benzaldehyde and heptanal.[110] The compound (**31**) has been found to show the best asymmetric induction in promoting the addition of Et_2Zn to various aldehydes, providing (*R*)-secondary alcohols in up to 98% *ee*. (*ee*)



(**31**)



(**32**)

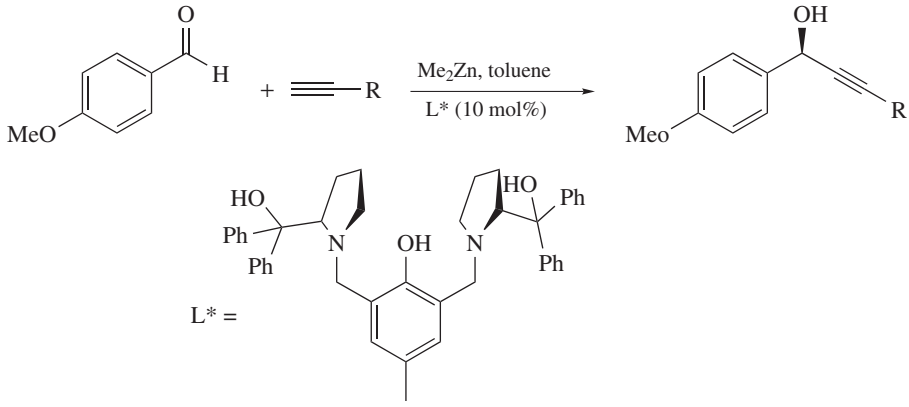


(**33**)

The chiral ligands (**32**) and (**33**) have been used as catalysts in the enantioselective addition of Et_2Zn to benzaldehyde.[111] It has been observed that the presence of the (*ee*) cyclohexane core gave better enantioselection, presumably owing to a more rigid transition state for the addition reaction in the former ligand.

Novel norephedrine-based chiral ligands with multiple stereogenic centers have been conveniently prepared from norephedrine and *N*-substituted pyrrole.[112] These novel chiral ligands have been used to catalyse the enantioselective addition of diethylzinc (*ee*) to aldehydes and to chalcone in high yields and with good to high enantioselectivities. The absolute configuration of products has been found to be affected by the stereogenic centres on the norephedrine part of the novel chiral ligands.

A practical and general alkynylation of aromatic and α,β-unsaturated aldehydes using a proline-derived dinuclear zinc catalyst system has been reported (Scheme 16).[113] The reaction proceeds with slightly higher enantiomeric excess at increased (*ee*) temperatures. Interestingly, electron-donating substituents have been found to be beneficial for both the yield and selectivity. Substituents in the *ortho* positions of the benzaldehyde raised both yields and *ee*s.



SCHEME 16

The direct strong steric interaction between substrate substituents and ligand substituents has been demonstrated in asymmetric addition of diethylzinc to aldehydes catalysed by sterically congested ferrocenyl aziridino alcohol derivatives.[114] In addition, this non-bonded steric repulsion influenced enantioselectivities significantly, and even led to inversion of the absolute configuration. This fact was further confirmed by theoretical calculations and the design of a new chiral ferrocenyl aziridino alcohol ligand. (ee)

New chiral Schiff base catalysts for the enantioselective addition of diethylzinc reagents to aldehydes have been developed.[115,116] The reaction of aldehyde with diethylzinc in the presence of 1–2 mol% of the chiral Schiff base catalyst has provided the corresponding secondary alcohol with excellent enantiomeric excess (up to 96% *ee*). (ee)

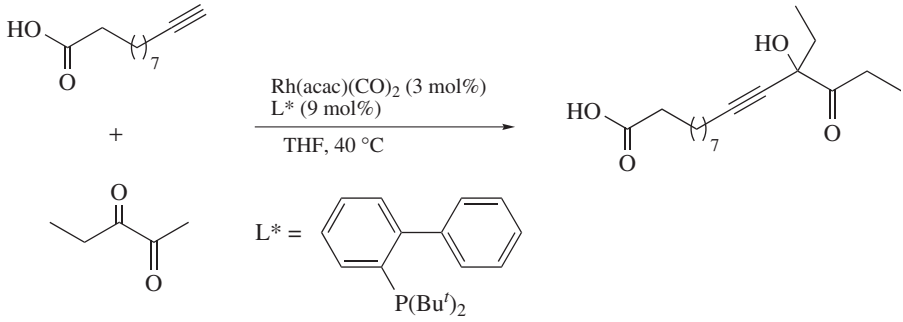
Enantioselective addition of diethylzinc to aldehydes has been catalyzed by diastereomeric monosubstituted [2.2]paracyclophane-based *N*,*O*-ligands.[117] A remarkable cooperative effect of planar and central chiralities has been observed. (ee)

The enantioselective addition of dialkylzinc to imine derivatives has been performed using copper,[118,119] titanium,[120] and rhodium catalysts;[121] high yields and excellent enantiocontrol (up to 99% *ee*) have been achieved. (ee)

Other organometallic species

Volume 8b of the *Science of Synthesis* series has reviewed the synthesis and applications in organic synthesis of the following organosodium compounds: alkylsodium,[122] alkenylsodium,[123] sodium acetylides,[124] allylsodium,[125] arylsodium compounds and sodium cyclopentadienide,[126] benzylsodium compounds,[127] 1,1-disubstituted organosodium compounds,[128] 1-monosubstituted organosodium compounds,[129] and α-sodio aldehydes, α-sodio ketones, and related compounds;[130] the volume also includes a review of the synthesis of organometallic compounds of rubidium and caesium and their applications to organic synthesis.[131]

The rhodium-catalysed addition of alkynes to 1,2-diketones, 1,2-keto esters, and aldehydes has provided a method for the synthesis of tertiary alkynyl alcohols under



SCHEME 17

mild conditions (Scheme 17).[132] The reaction tolerates many functional groups (such as carboxylic acids) that are incompatible with other methods. The alkyne addition reaction proceeded best using bulky phosphine ligands such as 2-(di-*t*-butylphosphino) biphenyl. This method fills a void in the more common zinc-catalysed processes, which give poor yields with enolizable 1,2-dicarbonyl substrates.

The enantioselective addition of allylstannanes to glyoxylates and glyoxals, and also simple aromatic and aliphatic aldehydes, catalysed by chiral (salen)Cr(III) complexes, has been studied.[133] The reaction proceeded smoothly for the reactive 2-oxoaldehydes (*ee*) and allyltributyltin in the presence of small amounts (1–2 mol%) of (salen)Cr(III)BF_4 under mild, undemanding conditions. The stereochemical results have been rationalized on the basis of the proposed model.

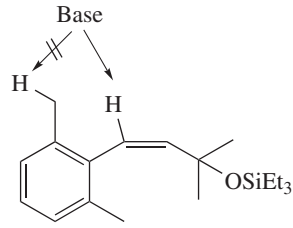
Proton-transfer Reactions

Enthalpies of activation, transition-state geometries, and primary semi-classical (without tunneling) kinetic isotope effects (KIEs) have been calculated for 11 bimolecular identity proton-transfer reactions, four intramolecular proton transfers, four non-identity proton-transfer reactions, 11 identity hydride transfers, and two 1,2-intramolecular hydride shifts at the HF/6–311+G**, MP2/6–311+G**, and B3LYP/6–311++ G** levels.[134] It has been found that the KIEs are systematically smaller for hydride transfers than for proton transfers. The differences between proton and hydride transfers have been rationalized by modeling the central ·C···H···C· unit of a proton-transfer transition state as a four-electron, three-centre (4-e 3-c) system and the same unit of a hydride-transfer transition state as a 2-e 3-c system.

The intrinsic acidity of dimethylhalonium ions has been determined, both by theoretical methods and by gas-phase reactions of the isolated ions with pyridine bases.[135] The calculated geometry of the dimethylhalonium ions shows a bent structure with the C–X–C angle decreasing in the order Cl > Br > I. Thermochemical calculations for the reaction of the dimethylhalonium ions with pyridine, 2,6-dimethylpyridine, and 2,6-di-*t*-butylpyridine indicated that proton transfer, with the formation of the dimethylhalonium ylide, is endothermic, whereas methyl transfer, with formation of methyl halide, is exothermic. The endothermicities for proton transfer are, nevertheless,

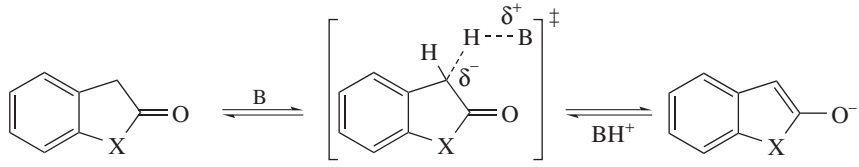
dependent on the steric hindrance of the base. The bulkier the bases, the less endothermic is the proton-transfer reaction.

A novel example of a vinylic hydrogen more reactive than a benzylic hydrogen has been found by treatment of a twisted styrene derivative (**34**) with a strong base followed by D_2O quenching.[136] A correlation between the reactivity of the vinyl hydrogens and the magnitude of the twist has been presented. The highly reactive vinyl hydrogens could be rationalized by considering the novel orbital interaction between the π^* orbital of the benzene ring and the σ orbital of the vinylic C–H bond in the twisted styrene derivatives.



(**34**)

A study on how the difference in the aromaticity between (**35**) and (**36**) may affect the intrinsic barriers to proton transfer has been reported (Scheme 18).[137] The intrinsic barriers for the deprotonation of the thiophene derivative by amines and OH^- have been found to be somewhat higher than for the furan analogue. This result has been attributed to a combination of steric, inductive, and π-donor effects which overshadow the aromaticity effect.



X = O (**35**)
X = S (**36**)

$\Delta G_0^{\ddagger}$ (**35**) < $\Delta G_0^{\ddagger}$ (**36**)

SCHEME 18

Rates of hydrogen exchange reactions promoted by methanolic sodium methoxide have been compared with gas-phase acidities, for fluorinated aromatic compounds.[138] Experimental hydrogen isotope effects of near unity found for 14 of the fluorinated benzylic compounds and pentafluorobenzene suggest that the amount of internal return associated with the exchange process is substantial. Density functional calculations using B3LYP/6–31+G(d,p) have been reported for the reactions of methanolic sodium methoxide with C_6F_5H, $C_6H_5CH(CF_3)_2$, $C_6H_5CHClCF_3$, and 9-phenylfluorene.

Asymmetric protonation of lithium enolates has been examined using commercially available amino acid derivatives as chiral proton sources.[139] Among the amino acid

derivatives tested, *N*-β-L-aspartyl-L-phenylalanine methyl ester has been found to cause significant asymmetric induction in the protonation of lithium enolates. The enantiomeric excess (up to 88% *ee*) of the products obtained in the presence of a (ee) catalytic amount of the chiral proton source has been higher than those obtained in the stoichiometric reaction.

Miscellaneous

The asymmetric ring opening of epoxides and aziridines with carbon nucleophiles has been reviewed.[140] A computational investigation of the mechanism and diastereos- (ee) electivity of aziridine formation from sulfur ylides and imines has been performed using DFT methods including a continuum model of solvent.[141] The results are in (de) very good agreement with observed *cis*/*trans* selectivities. This study has shown that betaine formation is non-reversible and that the transition-state structures are governed by the steric strain induced by the *N*-sulfonyl group.

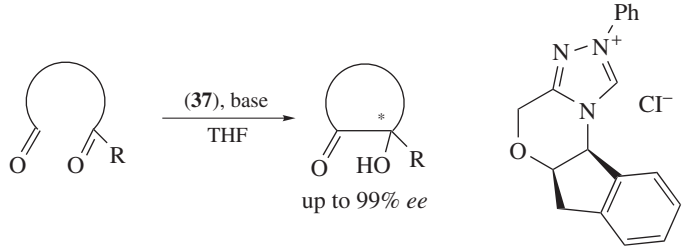
Theoretical calculations at the B3LYP/6–31+G(d), MP2/6–31+G(d), and G3(MP2) levels have been carried out to understand the alternative reaction pathways–the cyclopropyl ring cleavage (RC) and the retrocycloaddition reaction (rCA)–of a constrained tricyanocyclopropyl anionic derivative.[142] The more energetically favourable path has been found to be the RC process, a formally 'forbidden' rearrangement yielding an allylic anion system via a concerted transition structure, in agreement with experimental outcomes. An explanation for the low energy barrier associated with RC was furnished on the analysis of the evolution of the twisting (dis-/conrotatory) motions of cyano substituents in the cyclopropyl ring and also on the number and type of electron pairs provided by the electron localization function.

The nucleophilicity parameters for carbanions of nitronates and malonic acid derivatives have been investigated.[143] The nucleophilic reactivities do not correlate with the acidity constants of the conjugate CH acids, and from the poor correlation of the reactivities of the substituted α-nitrobenzyl anions with Hammett's σ-constants it can be inferred that the nucleophilic reactivities are strongly controlled by solvation.

Rate constants have been measured for the capture of *para*-substituted phenylchlorocarbenes by chloride ions to form aryldichloromethide carbanions and for the additions of these carbanions to acrylonitrile.[144] A conventional interpretation of the Hammett correlations has suggested that the reactions of carbenes with Cl^- traverse 'early' transition states.

The catalytic enantioselective crossed aldehyde–ketone benzoin cyclization has been reported.[145] The reactions have been performed in the presence of Rovis' aminoindanol- (ee) derived chiral triazolium salts (**37**) as catalysts with excellent enantioselectivities (up to 99% *ee*) (Scheme 19).

The reactive species in fluoride-mediated carbon–carbon bond-forming reactions has been investigated.[146] The regio- and diastereo-selectivities of silanes reacting with cyclohexenone in the presence of a catalytic amount of fluoride have been compared with the reactivity of analogous solvent-separated lithium ion pairs. Closely analogous behaviour has been observed, showing that carbanions and not siliconate complexes are the reactive species in the fluoride-catalysed reactions.

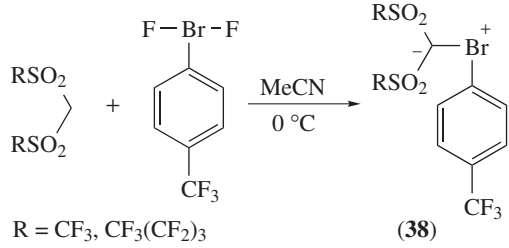


SCHEME 19

Recent advances in the Stevens rearrangement of ammonium ylides have been reviewed in terms of application to the synthesis of alkaloid natural products.[147]

The generation and reactivity of conjugated azomethine ylides has been reviewed.[148] 1,3-Dipolar cycloaddition and 1,5- and 1,7-electrocyclizations have been described as powerful strategies for the synthesis of monocyclic and annulated five- and seven-membered nitrogen heterocyclic compounds.

The synthesis, isolation, and characterization of the first stable aliphatic bromonium ylides (**38**) have been reported (Scheme 20).[149] The bromonium ylides (**38**) selectively undergo transfer of the aryl group to nitrogen heterocycles, such as pyridines, yielding *N*-arylpyridinium salts.



SCHEME 20

Electrophilic Aliphatic Substitution

The enantioselective α-fluorination of carbonyl compounds has been highlighted.[150–152] The catalytic asymmetric fluorination of various substrates has also been reviewed.[153,154] (*ee*)

The asymmetric fluorination of β-keto esters has been performed in the presence of various catalysts, such as $CpTiCl_3$,[155] chiral rare earth perfluorinated organophosphates,[156] and chiral palladium complexes.[157] (*ee*)

The structural and stereochemical aspects of the enantioselective halogenation of 1,3-dicarbonyl compounds catalysed by Ti(TADDOLato) complexes have been reported.[158] The observed absolute configuration at the fluorinated stereogenic centre has (*ee*)

been found to match the one inferred from the structural analysis of the Ti(TADDOLato) complexes.

Enantioselective α-amination of carbonyl compounds has been promoted by L-azetidinecarboxylic acid,[159] axially chiral guanidine derivative,[160] and chiral palladium complexes.[161] (ee)

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CHAPTER 10

Elimination Reactions

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*E*1cB Mechanisms

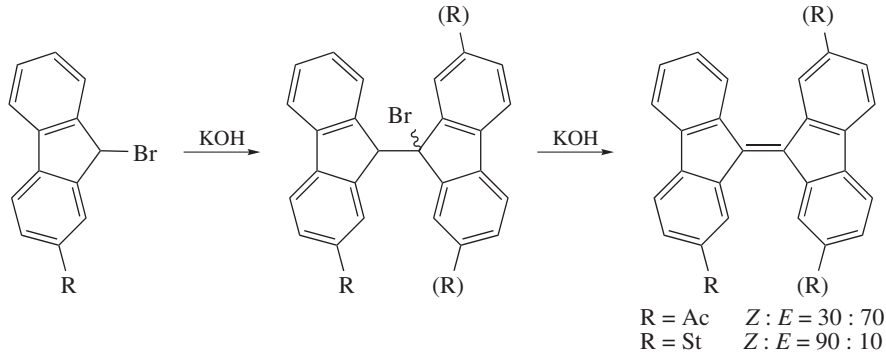
The mechanistic borderline between *E*2 and *E*1cB mechanisms has been studied under various conditions.[1,2] The mechanism of the elimination reaction of 2-(2-fluoroethyl)-1-methylpyridinium has been explored explored by Car–Parrinello molecular dynamics in aqueous solution.[3] The results indicated that the reaction mechanism effectively evolves through the potential energy region of the carbanion: the carbon–fluoride bond breaks only after the carbon-hydrogen bond.

*E*2 Mechanisms

It has been found that dehydrobromination of 9-bromo-9,9′-bifluorenyl derivatives (Scheme 1) occurred by *E*2 elimination, suggesting that the configuration of 9-bromo-9,9′-bifluorenyl isomers determined the stereochemistry of the product.[4] Facile (de) isomerization of the 9,9′-bifluorenylidenes formed may give the observed stereoselectivity depending on the length of the acyl side-chain.

The nature of the transition state for the *E*2 reaction of some 3-thiophenoxypropanones in aprotic solvents has been investigated.[5] The linear free energy correlation and the calculated activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ of the reactions suggested an unequal and synchronous *E*2cB mechanism via base-catalysed amine-elimination reaction.

Organic Reaction Mechanisms 2006. Edited by A. C. Knipe



SCHEME 1

The competition between nucleophilic substitution and base-induced elimination in the gas phase has been studied using deuterium kinetic isotope effects (KIE).[6] The overall reaction rate constants and KIE have been measured for the reactions of $RCl + ClO^-$ (R = Me, Et, *i*-Pr, and *t*-Bu). As the extent of substitution in the alkyl chloride increases, the KIE effects become increasingly more normal. These results indicated that the *E*2 pathway becomes the dominant channel as the alkyl group becomes more sterically hindered.

Solvolytic Reactions

High-level *ab initio* calculations have shown that the S_N2 reaction of the cyanide ion with ethyl chloride is catalysed by 1,4-benzenedimethanol in dipolar aprotic solvents through selective two hydrogen bonds.[7] In non-polar solvents, combined with phase-transfer catalysis, the 1,4-benzenedimethanol could replace some water molecules hydrating the cyanide ion and induce a substantial rate acceleration effect.

Cope elimination reactions of *threo*- and *erythro*-*N*,*N*-dimethyl-3-phenyl-2-butylamine oxide have been investigated using QM/MM calculations in water, THF, and DMSO.[8] The aprotic solvents provided rate accelerations of up to 106-fold. It has been found that the amine oxide oxygen is the acceptor of three hydrogen bonds from water molecules for the reactant but only one or two weaker ones at the transition state.

Solvent effects on the kinetics and mechanism of unimolecular heterolysis of commercial organohalogen compounds have been investigated.[9–11] The reaction rate is satisfactorily correlated by parameters for polarity, electrophilicity, and cohesion of the solvent, whereas the solvent nucleophilicity and polarizability exert no effect.

The solvent effect of ionic liquids on the decarboxylation of 1,3-dimethylorotic acid and its analogue has been investigated.[12] The rate acceleration observed has been attributed to stabilization of the zwitterionic intermediates by the charged groups available in these special solvents.

Pyrolytic Reactions

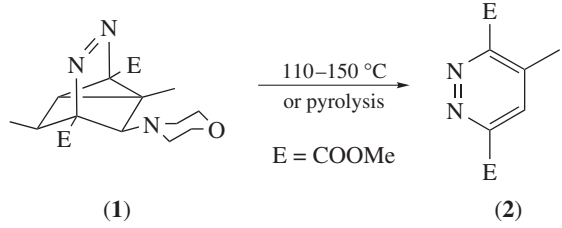
Cycloreversions

Density functional theory studies of intramolecular retro-ene reactions of allyldiazenes have shown that the reaction is a concerted process involving a six-centre cyclic transition state.[13] The *cis*- and *trans*-allyldiazenes can interconvert by rotation around the double bond or by nitrogen inversion, it being predicted that nitrogen inversion is favoured.

Experimental and theoretical results have revealed the influence of a neighbouring cyclopropane ring in a retro-Diels–Alder reaction at lower temperature.[14] The lower kinetic barrier for this reaction has been attributed to stabilization of the transition state by orbital interactions involving the cyclopropane bond orbitals.

An improved retro-cycloaddition of pyrrolidinofullerenes has been carried out in presence of metal Lewis acids.[15] The experimental data suggested that thermal treatment leads to the formation of the azomethine ylide, which is efficiently trapped by the dipolarophile that is present in the reaction medium.

A strained azo-bridged tricyclic system (**1**) undergoes a selective retro 'inverse electron-demand' Diels–Alder reaction on heating, leading through a cascade of tautomeric and sigmatropic shifts to the pyridazine derivative (**2**) (Scheme 2).[16] The proposed mechanism was supported by quantum chemical calculations and experimental evidence.



(**1**) (**2**)

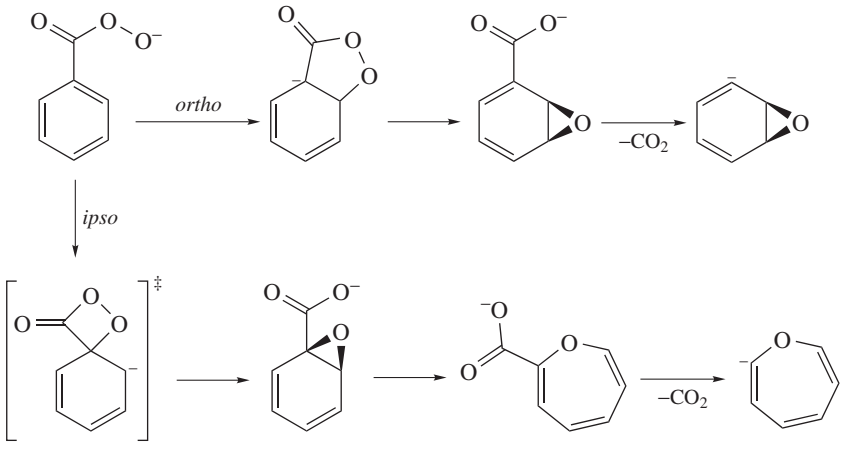
SCHEME 2

Acid Derivatives

An *ab initio* study on the unimolecular elimination reactions of methacrylonitrile has revealed a direct four-centre elimination of HCN and three-centre elimination of H_2 channels.[17] A methylcyanoethylidene intermediate has also been identified.

Decarboxylation of pyruvic acid and its isomers, including the enol tautomers and enantiomeric lactone structures, has been investigated at the B3LYP/6–311++G(3df, 3pd) level.[18] It has been found that a keto form with *trans* $C_{methyl}C_{keto}C_{acid}O_{hydroxyl}$ and *cis* $C_{keto}C_{acid}OH$, and with one methyl hydrogen in a synperiplanar position with respect to the keto oxygen, is the most stable.

The unimolecular reactivities of a range of perbenzoate anions have been investigated in the gas phase by electrospray ionization tandem mass spectrometry.[19] The



SCHEME 3

combination of substituent studies and electronic structure calculation have revealed competing *ortho* and *ipso* mechanisms that have similar activation energies directly influenced by the nature and position of substituents on the aromatic ring (Scheme 3). These data also indicated that the loss of carbon dioxide does not lead directly to the phenoxide product ions but rather proceeds via initial epoxidation of the benzene ring forming benzene oxide or oxepin anions that may subsequently rearrange to the global minimum.

Gas-phase elimination reactions of ethyl esters of α- and β-amino acids have been investigated in a static reaction system.[20,21] The first step of decomposition of these esters is formation of the corresponding carboxylic acids and ethylene through a concerted six-membered cyclic transition state. The intermediate β-amino acids decarboxylate via a semipolar six-membered cyclic transition state.

Activation barriers for geometric isomerism and tautomerization have been studied for carbamic acid and its mono- and di-chalcogenide analogues, $H_2NC(=X)YH$ (X, Y = O, S, Se), at the B3LYP/6–31+G*, MP2/6–31+G*, and G2MP2 theoretical levels.[22] The studies have indicated that carbamic acid with higher chalcogen prefers chalcogen at the chalcogenol position. Decomposition of carbamic acid and its analogues is believed to occur by a two-step pathway.

The gas-phase unimolecular elimination reactions of 2-substituted ethyl *N*,*N*-dimethylcarbamates[23,24] and several heterocyclic carbamates[25] have been studied using the Möller–Plesset MP2/6–31G method. On the basis of these calculations, the mechanism appears to be concerted, asynchronous, through a six-membered cyclic transition-state structure.

Theoretical studies on the gas-phase elimination of 2-substituted alkylethyl methylcarbonates were performed at the B3LYP/6–31G* and B3LYP/6–31+G** levels of theory.[26] The results of these calculations provide additional evidence that the mechanism for carbonates with a C_β–H bond proceeds through a concerted non-synchronous

six-membered cyclic transition state to produce methylcarbonic acid and the corresponding alkene. The unstable intermediate, methylcarbonic acid, rapidly decomposes through a four-membered cyclic transition state to methanol and carbon dioxide.

Theoretical evidence for the thermal decomposition mechanism for ethyl oxamate, ethyl oxanilate, and ethyl *N*,*N*-dimethyl oxamate have been provided.[27] Ethyl oxamate and ethyl oxanilate undergo rapid decarbonylation to give the corresponding carbamates. Ethyl *N*,*N*-dimethyloxamate elimination reaction yields in one step, through a six-membered cyclic transition state, dimethyloxamic acid and ethylene gas.

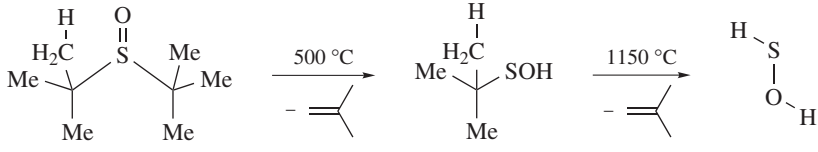
Other Pyrolytic Reactions

The Arrhenius parameters for the gas-phase unimolecular structural isomerizations of 1,1,2-trimethylcyclopropane[28] to three isomeric methylpentenes and two dimethylbutenes, and of 1,1,2,2-tetramethylcyclopropane[29] to 2,4-dimethylpent-2-ene have been determined over a wide range of temperatures. Despite previous reports on substantial decreases in activation energies for structural isomerizations of methyl-substituted cyclopropanes, this study has revealed that the trend does not continue beyond dimethylcyclopropane isomerization.

Activation energies and rate constants calculated for the thermolysis of α-hydroxyaldehydes at the MP2/6–311++G(d,p)//MP2(FC)/6–31G(d) level indicate that the thermolysis of α-hydroxyaldehydes is slower than the thermolysis of similar α-hydroxy ketones.[30] A positive inductive effect due to methyl groups, at either C(3) or C(4), accelerates the reaction with respect to the unsubstituted α-hydroxyaldehyde; the effect at C(4) is greater than that at C(3).

Kinetics of the gas-phase elimination of 2-hydroxynitroalkanes have been investigated at the MP2/6–31G* level of theory.[31] The thermal elimination of 2-hydroxynitroalkanes occurs in a retro-aldol type of mechanism with a six-membered transition state structure characterized by the transference of the hydroxyl hydrogen to the nitro group to give acetaldehyde and the corresponding nitroalkane for the secondary substrates and acetone and nitromethane for the tertiary substrate.

Sulfenic acid (**3**) has been synthesized in the gas phase by low-pressure, high-temperature pyrolysis of di-*t*-butyl sulfoxide (**4**) and characterized by means of matrix isolation and gas-phase IR spectroscopy (Scheme 4).[32] The mechanism of formation of (**3**) by flash pyrolysis of (**4**) has been studied by quantum chemical calculations, and different pyrolysis experiments monitored by mass spectrometry. In agreement

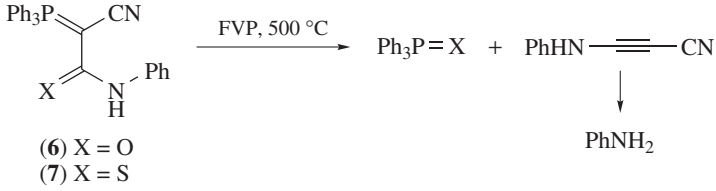


(**4**) (**5**) (**3**)

SCHEME 4

with theoretical and experimental results, (**3**) appears to be formed through several successive unimolecular steps via the primary decomposition product *t*-BuSOH (**5**).

A series of cyano(arylcarbamoyl)phosphorus ylides (**6**) and cyano(arylthiocarbamoyl)phosphorus ylides (**7**) have been prepared and fully characterized.[33] Pyrolytic reaction products obtained by FVP have shown that thermal extrusion of Ph_3PO or Ph_3PS occurs (Scheme 5). Kinetic study of the gas-phase pyrolysis of each ylide by a static method showed that these reactions are unimolecular and first order with no significant substituent effect, but the thiocarbamoyl ylides (**7**) react 40–65 times more rapidly than their carbamoyl analogues (**6**).



(**6**) X = O
(**7**) X = S

SCHEME 5

Elimination Reactions in Synthesis

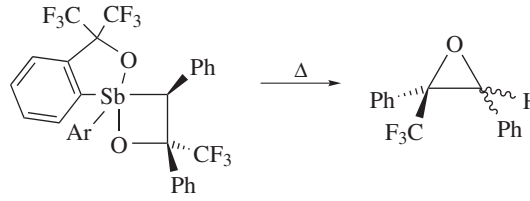
Metathesis of alkenes has been reviewed in terms of cross-metathesis, ring opening and closing, disproportionation, transmutation, and self-metathesis.[34] A review on catalytic processes involving β-carbon elimination has summarized recent progress on palladium-catalysed C–C bond cleavage in various cyclic and acyclic systems.[35]

The salt-free Wittig reaction of non-, semi-, and stabilized ylides has been investigated on realistic systems using DFT calculations, including continuum solvation.[36] These results provided unequivocal support for the generally accepted mechanism and are in very good agreement with experimental selectivities.

Intermolecular aza-Wittig reaction has been described for the one-step synthesis of pyrazolo[1,5-*a*]pyrimidine and imidazo[1,2-*b*]pyrazole derivatives.[37] The asymmetric synthesis of β-quaternary azacycles has been accomplished by aza-Wittig reaction mediated by chiral phosphorus(III) reagents.[38]

The existence of oxaarsetanes during an arsa-Wittig reaction has been proved by ^{1}H and ^{17}O NMR spectroscopy.[39] ^{75}As NMR spectra were obtained from the corresponding arsonium salts and arsane oxides. It has been demonstrated by various NMR methods that the mechanism of the arsa-Wittig reaction is identical to that of the phospha-Wittig reaction.

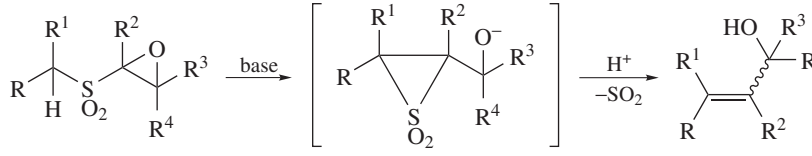
Pentacoordinate 1,2-oxastibetane (**8**) has been successfully synthesized by the reactions of the corresponding bromo-2-hydroxyalkylstiboranes with NaH.[40] 3-Phenyl-1,2-oxastibetane decomposed to give the corresponding oxirane with retention of configuration as the sole product, in sharp contrast to the result of the thermolysis of the 1,2-oxaphosphetane bearing the Martin ligand (Scheme 6). Thermolysis of the 3-phenyl-1,2-oxastibetane in the presence of LiBr and $LiBPh_4$.3DME gave selectively the oxirane with inversion of configuration and the corresponding alkene as the main product, respectively.



(**8**)

SCHEME 6

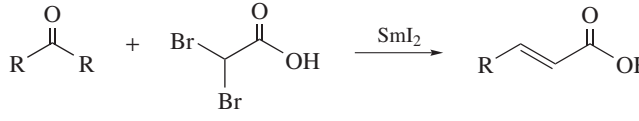
A variety of α,β-epoxy sulfones have been converted into a range of mono-, di-, and tri-substituted allylic alcohols using the epoxy-Ramberg–Bäcklund reaction (ERBR) (Scheme 7).[41] Modification of this method has enabled the preparation of enantio- (*ee*) enriched allylic alcohols following the diastereoselective epoxidation of enantio- (*de*) enriched vinyl sulfones that were accessed efficiently from the chiral pool.



R, R^1, R^2, R^3, R^4 = alkyl, aryl

SCHEME 7

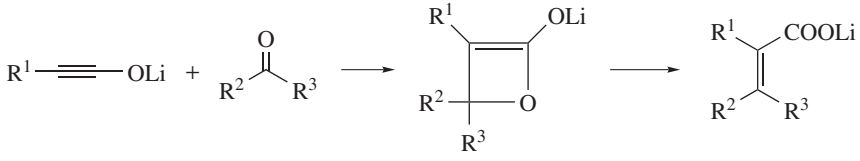
A reaction of dibromoacetic acid with different aldehydes promoted by SmI_2, followed by an elimination reaction also promoted by samarium diiodide, affords (*E*)-α,β-unsaturated carboxylic acids with total stereoselectivity (Scheme 8).[42] A mecha- (*de*) nism that involves chelation of the Sm(III) centre with the oxygen atom of the alcohol group through a six-membered chair-like transition state has been described.



SCHEME 8

A highly *Z*-selective olefination of α-oxy and α-amino ketones via ynolate anions has been reported (Scheme 9).[43] The stereocontrol mechanism has been explained by (*de*) orbital interactions between the *s* orbital of the breaking C–O bond or π orbital of the enolate and the s^* orbital of the C–O or C–N bonds of the substituent in the ring opening of the β-lactone enolate intermediates, and/or the chelation to lithium.

A clean and reagent-free generation of highly strained cycloalkynes from bi-3*H*-diazirin-3-yls has been described.[44] A new synthesis of alkynes has been achieved by



R^1, R^2, R^3 = alkyl

SCHEME 9

R^1, R^2 = alkyl, aryl

SCHEME 10

treatment of 1,2-dibromoalkanes with 5 equiv. of DBU (Scheme 10).[45] The inductive effect of oxygen substitution at the C(3) position plays a critical role in proton abstraction.

An unusual dehydroxymethylation has been observed in an acyclic primary alcoholic system.[46] The relief of steric congestion has been considered as the primary driving force in this reaction.

A new and readily available catalytic system has been developed to open the cyclopropane ring in 4 + 2 + 2-homo-Diels–Alder cycloadducts formed by reaction of norbornadienes and buta-1,3-diene.[47] The cobalt-mediated homo-Diels–Alder reaction followed by this $PtCl_2$-promoted isomerization is a key step in the efficient route to bicyclo[5.3.0]decanes.

A novel system for the enantioconvergent decarboxylative protonation of racemic β-keto esters has been developed.[48] The reaction tolerates a variety of substitution and functionality and delivers products of high enantiopurity in excellent yield. The enantioinduction in the observed protonated products is consistent with the intermediacy of an enolate that is intimately associated with a chiral Pd complex.

The molecular mechanism of the Hoffmann elimination involving (*N*-Cl)-*N*-methylethanolamine has been theoretically characterized by using DFT at the B3LYP/6–31++G** computing level.[49] The role of water as a solvent has been analysed by using both discrete and hybrid discrete–continuum models. The rearrangement proceeds by a water-assisted asynchronous concerted mechanism.

Other Reactions

The enantioselective palladium-catalysed decarboxylative allylic alkylation has been highlighted.[50]

Ultrafast molecular elimination of iodine from $IF_2C–CF_2I$ has been studied using the velocity map ion imaging technique in combination with femtosecond pump–probe laser excitation.[51] By varying the femtosecond delay between pump and probe pulse, it has been found that elimination of molecular iodine is a concerted process, although the two carbon–iodine bonds are not broken synchronously.

Experimental rate constants, kinetic isotope effects and chemical branching ratios for the $CF_3CFClCH_3$-d_0, -d_1, -d_2, and -d_3 molecules have been experimentally measured and interpreted using statistical unimolecular reaction rate theory.[52] The structural properties of the transition states needed for the theory have been calculated by DFT at the B3PW91/6–31G(d′,p′) level.

A kinetic study of the aminolysis of substituted (methylthio)benzylidene Meldrum's acids with aliphatic primary amines in aqueous DMSO has been reported.[53] With all amines the reactions are strictly second order and proceed via a three-step mechanism.

The effects of the addition of sugars, long-tailed *n*-alkyl pyranosides, *n*-alkyl glycerol ethers and *n*-alcohols on the properties of di-*n*-hexadecyldimethylammonium bromide (DHAB) vesicles have been studied.[54] Upon addition of most additives, an inhibiting effect on the decarboxylation reaction of 6-nitrobenzisoxazole-3-carboxylate anion has been observed relative to the reaction in vesicles without any additive. The largest inhibition was observed in the case of cholesterol.

A significant acceleration of the electrocyclic ring opening of benzocyclobutene derivatives has been disclosed under the influence of a β-silicon atom.[55] This effect has been associated with the adjacent anion-driven electrocyclic reactions such as oxy-Cope rearrangement.

A convenient route to trivinylphosphine has been developed by thiol elimination from tris[2-(phenylthio)ethyl]phosphine oxide.[56] The reaction mechanism involves a phosphoryl-stabilized carbanion, from which benzene thiolate anion is eliminated.

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CHAPTER 11

Addition Reactions: Polar Addition

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Reviews

During the coverage period of this chapter, reviews have appeared on the following topics: gold-catalysed hydroamination of C–C multiple bonds;[1] mechanism of hydrosilylation;[2] hydrostannation of activated alkynes mediated by Stryker's reagent;[3] synthesis, hydrometallation, and carbometallation of fluoroalkylated alkynes;[4] C_2-symmetrical bis(oxazoline) ligands in asymmetric catalysis;[5] enantioselective dihydroxylation of alkenes by osmium complexes;[6] transition metal-catalysed carbochalcogenation of alkynes;[7] synthesis of fine chemicals by the conjugate addition of nitroalkanes to electrophilic alkenes;[8] asymmetric aza-Michael reaction;[9] one-pot coupling of α,β-unsaturated carbonyl compounds bearing a chalcogen group and electrophiles using a Lewis acid;[10] the phospha-Michael addition in organic synthesis;[11] enantioselective 1,4-conjugate addition catalysed by Cu complexes;[12] and asymmetric synthesis using environmentally friendly reagents and catalyst versus kinetic resolution.[13]

Organic Reaction Mechanisms 2006. Edited by A. C. Knipe

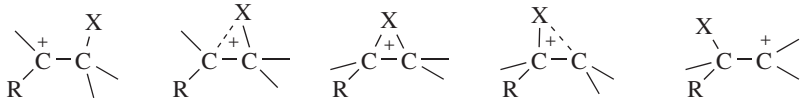
Electrophilic Additions

A study of the reactions of a series of gas-phase cations (NH_4^+, H_3O^+, SF_3^+, CF_3^+, CF^+, SF_5^+, SF_2^+, SF^+, CF_2^+, SF_4^+, O_2^+, Xe^+, N_2O^+, CO_2^+, Kr^+, CO^+, N^+, N_2^+, Ar^+, F^+, and Ne^+) with the three structural isomers of dichloroethene, i.e. $CH_2{=}CCl_2$, *cis*-ClCH=CHCl, and *trans*-ClCH=CHCl, has been reported.[14] The recombination energy (RE) of these ions spans the range 4.7–21.6 eV. Reaction rate coefficients and product branching ratios have been measured at 298 K in a selected ion flow tube (SIFT). Collisional rate coefficients were calculated by modified average dipole orientation (MADO) theory and compared with experimental data. Thermochemistry and mass balance have been used to predict the most feasible neutral products. Threshold photoelectron–photoion coincidence spectra have also been obtained for the three isomers of $C_2H_2Cl_2$ with photon energies in the range 10–23 eV. The fragment ion branching ratios have been compared with those of the flow tube study to determine the importance of long-range charge transfer. A strong influence of the isomeric structure of dichloroethene on the products of ion–molecule reactions was observed for H_3O^+, CF_3^+, and CF^+. For $CH_2{=}CCl_2$, the reaction with H_3O^+ proceeds at the collisional rate with the only ionic product being 1,1-$C_2H_2Cl_2H^+$. However, the same reaction yields two more ionic products in the case of *cis*-1,2- and *trans*-ClCH=CHCl, but proceeds with only 14% and 18% efficiency, respectively. The CF_3^+ reaction proceeds with 56–80% efficiency, the only ionic product for $CH_2{=}CCl_2$ being $C_2H_2Cl^+$ formed via Cl^- abstraction, whereas the only ionic product for both 1,2-isomers is $CHCl_2^+$, corresponding to a breaking of the C=C double bond. Less profound isomeric effects, but still resulting in different products for $CH_2{=}CCl_2$ and ClCH=CHCl isomers, have been found in the reactions of SF^+, CO_2^+, CO^+, N_2^+, and Ar^+. Although these five ions have REs above the ionization energy (IE) of any of the $C_2H_2Cl_2$ isomers, and hence the threshold for long-range charge transfer, the results suggest that the formation of a collision complex at short range between these ions and $C_2H_2Cl_2$ is responsible for the observed effects.[14]

An attempt has been made to analyse whether the electrophilicity index is a reliable descriptor of the kinetic behaviour. Relative experimental rates of Friedel–Crafts benzylation, acetylation, and benzoylation reactions were found to correlate well with the corresponding calculated electrophilicity values. In the case of chlorination of various substituted ethylenes and nitration of toluene and chlorobenzene, the correlation was generally poor but somewhat better in the case of the experimental and the calculated activation energies for selected Markovnikov and anti-Markovnikov addition reactions. Reaction electrophilicity, local electrophilicity, and activation hardness were used together to provide a transparent picture of reaction rates and also the orientation of aromatic electrophilic substitution reactions. Ambiguity in the definition of the electrophilicity was highlighted.[15]

Halogenation and Related Reactions

Calculated equilibrium geometries, bond lengths, and charge densities have been compared for halonium ions (**1**–**5**; X = Cl or Br) derived from the addition of halogen electrophiles to fluoro-substituted terminal alkenes (R = alkyl or perfluoroalkyl with



(**1**) (**2**) (**3**) (**4**) (**5**)

α- and β-substituents being H or F). The calculated structures were found to correlate with regiochemical product distributions from ring opening of halonium ions by anions or by methanol as solvent. Calculated halonium ion structures and the Hammond postulate were utilized to predict the regiochemical product distributions for reactions of halogens with fluoroalkenes that were not investigated experimentally.[16]

A mixture of molecular iodine and 4-iodotoluene difluoride has been found to generate *in situ* the couple 'IF', capable of adding to various alkenes and alkynes in a Markovnikov fashion in CH_2Cl_2 at 0–5 °C and with prevalent *anti*-stereoselectivity.[17] (*de*)

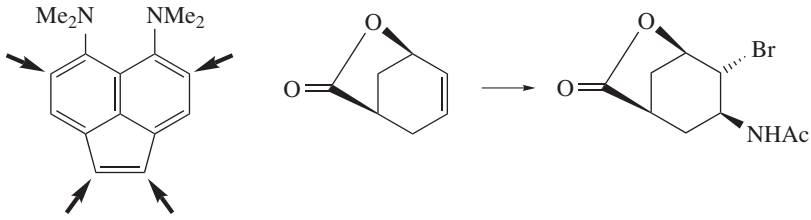
The mechanism for bromination of semibullvalene has been proposed, based on quantum chemical calculations. The reaction pathway involves concerted bromine addition and cyclopropane ring opening to form an allylic cation, without the intermediacy of a bromonium or a cyclopropylcarbinyl cation.[18]

The extent of substitution to be attained in unsaturated and brominated dodecahedranes through electrophilic and radical bromination have been elucidated as part of an effort directed at the C_{20} fullerene.[19]

Full geometric optimization of *endo*-tricyclo[3.2.1.$0^{2,4}$]oct-6-ene (*endo*-TCO) by *ab initio* and DFT methods has demonstrated the *endo*-pyramidalization of the double bond and non-equivalence of its two faces, with the *exo* face having regions with much higher electron density (qi, HOMO) and more negative electrostatic potential. The *endo*-TCO–Br_2 system was investigated at the B3LYP/6–311+G** level and the *endo*-TCO$\cdots$$Br_2$(*exo*) molecular complex was found to be considerably lower in energy than its *endo*-TCO$\cdots$$Br_2$(*endo*) stereoisomer, suggesting a high preference for the *exo*-facial selectivity. The study of the cationic intermediates of the bromination by *ab initio* and DFT methods revealed the bridged *exo*-bromonium cation to be relatively more stable than its *endo* counterpart. The non-classical rearranged cation was found to be the most stable ion among the cationic intermediates, implying that the ionic addition should occur via this cation.[20] (*de*)

Similar geometric optimization has been reported for bicyclo[3.2.2]nona-6,8-diene (BND). The double bond situated in the opposite direction to the methylene group was found to be more *exo*-pyramidalized than the other double bond and the electron density (qi, HOMO) of the former double bond in HOMO of the molecule higher than that of the latter double bond. The *exo* and *endo* faces of *exo*-pyramidalized double bonds proved not to be equal and the electron density was found to be higher on the *endo* faces. The *endo* molecular complexes with bromine have been found by the HF/321G* method to be more stable than their *exo* congeners; this was attributed to electronic and steric factors. As a result, *endo*-facial stereoselectivity of bromination predominates.[21] A related theoretical study of facial selectivity and regioselectivity of the electrophilic addition of chlorine to *exo*-tricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene (*exo*-TND) has also been reported.[22] (*de*)

5,6-Bis(dimethylamino)acenaphthylene (**6**) has been shown to react with X_2 (X = Cl, Br, I) and *N*-X-succinimides both as an electron-rich alkene and arene and as a proton sponge. Thus, addition of bromine or iodine to the C(1)=C(2) bond was found to be followed by immediate dehydrohalogenation, leading to the formation of the corresponding 1(2)-(di)halogenoacenaphthylenes in good yields. Reaction with chlorine allowed the isolation of only 1,4,7-trichloro-5,6-bis(dimethylamino)acenaphthylene. With *N*-halosuccinimides, the halogenation is directed mainly by the steric bulk of the entering halogen and then by solvent polarity, thus allowing a regioselective preparation of 1(2)- or 4(7)-(di)halides.[23]



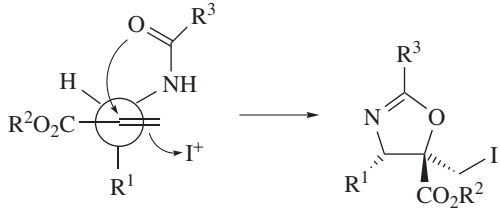
(**6**) (**7**) (**8**)

Metal triflates have been shown to catalyse 1,2-bromoazidation of alkenes $R^1CH{=}CHR^2$ with *N*-bromosuccinimide (NBS) and trimethylsilyl azide ($TMSN_3$). Among the metal triflates, $(TfO)_2Zn$ was identified as the best catalyst. This catalytic process represents a highly regio- and stereo-selective and high-yielding method for the synthesis of *anti*-1,2-bromoazides $R^1CH(N_3)–CH(Br)R^2$ from a variety of alkenes including α,β-unsaturated carbonyl compounds.[24]

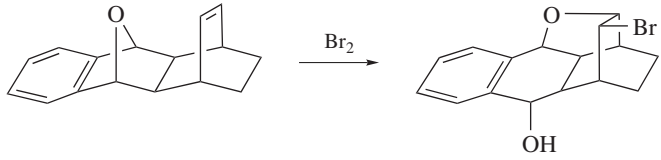
A general process for haloamidation of alkenes has been developed, which is characterized by the addition of a bromine atom and an amide nitrogen in an *anti* sense to the olefinic double bond [(**7**) → (**8**)]. The process involves the use of an *N*-bromoamide and a Lewis acid as a source of Br^+, which reacts with the alkene. The amide group is derived from a nitrile and a water molecule, which serve as nucleophiles for the overall three-component reaction. The reaction has been shown to be general for a broad range of alkenes and nitriles; an analogous chloroamidation reaction has also been demonstrated.[25]

In order to explain the high stereocontrol occurring in the iodocyclization of 3-acylamino-2-methylenealkanoates, the conformational space of the starting molecule and the potential energy surface (PES) for the cyclization reaction was explored at the DFT level; the polarized continuum formalism (PCM) for chloroform was used in order to consider the solvent effect. The observed stereoselection [(**9**) → (**10**)] was ascribed to a combination of the distribution of the near-attack conformations and the energy differences between the two possible and competitive cyclization pathways leading to *cis* and *trans* diastereoisomers.[26]

Bromination of 3,10-epoxycyclo[10.2.2.$0^{2,11}$.$0^{4,9}$]hexadeca-4,6,8,13-tetraene (**11**) gave (**12**) and several by-products. Acid cleavage of corresponding epoxide proceeded in a similar fashion.[27]

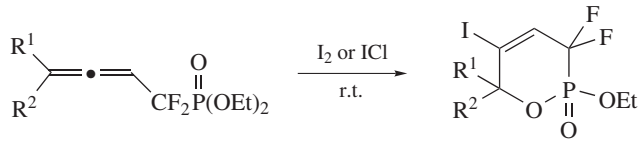


(**9**) (**10**)



(**11**) (**12**)

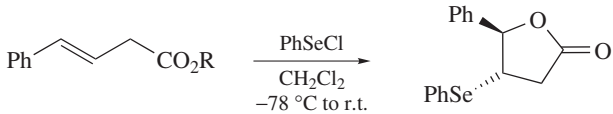
The iodocyclization reaction of diethyl β-allenic α,α-difluorophosphonates (**13**) using I_2 or ICl as the electrophile has been reported to produce six-membered α-difluoromethylenephostones (**14**) in moderate to good yields with high regioselectivities under mild conditions.[28]



(**13**) (**14**)

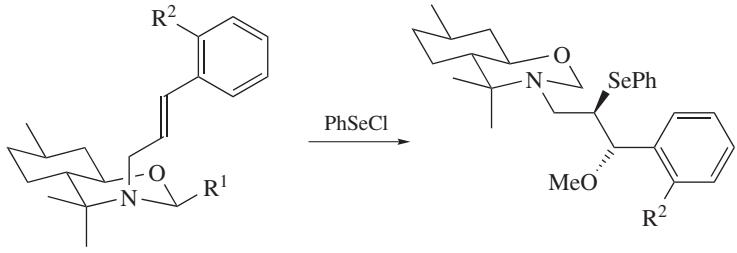
Additions of ArSX, ArSeX, and Related Reagents with Electrophilic Sulfur

The mechanism of selenocyclization of β,γ-unsaturated acids and their derivatives has been studied. The reactions of (*E*)-4-phenylbut-3-enoic acid and its silyl and alkyl esters (**15**; R = H, $SiMe_3$, alkyl) with benzeneselenenyl halide PhSeX (X = Cl, Br) have been examined by VT-NMR and *in situ* IR spectroscopic methods. Whereas the reactions of the acid in the presence of a base were irreproducible and complicated, reactions of the silyl esters were clean and spontaneously and quantitatively afforded the corresponding chloroselenylation adduct at $-70\,^{\circ}C$ as a single (Markovnikov) isomer. This adduct underwent three processes as the temperature was raised: (1) reversal to the starting materials, (2) isomerization to the anti-Markovnikov product, and (3) cyclization to the selenolactone (**16**). All of these processes are believed to proceed via a seleniranium ion, the intermediacy of which was established by independent synthesis and spectroscopic identification. The reversible formation of chloroselenide adducts was unambiguously established by crossover experiments. The reaction of (**15**) with PhSeBr was found to be rapid but thermodynamically unfavourable at room temperature.[29]



(**15**) (**16**)

Regio- and diastereo-selective methoxyselenenylation of cinnamylamines attached to a chiral perhydrobenzoxazine (**17**) proceeds in high yields in dichloromethane–methanol. The diastereoselection is dependent on the temperature and the nature of the substituent at C(2) and can be rationalized by accepting a 1,4-asymmetric induction process after coordination of the selenium to the nitrogen atom of the allylamine system.[30]



(**17**) (**18**)

Treatment of 2,3-allenoates $R^1R^2C{=}C{=}C(R^3)CO_2Et$ with PhSeCl in the presence of water gives rise to β-organoselenium substituted butenolides via $5(O)^{\pi,n}$-*endo*-*trig* cyclization.[31,32] The yields of the products depend largely on the structures of 2,3-allenoates. The addition of water proved to be crucial for some of these electrophilic cyclizations. The reaction of simple unsubstituted methyl buta-2,3-dienoate afforded methyl 4-chloro-3-phenylselanylbut-2(*Z*)-enoate in good yield and with high stereoselectivity.[31]

Additions of Hydrogen Halides and Other Brønsted Acids

Intermolecular Markovnikov-type addition of phenols (ArOH), carboxylic acids (RCO_2H), and protected amines ($TsNH_2$) to alkenes, such as 4-$MeOC_6H_4CH_2CH{=}CH_2$, can be catalysed by triflic acid in low concentrations (1–5%). Functional groups, such as the methoxyl on aromatics, can be tolerated if the concentration of triflic acid and the reaction temperature are controlled appropriately. This reaction provides one of the simplest alkene addition methods and can serve as an alternative to metal-catalysed reactions.[33]

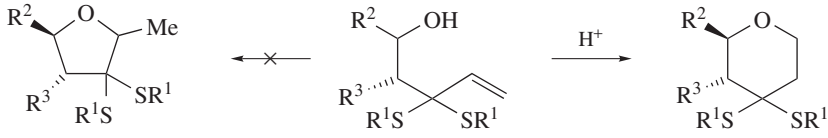
The kinetics of the hydration reaction of cyclopentene with a strongly acidic cation-exchange resin as catalyst have been studied. Parameters of the intrinsic kinetics model were solved by the Gauss–Newton method based on the experimental data, after excluding the influence factors of internal and external diffusion.[34]

The anti-Markovnikov alkylation of phenol (PhOH) with *t*-butyl alcohol (*t*-BuOH) can be achieved in supercritical water at 673 K in the absence of an added catalyst.

The reaction apparently proceeds via dehydration of *t*-BuOH to generate isobutene, which reacts with phenol to form 2-isobutylphenols as anti-Markovnikov products. The hydroxy group presumably participates in the anti-Markovnikov alkylation and is further assisted by the increased water density.[35]

Intermolecular additions of the O–H bonds of phenols and alcohols and the N–H bonds of sulfonamides and benzamide to alkenes catalysed by 1 mol% of triflic acid have been reported as tools for the synthesis of cyclic ethers and amines. This study contributed to defining the relationship between these reactions and those catalysed by metal triflates.[36]

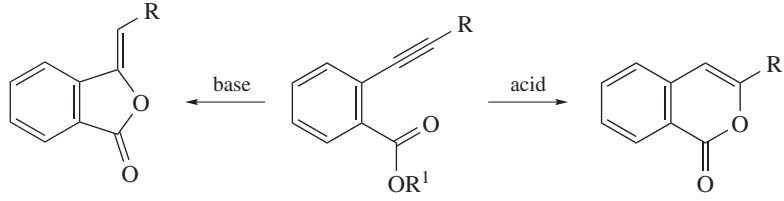
The acid-induced cyclization of unsaturated thioacetals (**19**) gives anti-Markovnikov products (**20**), apparently involving sulfur elimination and readdition.[37]



(**19**) (**20**)

Intermolecular hydroamination or hydroarylation reactions of norbornene and cyclohexadiene carried out with catalytic amounts of Brønsted or Lewis acid in ionic liquids have been found to provide higher selectivity and yields than those performed in classical organic solvents. This effect was attributed to the increases of the acidity of the medium and stabilization of ionic intermediates through the formation of supramolecular aggregates with the ionic liquid.[38]

The relationship between regioselectivity and acid–base effects in the cyclization of carboxylic acids with a pendant triple bond has been systematically investigated both experimentally and with the density functional theory calculations. Regiocontrolled cyclizations by acid or base catalyst has been developed [(**21**) → (**22**) or (**23**)].[39]



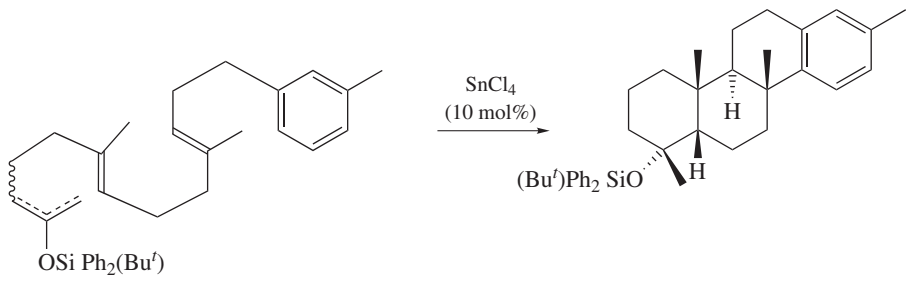
(**22**) (**21**) (**23**)

An efficient protocol for Markovnikov-type addition of *N*-heterocycles (imidazole, pyrazole, pyrrole, etc.) to the electron-rich double bond of vinyl esters using ionic liquid as a catalyst has been reported.[40]

A highly regio- and stereo-selective Brønsted acid-catalysed addition of aromatic heterocycles, such as pyrroles, furans, and indoles, to ynamides RC≡CN(R)(EWG), catalysed by Tf_2NH at −35 °C, has been developed as an equivalent of hydroarylation of ynamides.[41]

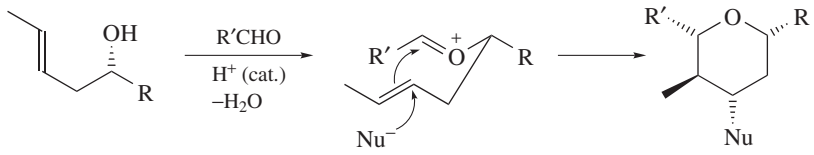
Additions of Electrophilic Carbon

A highly diastereoselective polycyclization of homo(polyprenyl)arenes, such as (**24**), bearing terminal siloxyvinyl groups can be catalysed by tin(IV) chloride (10 mol%). (*de*) The nucleophilicity and *E* geometry of the trisubstituted double bonds and a bulky silyl group favoured the formation of (**25**) (with the equatorial 4α-OSiR$_3$ group). By contrast, the less nucleophilic double bond at the junction of the B/C rings (to be) and the *Z* geometry of the other double bond, in conjunction with the less steric hindrance of a silyl group, gave mainly the 4β-OSiR$_3$ diastereoisomer.[42]



(**24**) (**25**) (91:91*dr*)

Prins cyclization reaction of scalemic homoallylic alcohols (**26**) with aldehydes (R′CHO), carried out in the presence of an acid catalyst (HX), affords tetrasub- (*ee*) stituted tetrahydropyrans (**27**) (99% *ee*) with high stereoselectively in good yields (Scheme 1).[43]



(**26**) Nu = AcO, TsO, F, Cl (**27**)

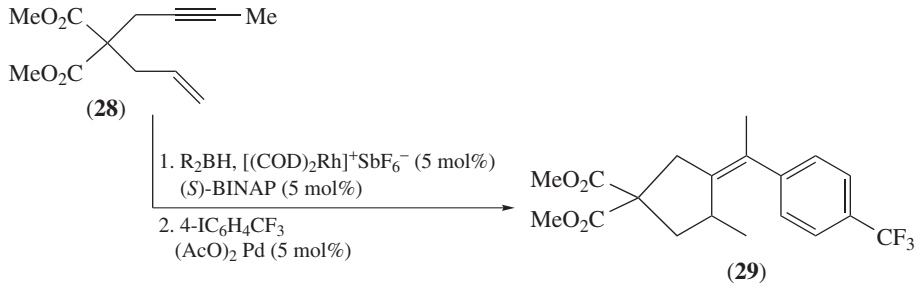
SCHEME 1

Additions Initiated by Metals and Metal Ions as Electrophiles

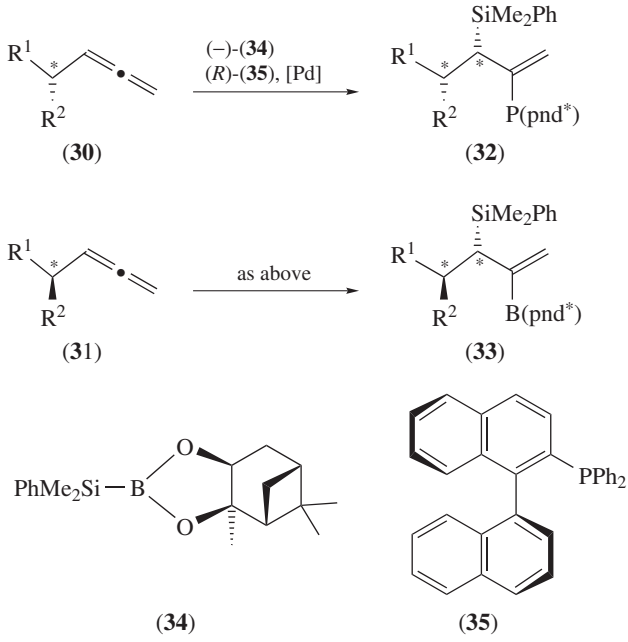
Hydroboration of bi(cyclopent-1-ene) and 3,3′-biindene with borane, thexylborane, or (−)-isopinocampheylborane afforded, after oxidation, the corresponding *meso*-1,4- (*de*) diols as the main products. No reaction was observed with 9-BBN.[44]

Alkynylboration has been achieved in the reaction of alkynyl(pinacol)boranes with alkynes in the presence of nickel catalysts, giving *cis*-1-borylbut-1-en-3-yne derivatives. 1-Arylalk-1-ynes underwent the alkynylboration regioselectively with the selec- (*de*) tive introduction of the alkynyl groups at their 1-positions, where the aryl groups were attached.[45]

Rhodium-catalysed asymmetric cyclization/hydroboration followed either by Pd-catalysed arylation or by oxidation was applied to the synthesis of a number of chiral, non-racemic carbocycles and heterocycles. Thus, reaction of enyne (**28**) with catecholborane, catalysed by a 1:1 mixture of $[Rh(COD)_2]^+$ SbF_6^- and (*S*)-BINAP (5 mol%), followed by Pd-catalysed arylation with *p*-$IC_6H_4CF_3$, afforded benzylidenecyclopentane (**29**) in 65% yield with 88% *ee*.[46]

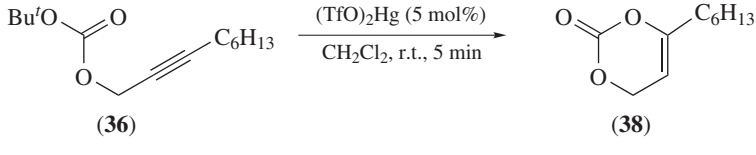


A highly enantioface-selective silaboration of chiral allenes (**30**) and (**31**) has been developed using a combination of a chiral silylborane, (−)-(**34**), and a chiral Pd–(*R*)-(**35**) catalyst (Scheme 2). The chiral reagent system efficiently controlled the stereochemistry of the new stereogenic centres even in the case of mismatched combinations.[47]

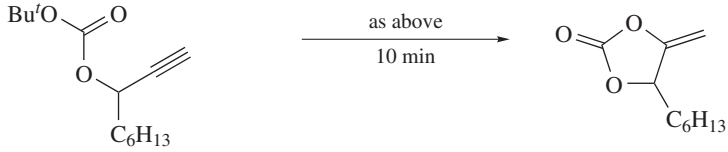


SCHEME 2

Mercuric triflate has been shown to be a powerful catalyst for the cyclization of alkynyl *t*-butylcarbonates (**36**) and (**37**) giving rise to cyclic enol carbonates under mild conditions. Internal alkynyl carbonate (**36**) afforded the *endo-dig* cyclization product (**38**) selectively, whereas terminal alkynyl carbonate (**37**) provided only the *exo-dig* product (**39**).[48]



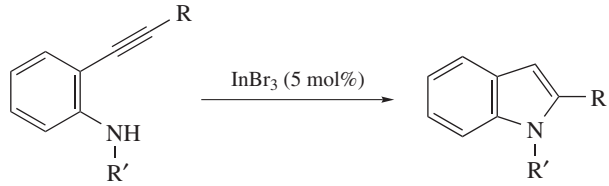
(**36**) (**38**)



(**37**) (**39**)

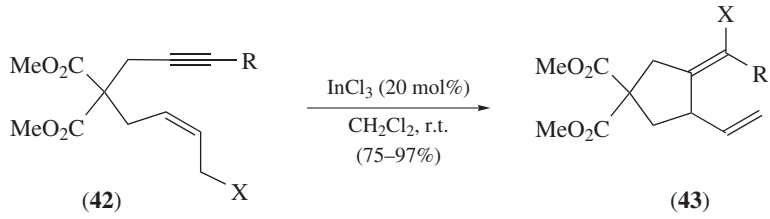
A remarkable acceleration by the phenyl-substituted silyl groups in hydroalumination and carbolithiation reactions of propargylic alcohols RR′C(OH)C≡C–$SiPh_2$(*t*-Bu) has been reported. The results show that an aryl silyl group can act not only as a protecting group but also as an activating group of the alkynyl moiety.[49]

Thiolate ions RS^-, generated *in situ* from dialkyl/diaryl disulfides RSSR by indium(I) iodide-promoted cleavage, add to a variety of styrenes $ArCH{=}CH_2$ in an anti-Markovnikov manner, to produce linear thioethers $ArCH_2CH_2SR$ in high yields.[50] On the other hand, indium(III) chloride and indium(III) trifluoromethanesulfonate were found to catalyse a Markovnikov-type addition of thiolacetic acid to non-activated alkenes; thus, e.g., *t*-$BuCH_2C(Me){=}CH_2$ produced *t*-$BuCH_2C(SAc)Me_2$. The reaction is highly regioselective and can be run in the presence of 1 mol% of catalyst.[51] An intramolecular addition of thiol to non-activated double bonds has also been reported.[52] Indium(III) bromide has been employed in a novel cyclization of 2-alkynylaniline derivatives (**40**) to afford indoles (**41**).[53]



(**40**) (**41**)

Indium trichloride was identified as an efficient catalyst for the atom-transfer cyclization of allylic halides with an alkyne pendant [(**42**) → (**43**)]. Mechanistic evidence supports a cationic reaction pathway with Lewis acid activation of the allylic halogen;



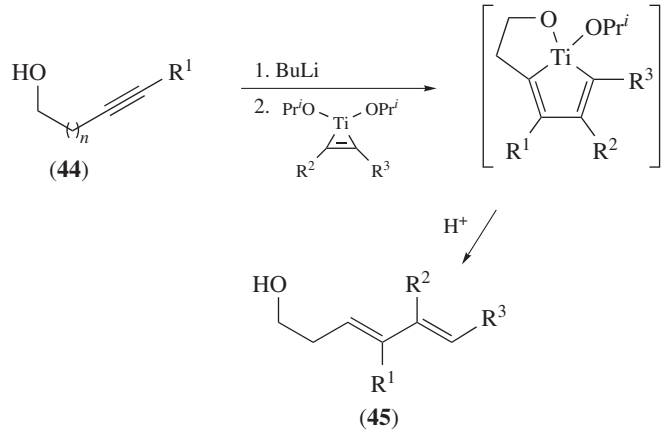
(**42**) (**43**)

concomitant nucleophilic attack by the alkyne and trapping the intermediate with halide leads to the atom transfer cyclization products. Depending on alkyne substitution, a bromine atom was transferred from the substrate or a chlorine atom was transferred from the solvent.[54]

Addition of 10 mol% of diphenyl diselenide to hydrostannylation reactions involving electron-rich alkenes resulted in a dramatic improvement in yield. For example, reaction of α-{[(*t*-butyl)dimethylsilyl]oxy}styrene with Ph_3SnH (1.1 equiv.) in the presence of PhSeSePh and 2,2′-azobis(2-methylpropanenitrile) (AIBN) afforded {2-{[(*t*-butyl)dimethylsilyl]oxy}-2-phenylethyl}triphenylstannane in 95% yield after 2 h. This reaction is believed to benefit from the increased rate of H-atom transfer, resulting from the *in situ*-generated polarity-reversal catalyst benzeneselenol.[55]

Several neutral titanium complexes have been shown to catalyse intramolecular hydroamination reactions of alkenes. The corresponding pyrrolidine and piperidine products were formed in up to 97% yields. However, only the geminally disubstituted aminoalkenes were successfully cyclized (Thorpe–Ingold effect).[56]

A regioselective, alkoxide-directed carbometallation has been reported to occur in all cases at the site distal to the tethered alkoxide to produce functionalized tetrasubstituted 1,3-dienes [(**44**) → (**45**)].[57]



(**44**) (**45**)

5-Hexenylsilane was introduced as a co-monomer into the organotitanium-mediated polymerization of ethylene to produce silane-terminated ethylene–5-hexenylsilane copolymers. High activities and narrow polydispersities were observed in the polymerization–chain transfer process. Ethylene–5-hexenylsilane copolymer molecular weights

were found to be inversely proportional to 5-hexenylsilane concentration, supporting a silanolytic chain transfer mechanism. Control experiments indicate that the chain transfer mechanism for the organotitanium-mediated ethylene polymerization of 5-hexenylsilane is significantly more efficient than that for *n*-hexylsilane. This study represents the first case in which a functionalized co-monomer is efficiently used to effect both propagation and chain transfer chemistry during alkene polymerization.[58]

Stereoselective synthesis of (*Z*)-α-arylsulfenylvinyl tellurides via hydrozirconation of alkynyltellurides has been reported.[59]

An ESI mass spectrometer coupled online to a microreactor was used to intercept the catalytically active cationic intermediates of the Ziegler–Natta polymerization of ethylene with the homogeneous catalyst system [$Cp_2Zr(Me)Cl$]–MAO (MAO = methylaluminoxane). For the first time these intermediates were studied directly in the solution and their catalytic activity proved.[60]

β-Hydrogen transfer to monomer has been identified as the dominant chain termination pathway for alkene polymerization promoted by group 4 metal catalysts; the transition state is characterized by a strong metal–hydrogen interaction. Further theoretical study of a series of homogeneous single-site polymerization catalysts revealed the existence of another transition state, competitive with the latter TS, which lacks direct metal–hydrogen interaction and strongly resembles that for the main group metal aluminium. The balance between the two reaction pathways is sensitive to the choice of metal and ligand structure.[61]

The reaction of ArI=NTs [Ar = 2-(*t*-butylsulfonyl)benzene; Ts = *p*-toluenesulfonyl] and (tpfc)Mn [tpfc = 5,10,15-tris(pentafluorophenyl)corrole] has been shown to afford the high-valent (tpfc)Mn^{V}=NTs on a stopped-flow time-scale. The reaction proceeds via the adduct [(tpfc)Mn^{III}(ArINTs)], with formation constant $K_3 = (10 \pm 2) \times 10^3$ l mol^{-1}. The latter species then undergoes a unimolecular group transfer to give (tpfc)Mn^{V}=NTs with the rate constant $k_4 = 0.26 \pm 0.07$ s^{-1} at 24.0 °C. The complex (tpfc)Mn catalyses the [NTs] group transfer from ArINTs to styrene substrates with low catalyst loading and without requirement of excess olefin. The catalytic aziridination reaction is most efficient in benzene because solvents, such as toluene, undergo a competing hydrogen atom transfer, resulting in H_2NTs and lowered aziridine yields. The high-valent manganese imido complex (tpfc)Mn=NTs does not transfer its [NTs] group to styrene. Double-labelling experiments with ArINTs and ArINTs$^{t\mathrm{Bu}}$ [Ts$^{t\mathrm{Bu}}$ = (*p*-*t*-butylphenyl)sulfonyl] established the source of [NR] transfer as a 'third oxidant', which is an adduct of Mn(V), [(tpfc)Mn(NTs$^{\mathrm{tBu}}$)(ArINTs)]. Formation of this oxidant is rate limiting in catalysis.[62]

Iron salts (e.g. $FeCl_3$) have been identified as new catalysts for intramolecular hydroamination. A number of olefinic tosylamides underwent the reaction at 80 °C to form the corresponding the *N*-tosylpyrrolidine derivatives in good yield.[63] The same salt can also catalyse Markovnikov addition of electron-rich arenes and heteroarenes to styrenes, giving rise to 1,1-diarylalkanes at 80 °C.[64]

The aminochlorination of methylenecyclopropanes and vinylidenecyclopropanes has been explored with use of $FeCl_3$ (20 mol%) as a Lewis acid catalyst in acetonitrile under convenient mild conditions. The aziridinium-based mechanism, accounting for

both regio- and stereo-selectivity, has been studied in detail. A linear free-energy relationship of this reaction confirms consistency with the Hammett equation.[65]

For the first time, an enantioselective cobalt-catalysed hydrovinylation of styrene was achieved with a cobalt-based system bearing a chiral bis(phosphine)amide ligand (*ee*) to produce $PhC^*H(Me)CH{=}CH_2$.[66]

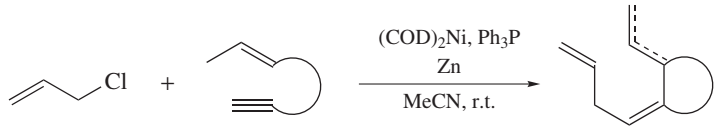
1-Alkylstyrenes $PhC(R){=}CH_2$ undergo efficient hydrovinylation (coupling with ethylene) in the presence of 1 mol% of a nickel catalyst prepared from $[(allyl)NiBr]_2$, $Na^+BAr_4^-$ (Ar = 3,5-bistrifluoromethylphenyl), and phosphoramidite ligands (derived from enantiopure binaphthols and 1-methylbenzylamines), giving products $PhC^*(R)(Me)CH{=}CH_2$ in excellent yields and enantioselectivities. The products contain a (*ee*) quaternary centre with two versatile latent functionalities, an arene and a vinyl group, useful for further synthetic elaborations.[67]

Aryl cyanides add to norbornene and norbornadiene under nickel catalysis to give (2*R**,3*S**)-3-aryl-2-cyanobicyclo[2.2.1]heptanes and (2*R**,3*S**)-3-aryl-2-cyanobicyclo[2.2.1]hept-5-enes in good yields with a broad substrate scope. On the other hand, (*ee*) the reaction of an aryl cyanide with triethoxy(vinyl)silane gives a Heck-type arylation product, suggesting the arylnickelation pathway in the catalytic cycle.[68]

Nickel(0)-catalysed hydrocyanation of certain 1,3-dienes with 1,2-bisdiarylphosphinites as chiral ligands has been developed as an efficient method. Thus, 1-phenylbuta-1,3-diene, 1-vinyl-3,4-dihydronaphthalene, and 1-vinylindene undergo highly regioselective hydrocyanation under ambient conditions to give exclusively the 1,2- (*ee*) adducts in good to excellent yields. Using bis-1,2-diarylphosphinites derived from D-glucose, the highest (to-date) enantioselectivities for asymmetric hydrocyanation of 1,3-dienes (70–83% *ee*) have been obtained.[69]

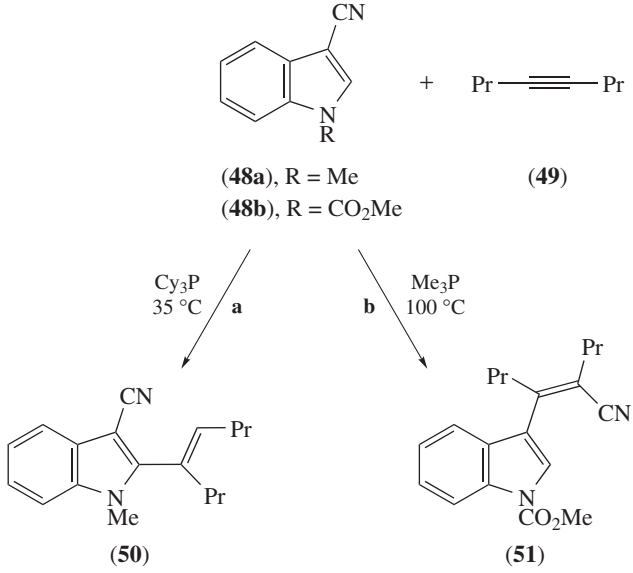
Allyl cyanides can be added across alkynes in the presence of a nickel catalyst prepared from $(COD)_2Ni$ and $(4\text{-}CF_3C_6H_4)_3P$ *in situ* to give functionalized di- or tri-substituted acrylonitriles in a highly stereoselective manner, presumably via π-allylnickel intermediates. α-Siloxyallyl cyanides also react at the γ-position of a cyano group with both internal and terminal alkynes to give silyl enol ethers, which can be converted into the corresponding aldehydes or ketones upon hydrolysis.[70]

Nickel-catalysed coupling of enynes (**46**) with allyl chlorides has been reported to occur in the presence of zinc; the reaction gives rise to the cyclic products (**47**) in good yields.[71]



(**46**) (**47**)

Nickel complexes catalyse hydroheteroarylation of alkynes (**49**) at 35 °C. Selective activation of an Ar–H bond over an Ar–CN bond of *N*-protected 3-cyanoindoles (**48**) can be achieved by a judicious choice of ligand and/or an *N*-protecting group.



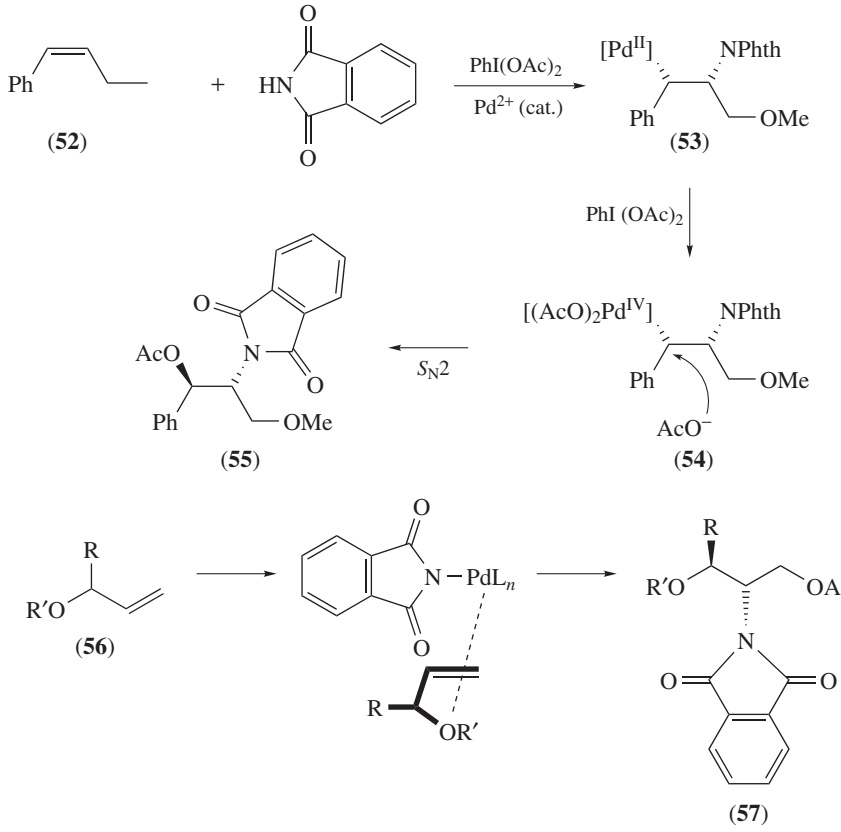
Thus, the former reaction is promoted by the bulky tri(cyclopentyl)phosphine ligand, Cyp_3P, with *N*-methylindole derivative (**48a**), giving rise to (**50**). By contrast, Me_3P as ligand and carbamate protecting group (**48b**) favour the CN activation to afford (*de*) adduct (**51**). The catalysis is applicable to a diverse range of heteroarenes to afford *cis*-hydroheteroarylation products in a highly chemo- and stereo-selective manner. Excellent regioselectivity was observed with unsymmetrical alkynes, which gave the corresponding heteroaryl-substituted ethenes with the larger substituent *trans* to the aryl group.[72]

The Pd[(−)-sparteine]Cl_2 complex catalyses the formation of dialkyl acetals ArC$(OMe)_2$Me from styrene derivatives ArCH=CH_2 with Markovnikov regioselectivity. Initial mechanistic studies indicate that the reaction proceeds through an enol ether intermediate and a Pd hydride.[73]

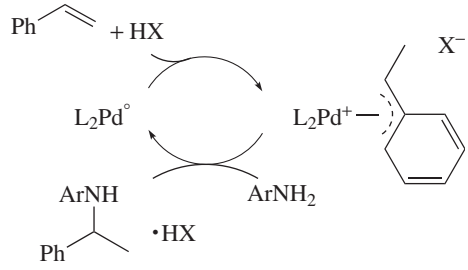
Pd(II)-catalysed acetalization of terminal alkenes with electron-withdrawing groups CH_2=CHX (X = CO_2-alkyl, CN) has been reported to proceed smoothly in supercritical carbon dioxide under an oxygen atmosphere to produce $(RO)_2CHCH_2X$; polystyrene-supported benzoquinone (PS-BQ) or Cu^{II} (Cu^{I}) chloride were employed as co-catalyst. The higher selectivity was achieved, without any chlorinated by-product detected, when using PS-BQ instead of the copper salts. PS-BQ was recycled with excellent catalytic activity remaining after each simple filtration. The chloride ion was shown to be a promoter. Different acetalization mechanisms were found to operate as a function of the subtle relationship of the chloride ion and BQ to the catalytic activity of $PdCl_2$–PS-BQ, Pd^{II}–$CuCl_2$, or $(AcO)_2$Pd–PS-BQ.[74]

The first example of intermolecular Pd-catalysed aminoacetoxylation of alkenes, such as (**52**), with phthalimide as the nitrogen source and $PhI(OAc)_2$ as the stoichiometric oxidant and source of acetate has been reported. The reaction is highly regio- and diastereo-selective; mechanistic studies revealed that the reaction proceeds

via *syn*-aminopalladation of the alkene [(**52**) → (**53**)], followed by oxidative cleavage of the intermediate Pd–C bond in the Pd(IV) intermediate (**54**) with an unusual inversion of stereochemistry to produce the *threo*-isomer (**55**).[75,76] The reaction is believed to commence by steering the approach of palladium by the alkoxy group [(**56**) →→ (**57**); R = Ar, Me, $PhCH_2$; R′ = Me, $PhCH_2$].[75]



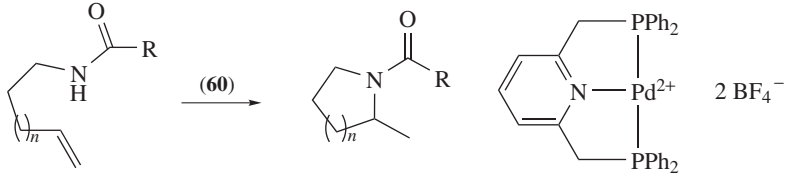
A very active catalyst for intermolecular hydroamination of vinylarenes and dienes (Scheme 3) can be generated from [(η^3-allyl)PdCl]$_2$ (with or without added TfOAg) or [$(CH_3CN)_4Pd$]$(BF_4)_2$ and Xantphos [9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene], which forms complexes with large P–Pd–P bite angles. The additions occur in the presence of potentially reactive functional groups, such as ketones with enolizable hydrogens, free hydroxyls, carboxyls, amides, nitriles, and esters. Studies on the rate of the C–N bond-forming step that occurs by attack of amine on an η^3-phenethyl and an η^3-allyl complex were conducted to determine the effect of the bite angle on the rate of this nucleophilic attack. Studies on model η^3-benzyl complexes containing various bisphosphines showed that the nucleophilic attack was faster for complexes with larger P–Pd–P bite angles. Studies of substituted unsymmetrical and unsubstituted symmetrical η^3-allyl complexes showed that nucleophilic attack on complexes ligated



SCHEME 3

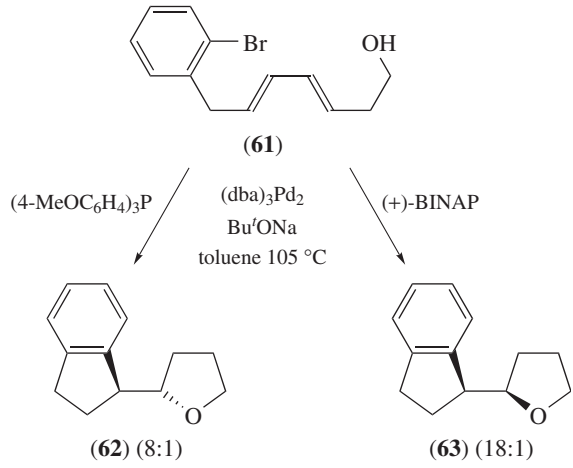
by Xantphos was faster than on complexes bearing ligands with smaller bite angles and that nucleophilic attack on unsymmetrical allyl complexes with larger bite angle ligands was faster than on unsymmetrical allyl complexes with smaller bite angle ligands. However, monitoring of catalytic reactions of dienes by ^{31}P NMR spectroscopy showed that the concentration of active catalyst was the major factor that controlled rates for the reactions of symmetrical dienes catalysed by complexes of phosphines with smaller bite angles. The identity of the counterion also affected the rate of attack: reactions of allylpalladium complexes with chloride counterion occurred faster than reactions of allylpalladium complexes with triflate or tetrafluoroborate counterion. As often observed before, the dynamics of the allyl and benzyl complexes were also found to be dependent on the identity of the counterion.[77]

A facile intramolecular hydroamination of unactivated alkenes (**58**), catalysed by the palladium complex (**60**), has been reported to take place at room temperature. The formation of hydroamination products (**59**) rather than oxidative amination products is believed to be due to the use of a tridentate ligand, which effectively inhibits β-hydride elimination.[78]



(**58**) (**59**) (**60**)

The intramolecular Pd-catalysed carboetherification of alkenes (**61**) affords 2-indan-1-yltetrahydrofuran products (**62**)/(**63**) in moderate to good yields with good to excellent levels of diastereoselectivity. The stereochemical outcome of these reactions is dependent on the structure of the Pd catalyst. Use of Cy_3P or $[(4\text{-MeO})C_6H_4]_3P$ as the ligand for Pd leads to *syn* addition of the arene and the oxygen atom across the double bond giving (**62**), whereas the use of (±)-BINAP or DPP–benzene affords products (**63**) of *anti* addition. This catalyst-induced change in stereochemistry apparently originates from a change in reaction mechanism. The *anti* addition product is believed



to arise from Wacker-type anti-oxypalladation, whereas the *syn* addition product is assumed to be derived from an unprecedented transannular alkene insertion of an 11-membered Pd(Ar)(OR) complex.[79]

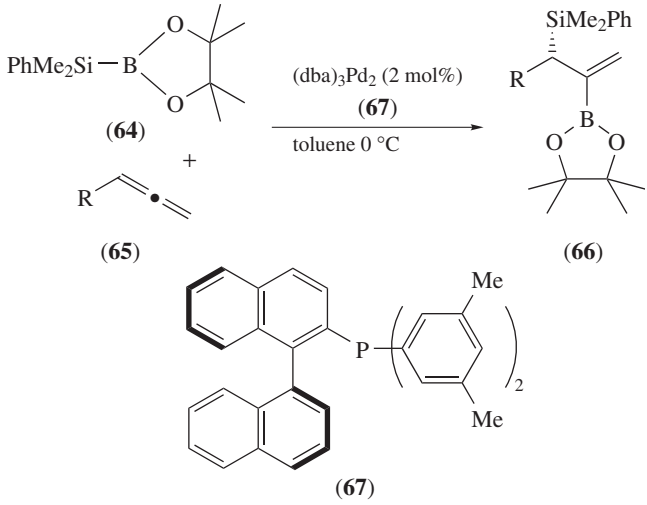
Phenylacetylenes substituted in the *ortho*-position with tethered amide functionality undergo an intramolecular *endo-dig* addition of the amide group to the C≡C in the presence of 5% $(Ph_3P)_2Pd(OAc)_2$ and KOH. This methodology is suitable for the synthesis of 3-benzazepinone.[80]

N,*N*-Dichloro-*p*-toluenesulfonamide ($TsNCl_2$) has been found to be an efficient nitrogen source for the aziridination of unfunctionalized alkenes using palladium catalysts. Among the palladium salts, $(AcO)_2Pd$ was the most effective catalyst.[81]

An enantioselective silaboration of allenes (**65**) was attained by using the achiral silylborane (**64**) in the presence of a palladium catalyst bearing the chiral monodentate phosphine ligand (*R*)-(**67**). The enantioselectivity depends on the steric bulk of the allene substituents: 91–93% *ee* (R = *t*- and *s*-alkyl), 88–90% *ee* (R = aryl), and 80–82% *ee* (R = *prim*-alkyl and Me) at 0 °C.[82]

Ligand effects on ethylene migratory insertion into a series of cationic phenylpalladium complexes (a model for Heck reaction) with diverse bidentate phosphine ligands have been studied by using the density functional methods. For the complexes with *n*-membered ring ligands ($n = 4–6$), a correlation was found between the ring size and the insertion barrier. This behaviour was explained by considering the P–Pd–P bite angle. In the case of complexes with ligands of different rigidity, almost no difference was found for the insertion barriers. Furthermore, the bidentate phosphine ligands were systematically substituted by Me, *t*-Bu, F, and Ph groups. It was found that the electron-donating substituents increased the insertion barrier, whereas the electron-withdrawing groups decreased it. The substantial increase of insertion barrier by the *t*-Bu group indicated that steric bulk also had a great effect on the migratory insertion.[83]

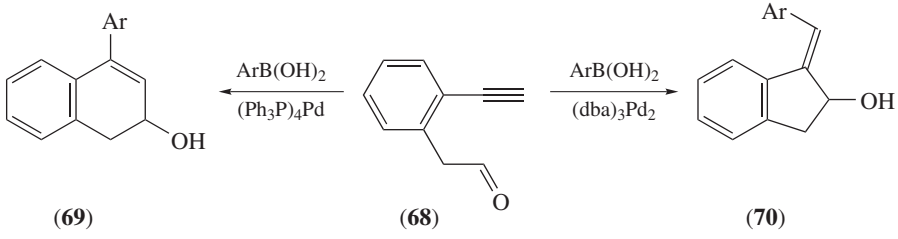
The Heck addition of aryl iodides (ArI) to $CH_2{=}CHCH(OH)CF_2CO_2Et$ can be catalysed by $(AcO)_2Pd$ in the presence of Et_3N under standard conditions.[84] The



Herrmann–Beller phosphapalladacycle has been reported to catalyse the addition (*de*) of terminal alkynes across one double bond of norbornadiene to afford *exo*-alk-5-ynylbicyclo[2.2.1]hept-2-enes. Insights into the mechanism of this reaction have been presented.[85] Palladium-catalysed allylation of alkynes RC≡CR′ with allyl alcohol in aqueous media gives 1,4-dienes RC(Cl)=C(R′)CH_2CH=CH_2 with high regio- and stereo-selectivity. A mechanism has been proposed, which involves competition between π-allylpalladation through cleavage of the C–O bond and the insertion of an alkene.[86] Palladium-catalysed addition of terminal alkynes to cyclopropenes affords alkynylcyclopropanes under mild conditions; a number of functional groups (esters, carboxylic acids, aldehydes, and alcohols) are tolerated.[87]

A highly efficient and regioselective methoxycarbonylation of terminal alkyl- and aryl-alkenes (RCH=CH_2) can be attained via a palladium–salicylic borate-catalysed protocol. The substrates include aliphatic alkenes, allylbenzenes, and styrene derivatives. The regioselectivity, in favour of the linear esters R$CH_2CH_2CO_2$Me, is up to quantitative, which is unprecedented in the case of styrenes.[88]

Palladium–monophosphine complexes catalyse *trans*-selective arylative, alkenylative, and alkylative cyclization reactions of alkynals [e.g. (**68**)] and alkynones with organoboronic reagents. These reactions afford six-membered allylic alcohols (**69**) (*de*) and/or their five-membered counterparts (**70**), whose ratios are dramatically affected



by alkyne substituents and by the phosphine ligand. The remarkable *trans* selectivity of the process results from the novel reaction mechanism involving oxidative addition without oxametallacycle formation.[89]

By using Josiphos ligands, palladium-catalysed hydrophosphorylation of norbornenes with hydrogen phosphonates proceeds efficiently to give the corresponding phosphonates in high enantioselectivities.[90]

The rate of cyclotrimerization of PhC≡CMe catalysed by the camphor-derived complexes of $PdCl_2$ has been found to be highly dependent on the R group, decreasing in the order R = Me_2N, *i*-Pr, C_6H_5. The effects of geometric and/or electronic parameters on the catalytic activity of the complexes were evaluated on the basis of X-ray and electrochemical data.[91]

The anti-Markovnikov hydration of terminal alkynes RC≡CH to give aldehydes $RCH_2CH{=}O$ can be catalysed by complexes derived *in situ* from the air-stable ruthenium complex [CpRu(η^6-naphthalene)]PF_6 and 6-aryl-2-diphenylphosphinopyridines. Increasing the size of the ligand C(6) aryl group in the order Ph < mesityl < 2,4,6-triisopropylphenyl < (2,4,6-triphenyl)phenyl gave hydration catalysts of the highest activity known to date.[92] Ruthenium complexes bearing bidentate ligands, generated by the self-assembly of monodentate ligands through complementary hydrogen bonding have been employed as catalysts in the regioselective hydration of terminal alkynes to produce the corresponding aldehydes.[93]

A catalytic amount of ruthenium(III) acetylacetonate (2 mol%) [Ru(acac)$_3$] permits solvent-free tetrahydropyranylation of various types of alcohols and phenols at ambient temperature in moderate to excellent yields.[94]

Hydroamidation of alkenes with *N*-substituted formamides has been performed with dodecacarbonyltriruthenium [$Ru_3(CO)_{12}$] at 180 °C under an N_2 or CO atmosphere in toluene and in a series of ionic liquids. Yields of 99% with 94–97% *exo* selectivity (*de*) were obtained for the addition of *N*-methylformamide to 2-norbornene under CO both in toluene and in the ionic liquid 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide [bmim][NTf_2]. The presence of CO or a phosphine is necessary for the reaction to occur, with CO being more effective than Ph_3P in all ionic liquids investigated. Acceptable yields were attained at low pressures, in contrast to most reported instances of hydroamidation. Conversion and selectivity decrease with increasing steric bulk of the *N*-formamide substituent; disubstituted formamides are inactive. Of the terminal alkenes investigated, only styrene can be hydroamidated.[95]

The complex formed *in situ* from bis(2-methylallyl)cycloocta-1,5-dieneruthenium(II) [(COD)Ru[met]$_2$], a phosphine, and $(TfO)_3Sc$ has been found to catalyse efficiently the anti-Markovnikov addition of imides $(RCO)_2NH$ to terminal alkynes (*de*) R′C≡CH to produce enimides $R'CH{=}CHN(OCR)_2$. Depending on the phosphine employed, *E*- and *Z*-isomers can be accessed stereoselectively.[96]

The presence of catalytic amounts of halide salts (e.g. Bu_4NI) was found to enhance dramatically the efficiency of hydroesterification of alkenes (e.g. cyclohexenone) and alkynes catalysed by [$(CO)_{12}Ru_3$] in the presence of the chelating 2-pyridylmethyl formate (2-$C_5H_4NCH_2OCHO$). On the basis of IR and NMR studies, the halide effect

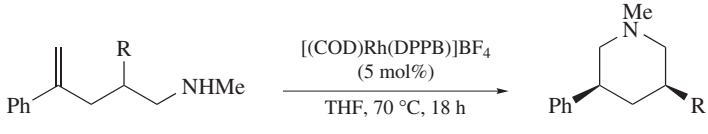
on the reaction was attributed mainly to the facile dissociation of the tricarbonyl precursor into the presumed active metal species. With these milder conditions, the substrate scope has been significantly broadened.[97]

A synthesis of the *Annonaceous* acetogenin asimicin and a side-chain analogue has been achieved by a highly convergent route in which Grubbs cross-metathesis played a key role.[98]

In the presence of a catalytic amount of a ruthenium complex coordinated to PBu_3, alkynylstannanes ($R^1C{\equiv}CSnBu_3$) have been found to add to terminal alkynes ($R^2C{\equiv}CH$) with a 1,2-shift of the stannyl group to give (*E*)- and (*Z*)-1-tributylstannyl-but-1-en-3-ynes [$Bu_3SnC(R^1){=}CHC{\equiv}CR^2$]. Various combinations of substrates having an aromatic and/or aliphatic substituent can be used, and the stereochemical outcome depends largely on the character of these substituents. The reaction of aliphatic terminal alkynes proceeds stereoselectively, and R^1 determines the configuration: *E* for R^1 = alkyl and *Z* for R^1 = aryl. By contrast, the reaction of arylalkynes gave a mixture of stereoisomers irrespective of the character of substituent R^1. Ruthenium–β-stannylvinylidene complexes generated from a ruthenium complex and an alkynylstannane with migration of the stannyl group are believed to be key intermediates, which insert into the C–H bond of terminal alkynes to give the corresponding stannylenynes. DFT calculation clearly showed that the 1,2-shift of the stannyl group on formation of ruthenium–β-stannylvinylidene complexes is more facile than the corresponding 1,2-hydrogen shift of the coordinating terminal alkynes.[99]

Rhodium(III) tetra(*p*-sulfonatophenyl)porphyrin [(TSPP)Rh] aquo and hydroxo complexes react with a series of alkenes in water to form β-hydroxyalkyl coordination compounds. Addition reactions of (TSPP)Rh-OH to unactivated terminal alkenes $CH_2{=}CHR$ invariably occur with both kinetic and thermodynamic preferences to place rhodium on the terminal carbon to form (TSPP)Rh–$CH_2CH(OH)R$ complexes. Acrylic and styrenic alkenes initially react to place rhodium on the terminal carbon to form [Rh]–$CH_2CH(OH)R$ as the kinetically preferred isomer, but subsequently proceed to an equilibrium distribution of regioisomers where [Rh]–$CH(CH_2OH)R$ is the predominant thermodynamic product. Equilibrium constants for reactions of the diaquo rhodium(III) compound $[(TSPP)Rh^{III}(H_2O)_2]^{3-}$ in water with a series of terminal alkenes that form β-hydroxyalkyl complexes were directly evaluated and used in deriving thermodynamic values for addition of the Rh–OH unit to alkenes. The ΔG° for reactions of the Rh–OH unit with alkenes in water was found to be approximately 3 kcal mol^{-1} less favourable than the comparable Rh–H reactions in water.[100]

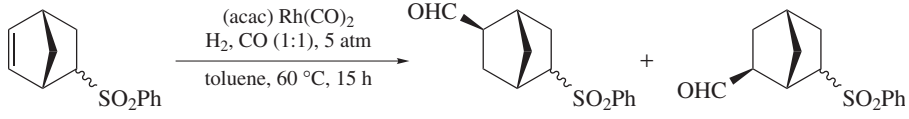
The intramolecular anti-Markovnikov hydroamination of 1-(3-aminopropyl)vinylarenes (**71**; R = H, Me, CH_2OMe, CH_2OTBS) in the presence of a rhodium catalyst to form 3-arylpiperidines (**72**) has been reported. In contrast to intermolecular hydroamination of vinylarenes, which occurs in high yields in the presence of rhodium catalysts



(**71**) (**72**)

containing DPEphos, the intramolecular reaction occurred in high yield in the presence of [Rh(COD)(DPPB)]BF_4 as catalyst. Reactants with substituents β- to the nitrogen produced 3,5-disubstituted piperidines with high yields and high diastereoisoisomeric excess. The regiochemistry of these cyclizations contrasts with the regiochemistry of intramolecular hydroaminations catalysed by lanthanide complexes, group III metal complexes, and platinum complexes, all of which have been reported previously to form cyclization products via Markovnikov addition.[101]

Hydroformylation of 2-phenylsulfonyl-substituted norbornene (**73**) and norbornadiene derivatives, catalysed by the unmodified (acac)$Rh(CO)_2$, has been reported to give, under standard conditions, *exo*-norbornane- and *exo*-norbornene-carboxaldehydes. The steric properties of the sulfonyl substituent, rather than its electronic effects, are believed to control the regioselectivity of the process.[102]



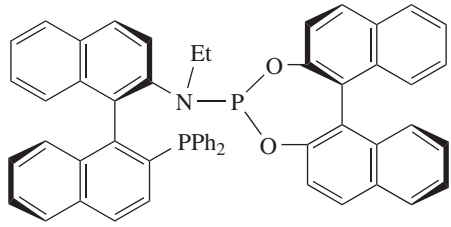
(**73**)

A comprehensive theoretical investigation into the mechanism of the Rh(I)-catalysed hydroformylation of 1-phenyl-1-(4-pyridyl)ethene, employing a non-local density functional method (B3LYP), has been carried out. The calculations have demonstrated that the overall catalytic cycle is strongly exothermic by >90 kJ mol^{-1}, and the rate-limiting step is the oxidative addition of H_2. The regioselectivity originates from the alkene insertion into the Rh–H bond. 3-Phenyl-3-(4-pyridyl)propanal, the predominant product, is formed as a result of both thermodynamic and kinetic control, in agreement with experimental studies.[103]

The hydroformylation of linalool using $[(AcO)Rh(COD)]_2$ as a catalyst precursor in the presence of triphenylphosphine or various diphosphines leads mainly to a mixture of *cis* and *trans* isomers of the corresponding hemiacetal, formally arising from the intramolecular cyclization of the primarily formed hydroxyaldehyde. An unexpected effect of the phosphorus ligands on the reaction rate was observed. With unmodified systems, linalool shows a very low reactivity under the hydroformylation conditions, probably due to the chelation of rhodium by the substrate. The introduction of (di)phosphine and the increase in its concentration exerts a great accelerating effect so that under optimized conditions (40–50 °C and 20 atm of $CO–H_2$) a virtually complete conversion of linalool has been achieved in 4–6 h. A good control of chemo- and stereo-selectivity was attained through the appropriate choice of reaction variables. Each of the two hemiacetal isomers can be obtained in ca 95% chemo- and 85% stereo-selectivity.[104]

The new hybrid phosphorus ligand (**74**), prepared from NOBIN (2-amino-2′-hydroxy-1,1′-binaphthyl),[105] has been reported to exhibit excellent enantioselectivities (up to 99% *ee*) in the Rh-catalysed asymmetric hydroformylations of styrene derivatives and vinyl acetate.[106]

A range of high-yielding quaternary selective hydroformylation reactions have been performed in the presence of a reactive phosphane-modified rhodium catalyst at



(**74**)

near ambient temperature; a range of unsaturated esters $R^1R^2C{=}C(R^3)CO_2Me$ have been hydroformylated with high regioselectivity towards the α-position to produce $R^1R^2CHC(R^3)(CHO)CO_2Me$.[107]

Hydrogenation of a mixture of styrenes $ArCH{=}CH_2$ (or reactive alkenes, such as norbornene or ethylene) and symmetric or mixed carboxylic anhydrides [$(RCO)_2O$ or $(RCO)O(COR')$] in the presence of cationic rhodium catalysts ligated by triphenylarsine (Ph_3As), generates hydroacylation products ArCH(Me)COR as single regioisomers in high yields.[108]

Asymmetric hydroarylation of diphenylphosphinylallenes $[Ph_2P(O)]C(R){=}C{=}CH_2$ with arylboronic acids $ArB(OH)_2$, catalysed by an Rh–BINAP complex, has been shown to proceed in high yields with high regio- and enantio-selectivity to afford chiral allylphosphine oxides $[Ph_2P(O)]CH(R)C(Ar){=}CH_2$ of up to 98% *ee*. A π-allylrhodium complex has been identified as the key intermediate.[109] (*ee*)

Rhodium(I)-catalysed inter- and intra-molecular addition of 3,4-dihydroquinazolines to unactivated alkenes has been reported.[110]

The iridium-catalysed hydrosilylation of alkynes in the presence of 4,4′,5,5′-tetramethylbiphosphinine (tmbp) has been explored and shown to proceed effectively to afford β-(*E*)-vinylsilanes with high selectivity in moderate to high yields, whereas a similar hydrosilylation in the absence of tmbp produced β-(*Z*)-vinylsilanes. This stereoselectivity reversal is believed to be a function of the electron-withdrawing properties of tmbp coordinated to iridium.[111] (*de*)

The hydrosilylation of styrenes $ArCH{=}CH_2$ with silanes R_3SiH can be catalysed by $(CO)_5ReBr$ in toluene at 120 °C to produce anti-Markovnikov adducts $ArCH_2CH_2SiR_3$ in good to high yields.[112] The same complex has been shown to catalyse an anti-Markovnikov addition of Et_2NH and CO_2 to terminal alkynes $RC{\equiv}CH$ (110 °C, 24 h), affording *E*–*Z* mixtures of alkenyl carbamates $RCH{=}COCONEt_2$.[113]

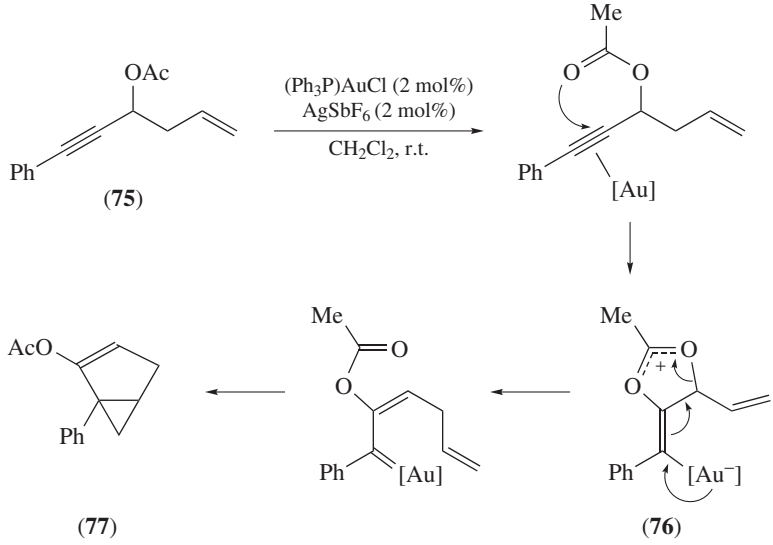
1,2-Hydroxysulfenylation of alkenes $R^1CH{=}CHR^2$ with disulfides R^3SSR^3 can be catalysed by (bipy)CuI in DMF–AcOH in air to produce the corresponding 1,2-acetoxysulfides $R^1CH(OAc)CH(SR^3)R^2$ with high *anti* selectivity.[114] (*de*)

$Ph_3PAuOTf$ has been shown to catalyse intra- and inter-molecular hydroamination of unactivated alkenes with sulfonamides in a Markovnikov fashion.[115] The same complex catalyses hydroamination of 1,3-dienes with carbamates (e.g. $PhCH_2OCONH_2$) and sulfonamides at room temperature.[116] An intramolecular version of the hydroamination with the Cbz group (benzyloxycarbonyl) has also been reported. The latter

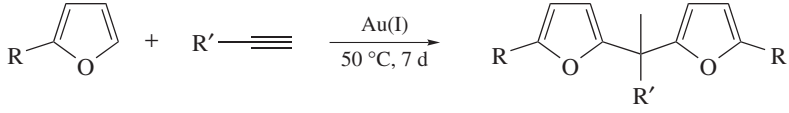
reaction is catalysed by a mixture of [{(*t*Bu)$_2$(*o*-biphenyl)P}Au]Cl and TfOAg to produce the corresponding pyrrolidines.[117]

Selective activation of alkyne functions of enynes to give products either of alkoxycyclization or of *exo*- and *endo*-skeletal rearrangement can be achieved by using alkynophilic cationic gold(I) complexes. The endocyclic cyclization catalysed by gold(I) proceeds via a mechanism different from those known for Pd(II), Hg(II), or Rh(I) catalysts.[118]

The key step in the gold-catalysed cycloisomerization of enynes (**75**) is believed to be the nucleophilic attack at the Au-coordinated C≡C triple bond to form a vinylic gold intermediate (**76**) that is eventually converted into the final product (**77**).[119]



The cationic binuclear complex [(Mes$_3$PAu)$_2$Cl]BF$_4$ has been found to catalyse the reaction of 2-methyl- or 2-pentyl-furan (**78**) with phenylacetylene, pent-1-yne, or hept-1-yne (**79**) to afford the products of a twofold hydroarylation of the alkyne (**80**).[120]



The Bi(OTf)$_3$–Cu(CH$_3$CN)$_4$PF$_6$ system has been reported to promote efficiently an intermolecular 1:1 hydroamination of 1,3-dienes R^{1}CH=CHCH=CHR^2 with various carbamates, sulfonamides, and carboxamides to afford allylic amines in Markovnikov

fashion and in good yields (≤96%). The reaction proceeded with 0.5–10 mol% catalyst loading at 25–100 °C (generally at 50 °C) in 1,4-dioxane within 24 h. Mechanistic studies led to the formulation of a plausible mechanism.[121]

In the presence of $BiCl_3$, the hydroarylation of styrenes $Ar'C(R)=CH_2$ with electron-rich arenes ArH afforded Markovnikov adducts $Ar'C(R)(Ar)Me$ selectively in good to high yields as a result of the C–H activation of ArH. Under arene-free conditions, the intermolecular hydroarylation of α-substituted styrenes and subsequent intramolecular hydroarylation produced the cyclic dimers of α-substituted styrenes in good yields.[122,123]

Ytterbium and lutetium ionic complexes, derived from enantiopure substituted (*R*)-binaphthylamine ligands of the general formula $[Li(THF)_n][Ln[(R)C_{20}H_{12}(NR)_2]_2]$, have been investigated as catalysts for hydroamination/cyclization of several unsaturated amines $CH_2=CH(CH_2)_nC(R_2)CH_2NH_2$ ($n = 1$ or 2). Complexes with isopropyl or cyclohexyl substituents on nitrogen atoms were found to be efficient catalysts for the formation of N-containing heterocycles under mild conditions with enantiomeric excesses up to 78%.[124] (ee)

The complete catalytic reaction course for the intramolecular hydroamination/cyclization of hepta-4,5-dien-1-ylamine in the presence of a prototypical $[(\eta^5\text{-}Me_5C_5)_2LuCH(SiMe_3)_2]$ precatalyst has been critically scrutinized by employing a reliable DFT method.[125]

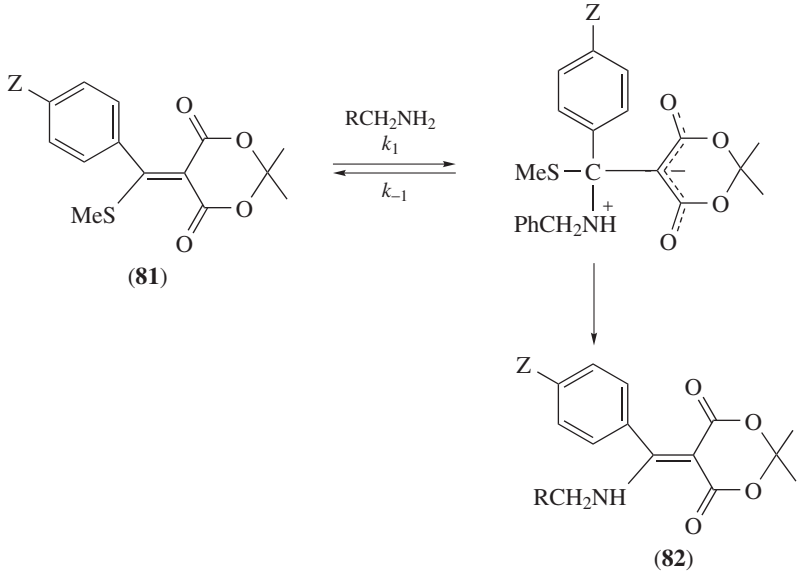
Miscellaneous Electrophilic Additions

1,1-Bis(trimethylsilyl)-2-adamantylidenesilane, a stabilized silene, has been generated by photolysis of a novel trisilacyclobutane derivative in various solvents and studied directly by kinetic UV spectrophotometry. The latter silene decays with second-order kinetics in a degassed hexane solution at 23 °C ($k/\epsilon = 8.6 \times 10^{-6}$ cm s^{-1}) via a head-to-head dimerization. It reacts rapidly with oxygen [$k(25\,^\circ C) \approx 3 \times 10^5$ l mol^{-1} s^{-1}] but ~10 orders of magnitude more slowly with MeOH than other silenes that have been studied previously. The data are consistent with a mechanism involving reaction with the hydrogen-bonded dimer of the alcohol [i.e. $(MeOH)_2$] ($k = 40 \pm 3$ l mol^{-1} s^{-1}; $k_H/k_D = 1.7 \pm 0.2$). The stable analogue of silene, namely 1-*t*-butyldimethylsilyl-1-trimethylsilyl-2-adamantylidenesilane, reacts ~50 times more slowly, but via the same mechanism. The mechanism for addition of water and methanol to both silenes and 1,1-bis(silyl)-2,2-dimethylsilene has been studied computationally at the B3LYP/6–31G(d) and MP2/6–31G(d) levels. Hydrogen-bonded complexes with monomeric and dimeric methanol, in which the Si=C bond acts as a nucleophile, have been located computationally for all three silenes. Reaction pathways have been characterized for the reaction of the three silenes with monomeric and dimeric ROH, which reveal significantly lower barriers for the reaction with the dimeric form of the alcohol in each case. The calculations indicate that *t*-butyldimethylsilyl-1-trimethylsilyl-2-adamantylidenesilane should be ~40-fold less reactive toward dimeric MeOH than 1,1-bis(trimethylsilyl)-2-adamantylidenesilane, in excellent agreement with the ~50-fold difference in the experimental rate constants for reaction in hexane solution.[126]

Nucleophilic Additions

Additions to Multiple Bonds Conjugated with C=O

A study of the aminolysis of substituted (methylthio)benzylidene Meldrum's acids (**81**; Z = MeO, Me, H, Br, CF_3) with a series of aliphatic primary amines in aqueous DMSO revealed second-order overall kinetics, i.e. first order in (**81**) and first order in the amine. A three-step mechanism has been proposed, the first step being the rate-limiting addition of amines to form the tetrahedral intermediate which is followed by fast acid–base equilibration and then formation of (**82**) by a fast expulsion of the leaving group, catalysed by RNH_3^+ or H_2O.[127]



The kinetics of the addition of *N*-acetyl-L-cysteine, *N*-acetylcysteamine, and N^2-acetyl-L-lysine (NAL) to *p*-methoxycinnamate, *p*-methoxycinnamide, anthranilate, and crotonyl or sorboyl thiol ester have been studied, and the thiol addition products identified. The reaction rates increased at higher pH and the crotyl thiol ester was found to be 7.9 times more reactive than a sorboyl thiol ester toward *N*-acetyl-L-cysteine addition. These unsaturated thiol esters may serve as a means of covalently binding UVA and UVB sunscreens to the outer layer of skin to provide long-lasting protection.[128]

Addition of thiophenols to chalcones in [bmim]PF_6, catalysed by L-proline and cinchonine in CH_2Cl_2, afforded products with $\leq$16% and 26% *ee*, respectively. The latter addition also occurred in neat ionic liquids in the absence of the latter catalysts but the rate of the reaction depended considerably on the structure of the ionic liquid.[129]

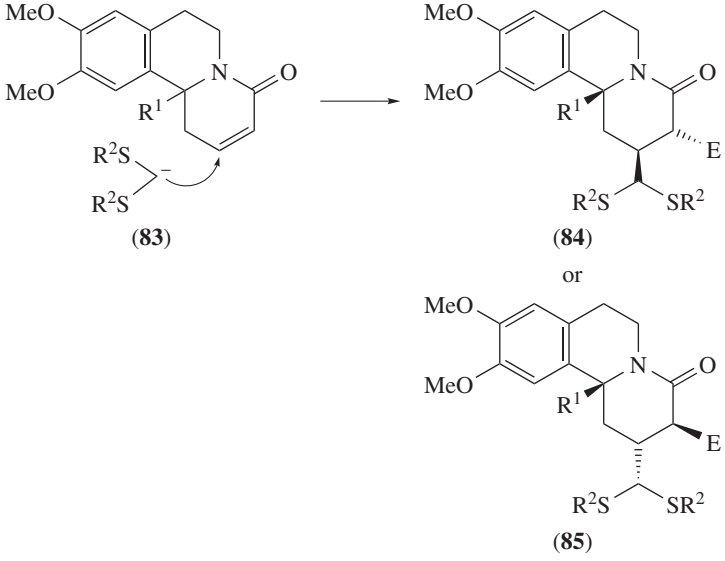
In the conjugate addition of thiols to α,β-unsaturated carbonyl compounds, carried out in aqueous conditions, water was found to play a dual role in simultaneously activating the α,β-unsaturated carbonyl compound and the thiol.[130]

While the Michael-type addition of thiolates to α,β-conjugate systems is expected to proceed faster if the thio donor contains an electron-rich group or the enone acceptor is highly electron deficient, the hard–soft acid–base (HSAB) principle predicts that this reaction is favoured when a soft–soft interaction between the reactants takes place. To analyse the apparent discrepancy, the effect of charge transfer of a *para*-substituent on the softness of sulfur in thiophenols, as well as its impact in the conjugate addition to cyclohex-2-en-1-one, has been investigated. Experiments-in-competition, net charge of the X-groups at the *para*-position of the aromatic ring, the global and local softness at sulfur, and the electrophilicity, obtained by density functional theory (DFT), revealed that the reaction is faster for electron-attracting thiophenols, as the softness at sulfur increases by delocalization of the charge through the aromatic ring.[131]

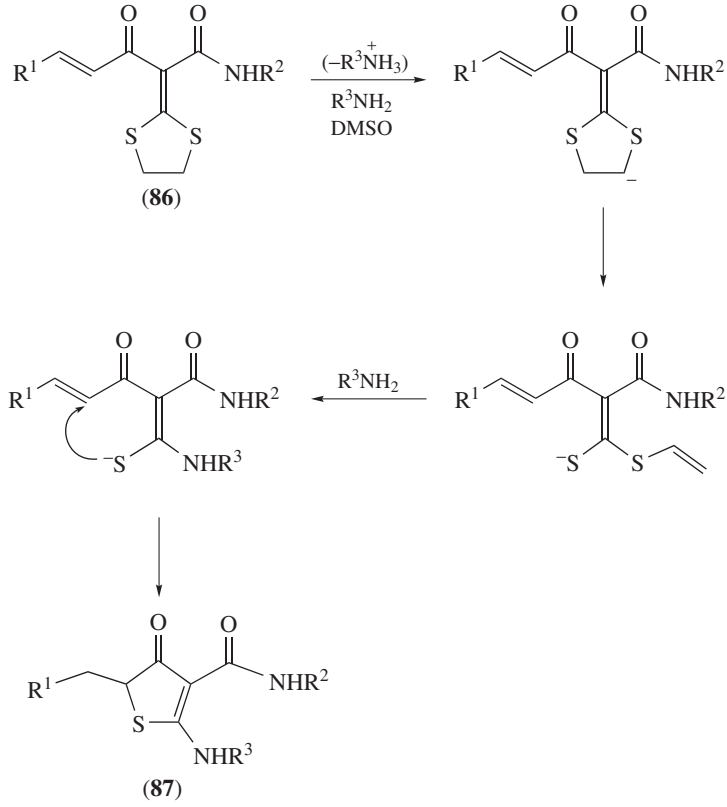
The asymmetric conjugate addition of thiophenol to (*E*)-3-crotonoyloxazolidin-2-one, catalysed by the scandium(III) triflate complex of Ph–PYBOX, gave the corresponding adduct in 66% *ee*. Lanthanoid triflates gave lower enantioselectivities (≤28% *ee*).[132] (*ee*)

Enantiopure α,β-unsaturated δ-lactams react stereoselectively with carbon-, nitrogen-, sulfur-, and oxygen-centred nucleophiles [N_3^-, $Me(CH_2)_{11}S^-$, MeO^-, and *n*-Bu^-]. The synthetic potential of these conjugate additions has been demonstrated through the synthesis of two new substituted indolizidines, (7*R*)-7-amino-8-deoxyswainsonine and (7*R*)-7-acetylaminoswainsonin.[133]

The stereochemical outcome of the conjugate addition of sulfur-stabilized nucleophiles to the δ-lactam unit of tetrahydrobenzo[*a*]benzoquinolizines (**83**) has been shown to depend on the nature of the substituent at the angular position (R^1); thus, 2,11b-*cis* or 2,11b-*trans* diastereoisomers (**84**) and (**85**) can be obtained selectively.[134] (*de*)



The intramolecular thia-anti-Michael addition has been reported to occur on treatment of dithiolane (**86**) with aliphatic primary amines, which produced a series of



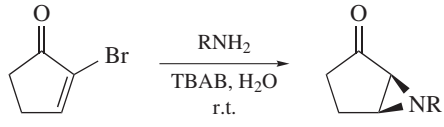
tetrasubstituted thiophene derivatives (**87**). Here, the amine played the dual role of a base and a nucleophile. The intramolecular thia-anti-Michael addition, as the key step, proceeded in a regioselective manner; a plausible mechanism was proposed.[135]

Cerium(IV) ammonium nitrate (CAN) has been reported to catalyse a facile and efficient aza-Michael addition of aromatic and aliphatic amines to α,β-unsaturated esters in the absence of solvent under ultrasound irradiation.[136] α,β-Unsaturated ketones react in aqueous solutions under these conditions but only with aliphatic (not aromatic) amines.[137]

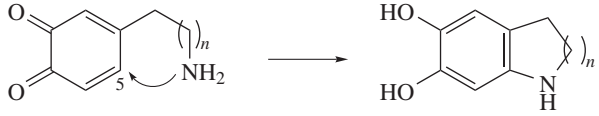
The basic ionic liquid [Bmim]OH has been introduced as a catalyst for the aza-Michael addition of aromatic amines and *N*-heterocycles to cyclic or acyclic ketones under solvent-free conditions.[138]

An efficient and highly selective synthesis of bicyclic-α-keto aziridines (**89**) from 2-bromocyclopent-2-enone (**88**) and aliphatic primary amines, mediated by phase-transfer catalysts (PTCs) in water at room temperature, has been demonstrated.[139]

Energy profiles for alternative intramolecular cyclizations of 4-(aminoalkyl)-*o*-quinones (**90**); ($n = 1$–3) have been calculated using the AM1 method and *ab initio* energies of the transition states have been determined. In all the cases, cyclization at position 5 to form (**91**) occurs via a significantly lower energy transition state



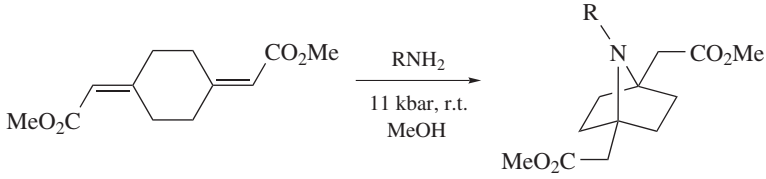
(**88**) (**89**)



(**90**) (**91**)

than cyclization at position 3, consistent with experimental observations. Optimal trajectories for attack have been determined from a study of the reactions of methylamine with 4-methyl-*o*-quinone. For cyclization of aminoalkyl derivatives deviation from the optimal direction is smaller for reaction at position 5 but constraint on angle of attack only partially accounts for the regioselectivity. Intrinsic differences in the electronic energies of the alternative transition states appear to be the main contributor to regioselectivity. The relative energies of transition states can be modified by variation of the substituent at position 4. The calculations suggest that seven-membered ring formation may occur via a boat transition state and steric hindrance in the seven-membered transition states may account for the experimentally observed influence of *N*-substituents on the mode of reaction.[140]

A double aza-Michael addition was enforced by high pressure in the reaction of primary amines with the α,β-unsaturated bis ester (**92**) to afford the azanorbornyl derivatives (**93**).[141]

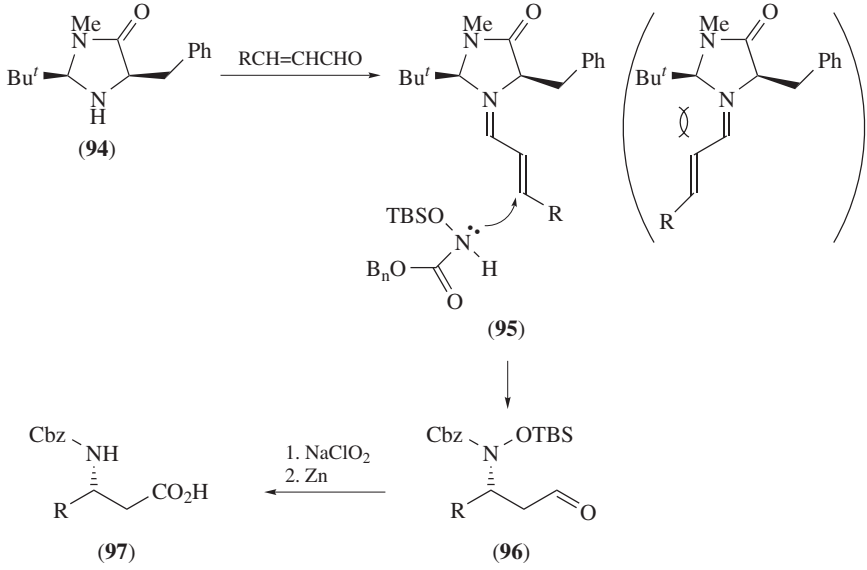


(**92**) (**93**)

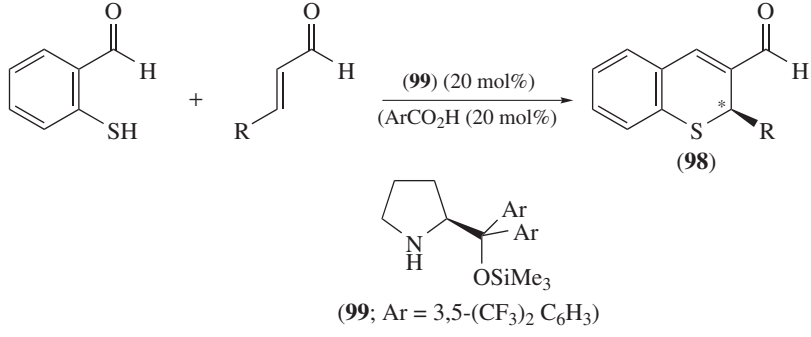
α-Ketoaziridines have been obtained via a novel amine-promoted direct aziridination of chalcones ArCH=CHCOAr′ using an aminimide, generated *in situ* from a tertiary amine and *O*-mesitylenesulfonylhydroxylamine, $NH_2OSO_2C_6H_2Me_3$, in the presence of a base. The aziridination proceeds well in the presence of a catalytic amount of the tertiary amine; non-racemic aziridines were obtained by using a chiral amine.[142]

Addition of a variety of alcohols R^3OH to enones $R^2CH{=}CHCOR^1$ was observed to occur in the presence of secondary amines R^3R^4NH and acids as catalysts (30 mol% each) at room temperature via the *in situ*-generated iminiums $R^2CH{=}CHC(R^1){=}N^+R^3R^4$.[143]

Imidazolidinone (**94**.*p*TSA) has been developed as an enantioselective organocatalyst for the addition of various silyloxycarbamate nucleophiles (e.g. BnOCONHOTBS, having a raised HOMO) to a range of α,β-unsaturated aldehydes RCH=CHCH=O, affording β-aminoaldehydes (**96**) ($\leq$96% *ee*), which can be converted into β-amino acids (**97**) in two steps. The reaction proceeds via the corresponding iminium species (**95**) with a lowered LUMO.[144]

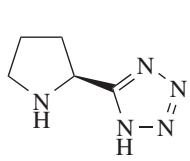


The asymmetric domino reactions between 2-mercaptobenzaldehyde and α,β-unsaturated aldehydes proceed with excellent chemo- and enantio-selectivities in the presence of (**99**) (20 mol%) as organocatalyst to afford 2*H*-1-benzothiopyrans (**98**) in high yields with 91–98% *ee*.[145]

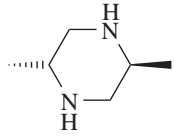


5-Pyrrolidin-2-yltetrazole (**100**) (15 mol%), in conjunction with the chiral piperazine (**101**) (1 equiv.), has been shown to catalyse the asymmetric conjugate addition

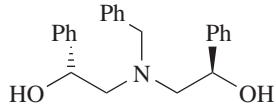
of nitroalkanes $RR'CHNO_2$ to enones. The addition requires short reaction times, tolerates a broad substrate scope, and is believed to proceed via an iminium species.[146] The same organocatalyst, in the presence of piperidine, has been employed to promote (ee) a highly enantioselective addition of malonates to enones.[147]



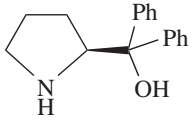
(**100**)



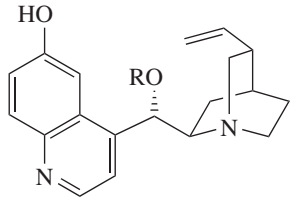
(**101**)



(**102**)



(**103**)



(**104**; R = 9-phenanthryl)

Significant rate acceleration of metal-catalysed Michael addition reactions of β-dicarbonyls to α,β-enones in water was observed upon addition of dibasic ligands. Ytterbium triflate and TMEDA was the most effective combination leading to a nearly 20-fold faster reaction than in the absence of ligand.[148]

Asymmetric 1,4-addition of various malonates to enones has been carried out using $Bu_4N^+BH_4^-$ in the presence of a chiral ligand, such as (*R*,*R*)-(**102**). The Michael (ee) adducts were formed in good yields (61–67%) with moderate enantioselectivity at 0 °C. ^{11}B NMR spectroscopy suggests that the reaction proceeds via the formation of an aminodiol borate complex.[149]

Selective and efficient Michael additions of heterocyclic enamines (e.g. indoles, pyrroles, and pyrazoles) to enones can be catalysed by $ZrCl_4$ (2 mol%).[150] Michael addition of α-cyanoketene-*S*,*S*-acetals $(RS)_2C{=}CHCN$ to enones $R^1CH{=}CHCOR^2$ can be promoted by $TiCl_4$.[151] Addition of the lithium enolate, generated from (2*S*,5*S*)- (de) *cis*-1,3-dioxolan-4-one, which in turn was prepared from (*S*)-mandelic acid and pivalaldehyde, to several 2-arylidene-1,3-diketones, gives the Michael adducts in good yields and diastereoselectivities.[152]

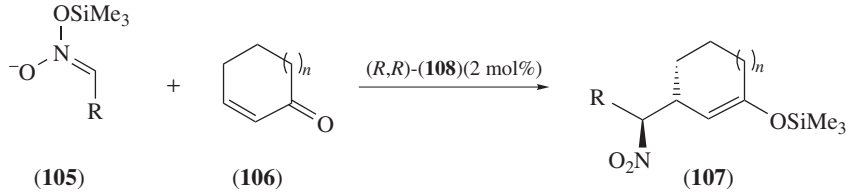
The first highly regio-, chemo-, diastereo-, and enantio-selective vinylogous Michael addition of α,α-dicyanoalkenes to α,β-unsaturated aldehydes employs salts of α,α-diarylprolinol (**103**) (20 mol%) as organocatalysts. The reaction presumably involves the formation of an iminium species from the aldehyde as the first step of the cascade.[153]

The catalytic application of L-proline in the asymmetric Michael addition of unmodified aldehydes or ketones with nitroalkenes in ionic liquids has been studied. The (ee)

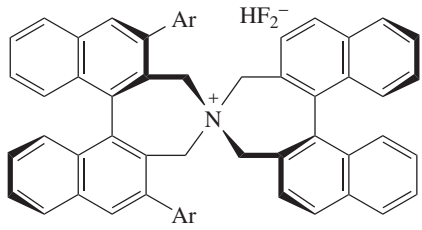
1*R*,2*S* configuration of the Michael adduct resulting from the reaction of cyclohexanone with β-nitrostyrene indicates the *Re*-face attack on β-nitrostyrene by an enamine intermediate. The enantioselectivities observed ($\leq$70% *ee*) were rather modest.[154]

The conjugate addition of cyclic or acyclic α-substituted β-keto esters to α,β-unsaturated ketones can be achieved with good diastereo- and enantio-selectivity (*de*) ($\leq$98% *ee*) by using derivatives of *Cinchona* alkaloids, such as (**104**), a chiral organocatalysts.[155] (*ee*)

Highly enantioselective Michael addition of silyl nitronates (**105**) to cyclic α,β-unsaturated ketones (**106**; $n = 0$–2) has been accomplished by the utilization of *N*-spiro C_2-symmetric chiral quaternary ammonium bifluoride (**108**) as an organocatalyst, offering a new route to the enol silyl ethers of scalemic γ-nitro ketones (**107**; 70–90% *ee*).[156] (*ee*)



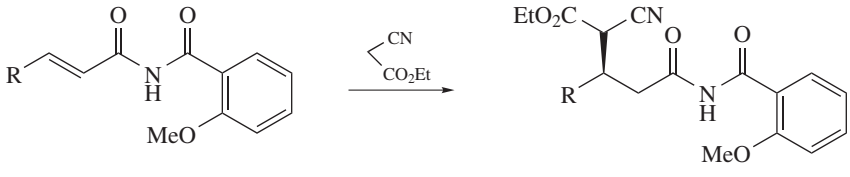
(**105**) (**106**) (**107**)



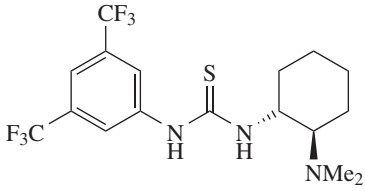
(**108**; Ar = 3,5-[3,5$(CF_3)_2C_6H_3$]C_6H_3)

Allylic C–C bond-forming addition of activated alkylidenes $RCH_2CH{=}C(CN)CO_2R'$ to acrolein has been achieved with good yield and regio- and enantio-selectivity (*ee*) in the presence of *Cinchona* alkaloid-derived organocatalysts. The reaction is characterized by an unusual α-selectivity of the C–C bond-forming step and represents an example of deconjugative Michael addition.[157]

A thiourea-catalysed asymmetric Michael addition of activated methylene compounds to α,β-unsaturated imides, derived from 2-pyrrolidinone and 2-methoxybenzamide (**109**), has been developed. In the case of 2-pyrrolidinone derivatives, the reaction with malononitrile proceeded in toluene with high enantioselectivity, providing the Michael adducts in good yields. However, the nucleophiles that could be used for this reaction were limited to malononitrile due to poor reactivity of the substrate. Further examination revealed that *N*-alkenoyl-2-methoxybenzamide (**109**) was the best substrate among the corresponding benzamide derivatives bearing different substituents on the aromatic ring. Indeed, several activated methylene compounds, such as malononitrile, methyl α-cyanoacetate, and nitromethane, could be employed as nucleophiles to give the Michael adducts (**110**) in good to excellent yields with



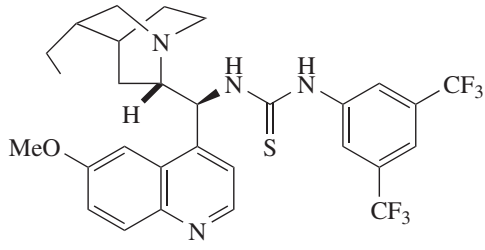
(**109**) (**110**)



(**111**)

up to 93% *ee*. Spectroscopic experiments revealed that this enhanced reactivity can (*ee*) be attributed to the intramolecular hydrogen bonding between the N–H of the imide and the methoxy group of the benzamide moiety. Thus, the key to the success of the catalytic enantioselective Michael addition is a dual activation of the substrate by both intramolecular hydrogen bonding in the imide and intermolecular hydrogen bonding with the bifunctional thiourea catalyst (**111**), in addition to the activation of a nucleophile by the tertiary amino group of (**111**).[158] The chiral thiourea catalyst (*ee*) (**111**) has also been used for the enantioselective Michael addition of thioacetic acid to enones (≤63% *ee*).[159]

The *Cinchona* alkaloid-derived thiourea (**112**), has been developed as an organocatalyst for conjugate addition of a wide range of nucleophilic enol species to enones. The (*ee*) reaction is characterized by high enantioselectivities and mild reaction condition.[160]



(**112**)

Diastereo- and enantio-selective cascade of Michael addition and lactonization (*de*) between various silyl enolates derived from phenyl carboxylates and α,β-unsaturated ketones were successfully carried out by using an efficient organic catalyst, a cinchoni- (*ee*) dine-derived chiral quaternary ammonium phenoxide. In this asymmetric domino reaction, the corresponding *trans*-3,4-dihydropyran-2-ones were obtained in high yields with almost complete diastereoselectivities and good to excellent enantioselectivities.[161]

D-Camphorsulfonic acid (D-CSA) was identified as catalyst for the enantioselective Michael-type Friedel–Crafts reactions of indoles with aromatic enones ArCH=CHCOAr′ to afford the corresponding β-indolyl ketones in excellent yields and moderate enantioselectivities. A surprising synergistic effect was discovered between [Bmim]Br and D-CSA, which may originate from the catalytic Lewis acid activation of the Brønsted acid.[162] (ee)

Heteropoly acids can catalyse conjugate addition of indoles and pyrrole to unsaturated carbonyl compounds and nitroalkene in water at ambient temperature in good to excellent yields.[163] Reactions of indoles and α,β-unsaturated ketones can also be catalysed by using gallium triiodide (10 mol%) to give the corresponding Michael adducts in good to excellent yields.[164] Finally, the $Na[AuCl_4].2H_2O$-catalysed addition of 7-azaindole derivatives to α,β-enones has been described and factors directing the $C(3)$ versus $N(1)$-alkylation reaction on the 7-azaindole nucleus were explored. Thus, the reaction of 7-azaindole with β-unsubstituted α,β-enones afforded 1-substituted-7-azaindoles through an aza-Michael-type reaction. By contrast, 6-substituted 7-azaindoles underwent a regioselective $C(3)$ alkylation. In analogy, the $Na[AuCl_4].2H_2O$-catalysed reaction of 7-azaindole derivatives with β-aryl-substituted α,β-enones gave 3-substituted 7-azaindoles in moderate to satisfactory yields and the reaction of 1-substituted 7-azaindoles with α,β-enones allowed an easy entry to 1,3-disubstituted 7-azaindoles in moderate to high yields.[165]

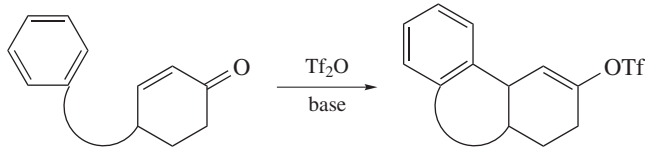
Simple bis(oxazoline) ligands, especially azabis(oxazolines), can catalyse the addition of indoles to benzylidene malonates in up to 99% *ee*, provided that excess of the chiral ligand is avoided.[166] The paradigm followed in many asymmetric catalytic reactions that an excess of the chiral ligand with respect to the metal should improve enantioselectivity because the background reaction catalysed by a free metal is suppressed, was shown not to be applicable here,[166] which might call for revisiting some of the many copper(II)–bis(oxazoline)-catalysed processes known. Enantioselective additions of pyrroles and indoles to α,β-unsaturated 2-acylimidazoles catalysed by the bis(oxazolinyl)pyridine–scandium(III) triflate complex have been accomplished.[167] (ee) (ee)

HF calculations with the 6–31G(d) basis set were used to study the mechanism of the Michael addition (or Friedel–Crafts alkylation) reaction of indole with dimethyl alkylidenemalonate. This reaction proceeds through two transition states, TS_1 and TS_2: in the first step, assumed to be rate determining, the new C–C bond is formed, whereas in the second step, proton transfer from indole to malonate occurs with the formation of the new C–H bond. The calculations show that the transfer and interaction of the π-electrons in the reactant molecules may play an important role in the cleavage of the original C=C bond and the formation of the new bonds (C–C and C–H); the electron transfer is believed to be the driving force for the reaction to occur. The solvent effects (alcohol vs 1,2-dichloroethane) were elucidated with single-point energy calculations at the MP2/6–311+G(d,p) level, using the polarized continuum model (PCM) implemented in the Gaussian 03 package. The PCM results indicate that the energy barriers of the reaction are reduced in the presence of solvents, and the proton of the alcohol may participate in the H-transfer process, thereafter making this step a rate-determining event in alcohol as solvent. By contrast, dichloroethane has little influence on the reaction pathway compared with that taking place in the

gas phase. The calculated results explain why a deuterated product is formed if this reaction takes place in CH_3OD.[168]

Cobalt(II) complexes prepared *in situ* from $(AcO)_2Co$ and two novel chiral spiro nitrogen-containing ligands, 7,7′-bis(2-pyridinecarboxamido)-1,1′-spirobiindane (SIPAD) and 7,7′-bis(2-quinolinecarboxamido)-1,1′-spirobiindane (SIQAD), are efficient catalysts for the asymmetric Michael addition of malonates to chalcone derivatives. The alkylation products were obtained in high yields with moderate enantioselectives.[169] (ee)

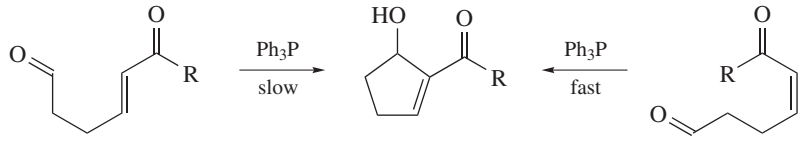
Triflic anhydride has been shown to activate enones (**113**) with an electron-rich aromatic pendant to undergo a Friedel–Crafts-like cyclization, affording the cyclic enol triflate (**114**).[170]



(**113**) (**114**)

The Morita–Baylis–Hillman reaction can be accelerated by a catalytic amount of lithium bromide and 1,8-diazabicyclo[5.4.0]undec-7-ene in a solvent-free medium.[171]

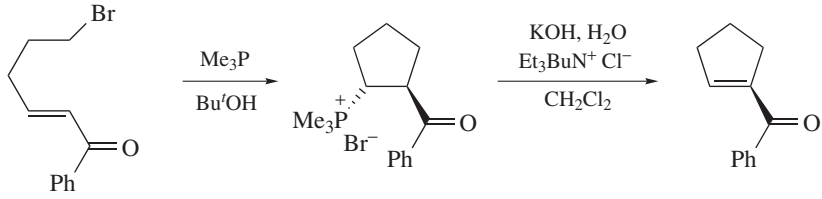
A study of the effect of the Michael acceptor configuration on the efficiency of intramolecular Morita–Baylis–Hillman reactions has been performed. Enones containing a pendant aldehyde moiety attached at the β-position of the alkene group were employed as substrates and the reactions were catalysed by a phosphine. In all cases examined, with Ph_3P as the catalyst, cyclization of (*Z*)-alkene (**117**) gave 2.5–8.5 times higher yield than with the *E*-isomer (**115**) under identical reaction conditions, both affording the same product (**116**). Steric effects are believed to be the source of this difference in reactivity.[172]



(**115**) (**116**) (**117**)

With the weakly basic counterion produced in the Morita–Baylis–Hillman alkylation and allylation [(**118**) → (**120**)], the reaction can be stopped after electrophilic attack on the zwitterionic enolate and the intermediate (**119**) isolated. The *trans* configuration of (**119**) suggests that there is no electrostatic interaction between phosphorus and oxygen in the zwitterionic enolate that undergoes alkylation, thus giving a new mechanistic insight into the Morita–Baylis–Hillman reaction.[173]

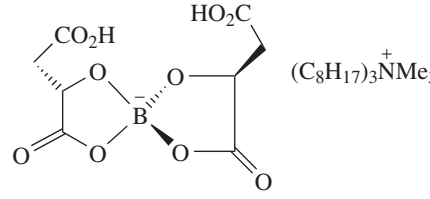
1,3-Bis[2-(naphthalene-2-yloxy)propyl]imidazolium bromide has been reported as a new ionic liquid catalyst promoting the Morita–Baylis–Hillman reaction of various arylaldehydes in the absence of solvents.[174]



(**118**) (**119**) (**120**)

Using electrospray ionization mass spectrometry in both positive and negative ion modes, the on-line scanning of the Morita–Baylis–Hillman reaction in the presence of imidazolium ionic liquids has been investigated. The interception of several supramolecular species indicated that ionic liquids co-catalyse the reactions by activating the aldehyde toward nucleophilic enolate attack and by stabilizing the zwitterionic species that act as the main intermediates.[175]

The aza-Baylis–Hillman reaction of 4-X-$C_6H_4CH{=}NTs$ with $CH_2{=}CHCOMe$, catalysed by Ph_3P in the newly designed chiral ionic liquid (**121**), derived from L-(−)-malic acid, gave products with up to 84% *ee*. This example represents the first highly enantioselective asymmetric reaction in which a chiral medium is the sole source of chirality.[176] (*ee*)

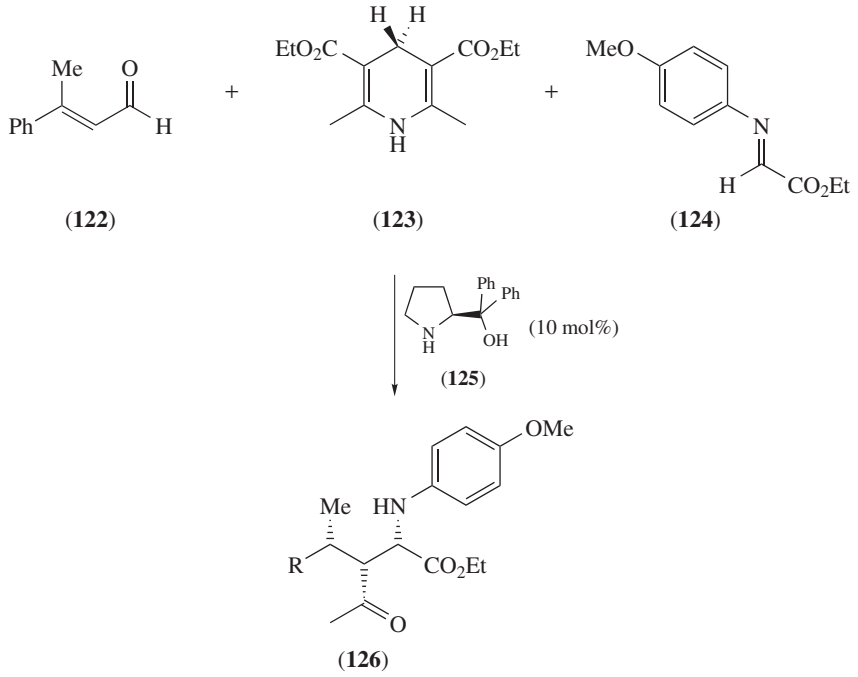


(**121**)

A series of *N*-*p*-nitrobenzenesulfonylimines have been reported to undergo asymmetric aza-Morita–Baylis–Hillman reactions with methyl acrylate mediated by DABCO in the presence of chiral thiourea organocatalysts with unprecedented levels of enantioselectivity (87–99% *ee*), albeit only in modest yields (25–49%). Isolation of a DABCO–acrylate–imine adduct as a key intermediate, kinetic investigation, and isotopic labelling, have been employed to determine the mechanism.[177] (*ee*)

Intramolecular hydrogen bonding has been proposed to facilitate nucleophilic addition of sulfones to the Morita–Baylis–Hillman adducts in a single step to produce the substituted allyl sulfones.[178]

A direct asymmetric reductive Mannich-type reaction that allows for the formation of three contiguous stereocentres with high chemo-, diastereo-, and enantio-selectivity (10:1 to 50:1 *dr*; 96–99% *ee*) has been presented (Scheme 4). The reaction commences with the formation of the corresponding iminium ion from aldehyde (**122**) and prolinol catalyst (**125**), followed by conjugate reduction with Hantzsch ester (**123**) to generate an enamine, which then undergoes Mannich reaction with imine (**124**) to produce (**126**).[179] (*ee*) (*de*)

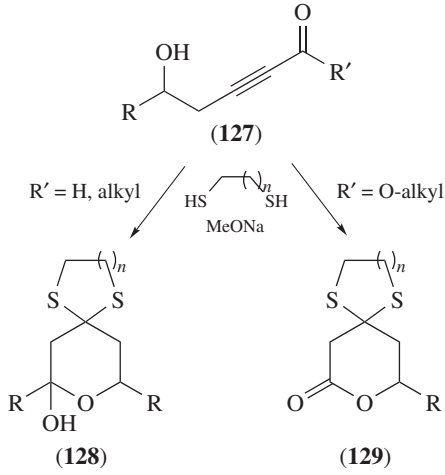


SCHEME 4

Nucleophilic addition of α-halo-4-tolylsulfonyl methyl anions to quinone methides has been reported to afford three kinds of products as a result of domino reactions. Two of them were identified as rearrangement products and one as the vicarious nucleophilic substitution (VNS) product. An unexpected 1,2-migration of the tosyl group was observed.[180]

The kinetics of the addition of aniline ($PhNH_2$) to ethyl propiolate ($HC{\equiv}CCO_2Et$) in DMSO as solvent has been studied by spectrophotometry at 399 nm using the variable time method. The initial rate method was employed to determine the order of the reaction with respect to the reactants, and a pseudo-first-order method was used to calculate the rate constant. The Arrhenius equation $\log k = 6.07 - (12.96/2.303RT)$ was obtained; the activation parameters, E_a, $\Delta H^{\neq}$, $\Delta G^{\neq}$, and $\Delta S^{\neq}$ at 300 K were found to be 12.96, 13.55, 23.31 kcal mol^{-1} and -32.76 cal mol^{-1} K^{-1}, respectively. The results revealed a first-order reaction with respect to both aniline and ethyl propiolate. In addition, combination of the experimental results and calculations using density functional theory (DFT) at the B3LYP/6–31G* level, a mechanism for this reaction was proposed.[181]

An efficient double conjugate addition of ethane and propane dithiols in the presence of sodium methoxide to propargylic carbonyl compounds (**127**) has been developed. The corresponding amino-substituted propargylic aldehydes afforded piperidine derivatives.[182]



Additions to Multiple Bonds Activated by Other Electron-withdrawing Groups

Nucleophilic addition reactions of *para*-substituted benzylamines ($XC_6H_4CH_2NH_2$) to α-phenyl-β-thiophenylacrylonitriles [$Y(C_4SH_2)CH{=}C(CN)C_6H_4Y'$] have been studied in acetonitrile at 25.0, 30.0, and 35.0 °C. The reactions apparently take place in a single step in which the C_β–N bond formation and proton transfer to C_α of α-phenyl-β-thiophenylacrylonitriles occur concurrently with a four-membered cyclic transition structure. These mechanistic conclusions were deduced from the following: (i) the large negative ρ_X and large positive $\rho_{Y'}$ values; (ii) the negative sign and large value of the cross-interaction constants (ρ_{XY}); (iii) the normal kinetic isotope effects ($k_H/k_D > 1.0$); and (iv) relatively low $\Delta H^{\neq}$ and large negative $\Delta S^{\neq}$ values.[183]

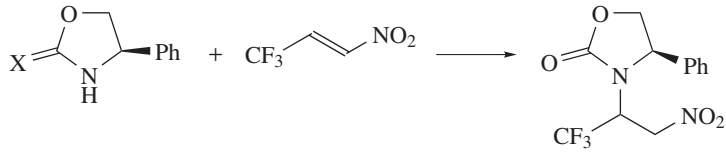
Investigation of the stereochemistry of the nucleophilic addition of amines to 1,3-dienylsulfone revealed that the *Z*/*E* ratios of the resulting allylic sulfones varied with amines, solvents, temperature, and concentrations. The predominant formation of (*Z*)-isomer was rationalized by a '*syn*-effect', which could be mainly regarded as a result of the $n/\sigma \rightarrow \pi^*$ interactions.[184] (de)

The Michael addition of oxygen nucleophiles to vinyl sulfones[185] and the addition of dimethyl malonate and ethyl cyanoacetate to α,β-unsaturated sulfones in the presence of Triton-B and K_2CO_3 have been studied.[186]

The relative Michael-acceptor abilities of a variety of substituted aromatic and aliphatic nitroalkenes have been elucidated by computational methods. Several global and local reactivity indices were evaluated with the incorporation of the natural charge obtained from natural bond orbital (NBO) analysis. Natural charges at the carbon atom β to the NO_2 group and the condensed Fukui functions derived by this method were found to be consistent with the reactivity.[187]

Secondary acyclic formamides RNHCH=O can serve as efficient *N*-nucleophiles in the addition to nitroalkenes $R^1CH{=}C(R^2)NO_2$ to afford the corresponding Michael adducts in good yields.[188]

A diastereoselective version of the latter Michael-like addition employed cyclic amides, oxazolidinones, and thiazolidinones (**130**; X = O or S) to afford the respective adducts (**131**) with 92% *de* (X = O) and >99% *de* (X = S), respectively.[189] (*de*)

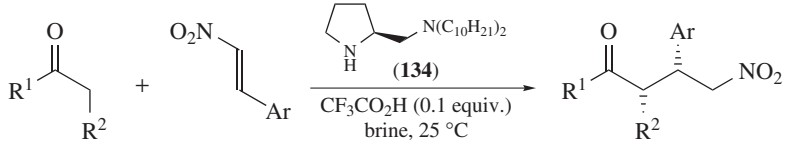


(**130**) (**131**)

Michael addition of β-keto esters to nitroalkenes catalysed by $TfOAg.PPh_3$ has been reported to proceed efficiently only in water.[190]

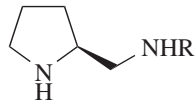
The α-addition of alkyl or aryl thionucleophiles R^1SH to β-nitroacrylates $R^2(NO_2)C{=}CCO_2R^3$ in THF in the presence of Et_3N or DBU does not stop at β-nitro-α-thioalkanoates $R^2CH(NO_2)CH(SR^1)CO_2R^3$, but proceeds further with concomitant elimination of nitrous acid to afford α-thioacrylates $R^2CH{=}C(SR^1)CO_2R^3$.[191]

The organocatalytic asymmetric Michael addition of aldehydes $RCH_2CH{=}O$ to β-nitroacrolein dimethyl acetal $[(MeO)_2CHCH{=}CHNO_2]$ has been studied in detail. The reaction took place with excellent yields and good stereoselectivities (≤88% *ee*) when a chiral β-amino alcohol, such as L-prolinol (10 mol%), was employed as the catalyst.[192] On the other hand, bis(3,5-dimethylphenyl)(pyrrolidin-2-yl)methanol (30 mol%), readily obtained from L-proline, catalysed Michael addition of malonates to nitroalkenes with only ≤56% *ee*.[193] Another Michael addition of aldehydes to nitrostyrenes using a series of chiral 2-trimethylsilanyloxymethylpyrrolidine-based dendronic catalysts has been described. Good yields (≤82%), and high diastereoselectivities (up to *syn*:*anti* = 95:5) and enantioselectivities (≤99% *ee*) have been obtained.[194] With the proline-derived bifunctional catalyst (**134**) having long hydrophobic alkyl chains, Michael addition of ketones and aldehydes (**132**) to β-nitrostyrenes (**133**) can be performed in brine or seawater without addition of organic solvents. The products (**135**) were obtained in excellent yields (≤99%) with high enantiomeric excess (≤96% *de* and ≤97% *ee*), even when only an equal molar ratio of the donor to acceptor was used.[195] (*de*) (*ee*)



(**132**) (**133**) (**134**) (**135**)

Pyrrolidine-based diamine (**136**) and triamine derivatives that incorporate the secondary diamine motif have been developed as additional organocatalysts for the highly diastereoselective and enantioselective Michael addition of cyclic ketones to



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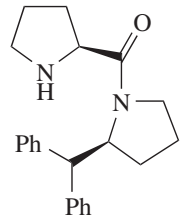

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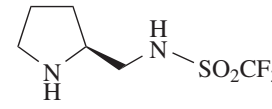
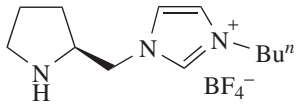
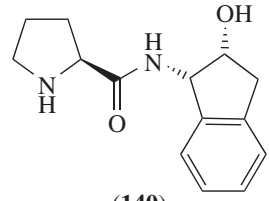


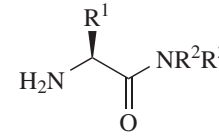
(**138**)



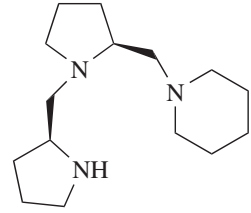
(**139**)



(**140**)



(**141**)

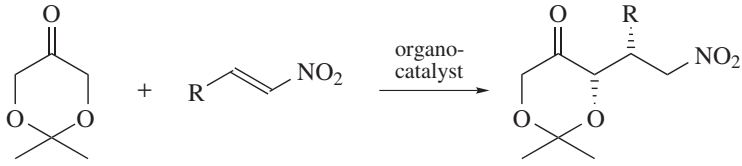


(**142**)

2-nitrovinylarenes. The highest selectivities were obtained when these catalysts were used in conjunction with Brønsted acids.[196] Catalyst (**137**) promotes the Michael addition of aldehydes to nitroalkenes with the lowest catalyst loading and lowest stoichiometric ratio of reactant aldehyde reported to date.[197] (*S*)-Pyrrolidinesulfonamide (**138**) represents another addition to the portfolio of the organocatalysts for the latter reaction; mechanistic studies have been conducted to understand the origin of its high catalytic activities.[198] The functionalized chiral ionic liquid (**139**) can also act as a highly efficient and reusable organocatalyst for the asymmetric Michael addition of ketones and aldehydes to nitroalkenes.[199] The same catalyst also works in water in the absence of organic solvents or other additives.[200] The L-prolinamide (**140**) represents another variation of bifunctional catalysts for the direct Michael addition of ketones to *β*-nitrostyrenes with ≤94% *de* and ≤80% *ee*.[201] Amides (**141**), derived from primary amino acids, catalyse the enantioselective addition of ketones to nitroalkenes with high stereocontrol (>38:1 *dr*; ≤99% *ee*).[202] Triamine (**142**) has been reported to catalyse the Michael addition of cyclic ketones to nitroalkenes with high diastereoselectivity (≤99:1) and enantioselectivity (≤91% *ee*).[203]

(*de*) (*ee*) (*de*) (*ee*)

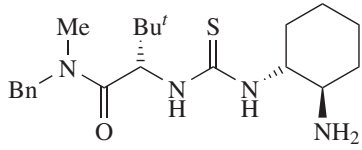
The organocatalytic asymmetric Michael addition of 2,2-dimethyl-1,3-dioxan-5-one (**143**) to various nitroalkenes (**144**), using a number of proline-based catalysts, afforded



(**143**) (**144**) (**145**)

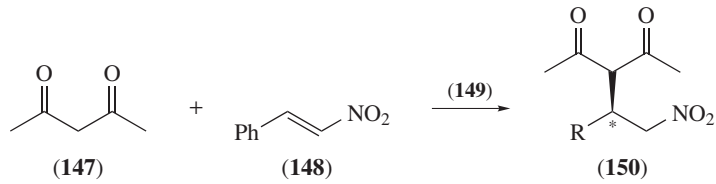
polyfunctional nitro ketones (**145**). Reverse diastereoselectivity was observed with the diphenylprolinol catalyst (**103**), and the best diastereoisomeric and enantiomeric excesses were achieved with the sulfonamide catalyst (**138**) (84–98% *de*; 81–86% *ee*).[204]

Primary amine–thiourea derivative (**146**) has been developed as an active and highly enantioselective catalyst for the conjugate addition of ketones to nitroalkenes. The reaction is characterized by a broad substrate spectrum, with nitroalkenes bearing either aromatic or aliphatic substituents and a wide variety of ketones. Ethyl ketones react preferentially, generating *anti*-configured products with good to excellent diastereoselectivity. An enamine mechanism has been suggested, with cooperative activation of the electrophile by the thiourea and of the ketone by the primary amino group.[205]

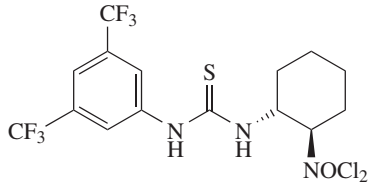


(**146**)

The mechanism of enantioselective Michael addition of acetylacetone (**147**) to β-nitrostyrene (**148**), catalysed by a thiourea-based chiral bifunctional organocatalyst (**149**), has been investigated theoretically, using DFT calculations. A systematic conformational analysis was presented for the catalyst; both substrates apparently coordinate preferentially via bidentate hydrogen bonds. The deprotonation of the enol form of acetylacetone by the amino group of the catalyst occurs easily, leading to an ion pair characterized by multiple H-bonds also involving the thiourea unit. Two distinct reaction pathways were explored toward the formation of the Michael adduct that differ in the mode of the electrophile activation: (1) one which involves a bidentate hydrogen bonding of the electrophilic partner (**151**), while the approaching nucleophile is directed by the hydrogen bonding from the protonated Me_2N group; (2) an opposite scenario, where the nucleophile is bonded by the protons of the thiourea moiety (**152**), while the protonated Me_2N group steers the approach of the electrophile. Both reaction channels were shown to be consistent with the notion of non-covalent organocatalysis in that the transition states leading to the Michael adduct are stabilized by extensive H-bonded networks. The comparison of the energetics for the two pathways showed the latter mechanism (**152**) to be slightly lower in energy and, therefore, more likely.[206] A similar study has been reported for the bifunctional catalysis by urea.[207]



(**147**) (**148**) (**150**)



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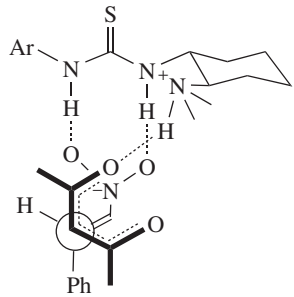
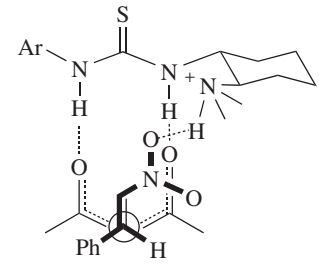
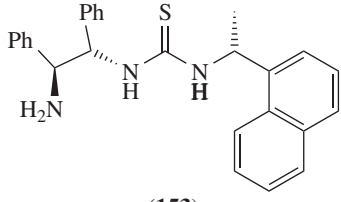


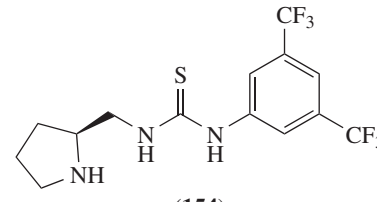


(**151**) (**152**)

The chiral thiourea catalyst (**153**) (15 mol%) and AcOH−H_2O additive converts ketones into addition products with nitro ketones in high yields (82–99%) and enantioselectivities (90–99%).[208] The transition-state geometries for formation of *R*- and *S*- enantiomers suggest that only one oxygen atom of the nitro group is coordinated to the thiourea moiety of this catalyst.[209] This is in conflict with the earlier working hypotheses, which involve a bonding of both oxygens, but in agreement with the most recent calculations by another group (see above[206]). The theoretical and experimental *ee* values showed good agreement, demonstrating the predictive power of the calculations.[209]

ee





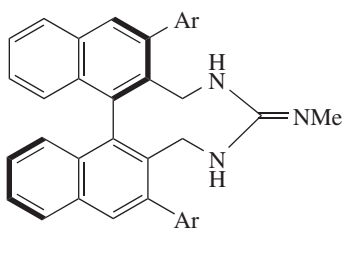
(**153**) (**154**)

The proline-derived thiourea organocatalyst (**154**) (20 mol%) in conjunction with *n*-butyric acid (10 mol%) exhibited high stereoselectivity (≤99:1 *syn*:*anti* and ≤98% *de*)

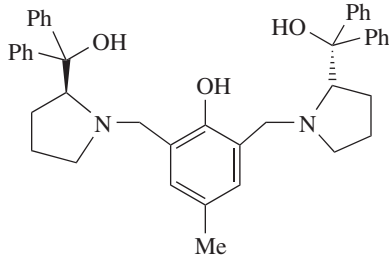
de

ee) in the asymmetric Michael additions of cyclohexanone to both aryl and alkyl nitroalkenes.[210] (ee)

The axially chiral guanidine catalyst (**155**) (0.4–5 mol%) has been developed to facilitate the highly enantioselective Michael addition of 1,3-dicarbonyl compounds to a broad range of conjugated nitroalkenes (≤98% *ee*).[211] (ee)

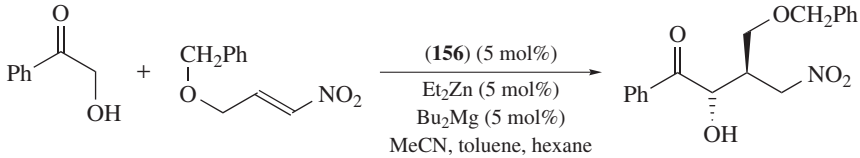


(**155**; Ar = 3,5-(3,5-Bu^{t}C$_6$H$_3$)C$_6$H$_3$)



(**156**)

The bis-prolinol-derived phenol (**156**) has been designed to facilitate the formation of heterodinuclear complexes based upon the large difference in pK_a of the phenolic OH group and the tertiary OH groups. The first examples of its application involve hydroxyacetophenones (**157**) as donors in the asymmetric Michael addition to nitroalkene acceptors (**158**); the best stereocontrol was observed with a zinc–magnesium dinuclear complex, where enantiomeric excesses ranged up to 92% for the major *anti* diastereoisomer (**159**).[212] (ee)

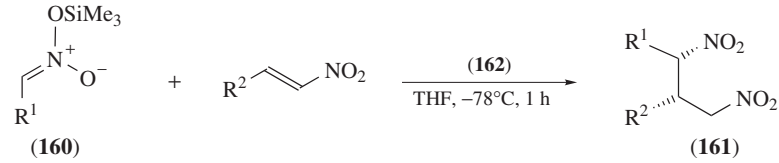


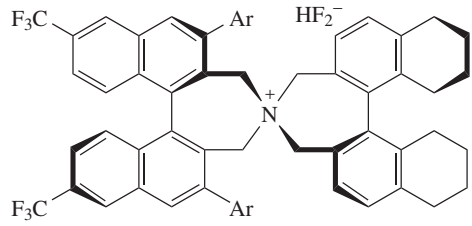
(**157**) (**158**) (**159**)

The chiral quaternary ammonium bifluoride (**162**) has been shown to catalyse a highly diastereo- and enantio-selective conjugate addition of silyl nitronates (**160**) to nitroalkenes, giving rise to 1,3-dinitro compounds (**161**) (76–96% *ee*).[213] (de) (ee)

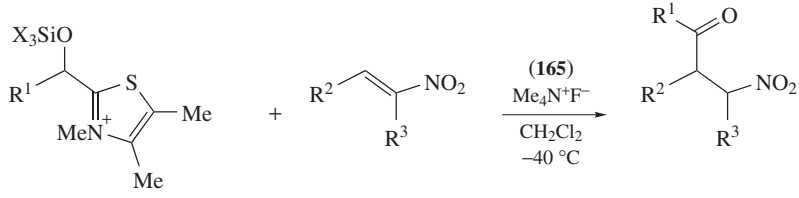
Direct nucleophilic acylation of nitroalkenes (**164**), promoted by a combination of fluoride anion and thiourea catalyst (**165**), has been developed, using the thiazolium derivative (**163**) as the umpolung reagent (≤20:1 *dr*; 74% *ee*).[214] (de) (ee)

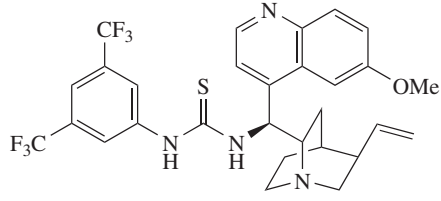
Cinchona alkaloids and their derivatives have been reported to catalyse the Michael addition of *N*-heterocycles, such as benztriazole, to nitroalkenes in moderate to high enantioselectivities (≤94% *ee*).[215] The thiourea derivative (**149**) catalysed Michael addition of thioacetic acid to a range of *trans*-β-nitrostyrenes to afford RCH(SAc)–CH$_2$NO$_2$ (≤70% *ee*).[216] The thiourea derivative (**149**) and its congeners have been identified as efficient organocatalysts for the Michael addition of α-substituted cyanoacetates RCH(CN)CO$_2$Et to vinyl sulfones CH$_2$=C(R)SO$_2$Ph (72–96% *ee*).[217] (ee) (ee) (ee)





(**162**; Ar = 3,5-(3,5-Bu^{t}C$_6$H$_3$)$_2$C$_6$H$_3$)



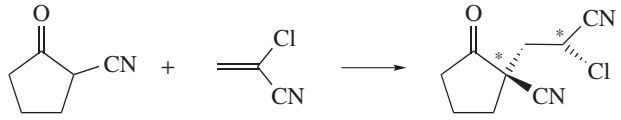


(**165**)

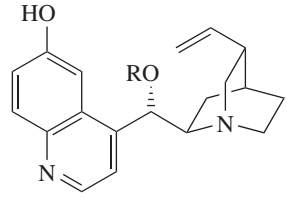
A highly enantioselective and diastereoselective addition of trisubstituted carbon donors, such as (**166**), to 2-chloroacrylonitrile (**167**), catalysed by bifunctional *Cinchona* alkaloid catalysts, e.g. (**169**), has been reported as the first example of an asymmetric cascade that includes conjugate addition and protonation with efficient catalytic control at two non-adjacent stereocentres (**168**).[218] (*ee*) (*de*)

Conditions were found under which 2,4,6-trinitrostyrene adds nucleophiles (thiophenol, aniline, and aliphatic amines) at the vinyl moiety to form the corresponding β-X-ethyl-2,4,6-trinitrobenzenes (X = PhS, PhNH, or R_2N). In the reactions with primary aromatic amines, the initially formed adducts undergo an intramolecular replacement of the nitro group followed by aromatization of the indolines, giving rise to the corresponding *N*-substituted 4,6-dinitroindoles.[219]

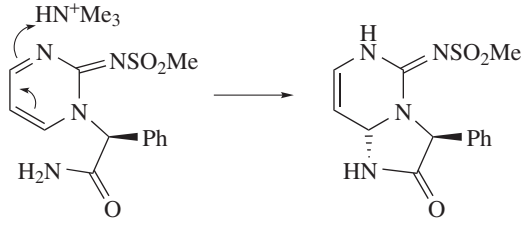
The formation of imidazo[1,2-*c*]pyrimidines (**171**) via a ring closure of 2-(2-sulfonylimino-1,2-dihydro-1-pyrimidinyl)acetamides (**170**) has been studied using DFT methods, which revealed the requirement for Brønsted acid catalysis.[220]



(**166**) (**167**) (**168**) (7:1 *dr*; 91% *ee*)



(**169**; R = 9-phenanthryl)



(**170**) (**171**)

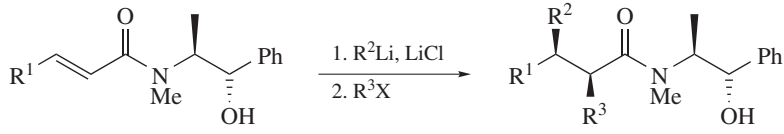
Experimental and theoretical study of the Diels–Alder reactions of the furans and methyl 3-nitroacrylate has demonstrated that the initial cycloadducts arise via a concerted mechanism. The latter adducts then undergo retro-Diels–Alder reactions to give the Michael adducts via a stepwise mechanism. To account for the selectivity observed in these additions, the frontier molecular orbitals were examined and the transition states were located by employing density functional calculation at the B3LYP/6–31G* level. The experimentally observed regio- and stereo-selectivities were explained by a comparison of the calculated activation energies, which ranged from 11 to 18 kcal mol^{-1} for the individual isomers. The *s-cis* forms of the dienophile were found to be more stable than the *s-trans* forms, both in the ground state and in the transition state. Furthermore, the *endo* transition structures for the ester group exhibited a lower energy barrier by 0.3 kcal mol^{-1} than their *exo* counterparts, a value that is in disagreement with the experimental results. The presence of the nitro group in the dienophile may play an important role in determining the selectivity. Attempts to find a stepwise mechanism leading to the Diels–Alder adduct via a zwitterion were unsuccessful. Two stepwise processes were found, which lead to the formation of Michael adducts generated via an electrophilic attack by the nitroacrylate at the α-position of the furan ring, and an intramolecular proton transfer mediated by the formation of a four-membered structure. The potential energies for these reactions showed values in the range 11–17 kcal mol^{-1} for the first step and 41–51 kcal mol^{-1} for the proton transfer. Solvent effects in chloroform on the Michael addition did not

appear in the electrophilic attack step (less than 4 kcal mol^{-1}) but the transition state of the latter process was stabilized by 6–13 kcal mol^{-1}.[221]

Additions of Organometallics to Activated Double Bonds

The effect of donor ligands, usually expected to enhance the reactivity of organolithiums, was studied in the case of the addition of PhLi to (*E*)-cinnamaldehyde in THF, under conditions that lead to 1,3-diphenylpropanone. TMEDA and HMPT were found to decelerate the reaction and with an [HMPA]:[PhLi] ratio $\geq$4, the reaction became almost completely inhibited. These results show the complexity of solvation effects and the specificity of the substrate–reagent–ligand–solvent interactions.[222]

Organolithium reagents undergo highly regio- and diastereo-selective 1,4-addition to α,β-unsaturated amides (**172**) derived from (*S*,*S*)-(+)-pseudoephedrine, furnishing the corresponding β-alkyl-substituted adducts in excellent yields and diastereoselectivities. Furthermore, the intermediate lithium enolates, generated in the conjugate addition step, undergo a highly diastereoselective alkylation reaction to afford α,β-dialkyl-substituted amides (**173**) in high yields.[223]



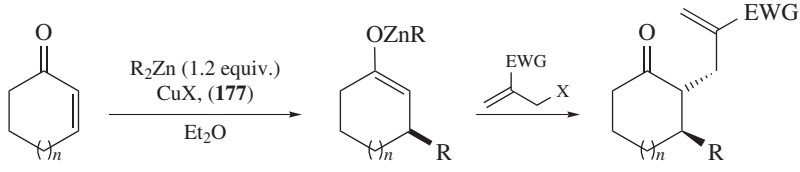
(**172**) (**173**)

Mixed aggregates of chiral lithium amide and lithium ester enolate have been employed in the enantioselective conjugate addition on α,β-unsaturated esters. Michael adducts were obtained in up to 76% *ee* by combining a lithium enolate and a chiral 3-aminopyrrolidine lithium amide. The sense of the induction was found to be determined by both the relative configuration of the stereogenic centres borne by the amide and the solvent in which the reaction was conducted.[224]

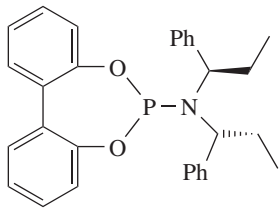
A new study has revealed that allylmagnesium, allylindium, and allylbismuth generally exhibit a preference for axial addition to cyclohexenones (in the 1,2-addition). Allylmagnesium was found to be the most stereoselective reagent. Reactions with carvone (an α-methylated enone) were most selective, except that allylbismuth was inert to this substrate.[225]

A simple trick proved generally valuable for asymmetric copper-catalysed conjugate addition reactions: it was found that the enantioselectivities of Et_2Zn or Me_3Al reagents in reaction with α-halo enones, carried out in the presence of chiral phosphorimidite ligands, were dramatically improved upon the addition of styrene, which acts as a radical scavenger to suppress the competitive non-asymmetric radical pathway.[226]

The copper-catalysed asymmetric conjugate addition of dialkylzinc to enones (**174**; $n = 1$ or 2) generates homochiral zinc enolates (**175**), which can be trapped *in situ* with activated allylic electrophiles to produce (**176**). High *trans* selectivity (85:15 to



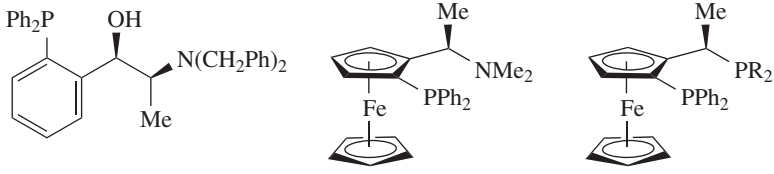
(**174**) (**175**) (**176**)



(**177**)

>99:1) and excellent enantioselectivities (91–99% *ee*) were attained in the presence of ligand (**177**).[227] (*de*)

The new tridentate aminohydroxyphosphine ligand (**178**) has been developed for the copper-catalysed asymmetric conjugate addition of organozinc reagents to acyclic α,β-unsaturated carbonyl compounds $R^1CH{=}CHCO_2R^2$; the addition is characterized by high enantioselectivity (≤98% *ee*). Theoretical analysis suggests that the C–C bond formation takes place through a highly ordered transition state by the coordination of the phosphorus and nitrogen atoms to the copper(III) and zinc(II) atoms, respectively, and of the oxygen anion to both the metal centers.[228] (*ee*)

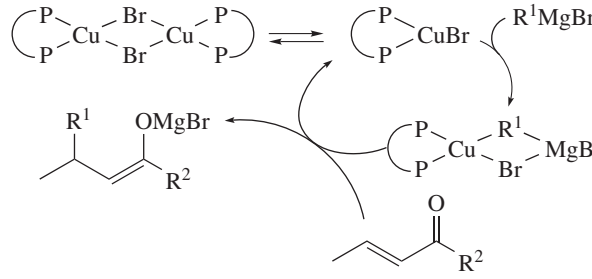


(**178**) (**179**) (**180**)

The copper-catalysed enantioselective 1,4-conjugate addition of Et_2Zn to chalcones was investigated in the presence of a catalytic amount of *N*,*P*-ferrocenyl ligand (**179**) with central and planar chirality under mild conditions (0 °C to room temperature). Chalcones with *ortho*-substituents (from *ortho*-substituted benzaldehydes and acetophenones) exhibited a dramatic improvement in the enantioselectivities (≤92% *ee*).[229] (*ee*)

The mechanism of the enantioselective 1,4-addition of Grignard reagents to α,β-unsaturated carbonyl compounds (Scheme 5; R^1 = alkyl; R^2 = alkyl, OR^3), promoted by copper complexes of chiral ferrocenyl diphosphines (**180**), has been explored using kinetic, spectroscopic, and electrochemical analysis. The roles of the solvent, copper halide, and the Grignard reagent have been thoroughly examined. Kinetic studies support a reductive elimination as the rate-limiting step, in which the chiral catalyst, (*ee*)

the substrate, and the Grignard reagent are involved. The thermodynamic activation parameters were determined from the temperature dependence of the reaction rate. The putative active species and the catalytic cycle of the reaction (Scheme 5) were proposed.[230]



SCHEME 5

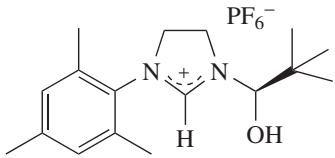
The copper-catalysed asymmetric conjugate addition of Grignard reagents to trisubstituted cyclic enones, carried out in the presence of a chiral carbene ligand, generated *in situ* from (**181**), afforded enantioenriched all-carbon quaternary centres with up to 96% *ee*. Interestingly, this is the only method that allows the addition of PhMgX to these enones.[231] Another example of the Cu-catalysed enantioselective conjugate additions of alkyl- and aryl-zinc reagents to cyclic β-substituted enones utilized the chiral NHC-based Cu complex (2.5–15 mol%), generated from the silver precursor (**182**). The latter reaction afforded the products bearing all-carbon quaternary stereogenic centres in 67–98% yield and in 74–97% *ee*. Mechanistic models accounting for the observed levels and trends in enantioselectivity were provided.[232]

The CuH-catalysed asymmetric conjugate reduction of (*E*)- and (*Z*)-β-silyl-α,β-unsaturated esters $PhMe_2SiC(R)=CHCO_2R'$ has been developed. Using polymethylhydrosiloxane (PMHS) as a stoichiometric source of hydride and the *in situ*-generated CuH ligated by the JOSIPHOS analogue PPF–P(*t*-Bu)$_2$ (**183**), highly enantioselective 1,4-reductions were attained. By contrast, the SEGPHOS analogue (**184**) gave inferior results.[233]

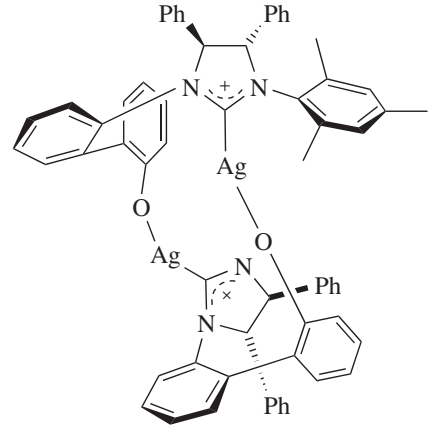
A highly enantioselective synthesis of α-dehydroamino acids (**186**) with a stereogenic centre at the γ-position has been developed, which employs a copper-catalysed asymmetric conjugate addition of diethylzinc to α,β-unsaturated imines (**185**) with the TADDOL-derived phosphoramidite (**187**) as a chiral ligand.[234]

The reaction of allyl carbamates (**189**) with activated enones (**188**) catalysed by $(Ph_3P)_4Pd$ in THF proceeded smoothly at room temperature to give the corresponding α,β-bis-adducts (**190**) in high yields.[235]

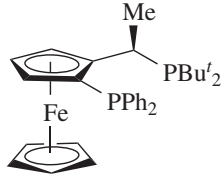
1,4-Addition of arylboronic acids to α,β-unsaturated ketones can be catalysed by palladium(0)–phosphine complexes with chloroform in the presence of a base. It is remarkable that the palladium(0) complexes are inactive in the absence of chloroform.[236] Palladium acetate–bipyridine complex has been reported to catalyse conjugate addition of arylboronic acids to α,β-unsaturated carbonyl compounds in aqueous media with high yields.[237]



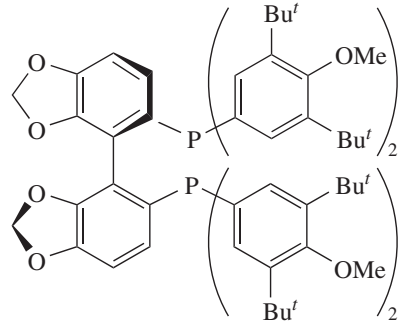
(**181**)



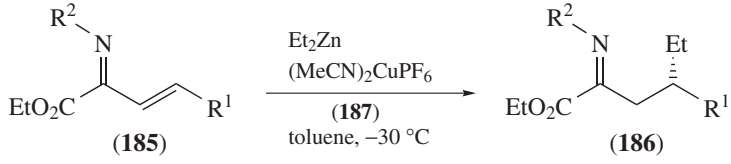
(**182**)



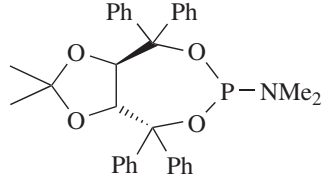
(**183**)



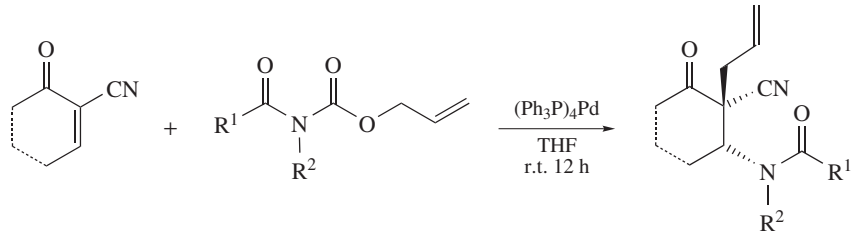
(**184**)



(**185**) (**186**)



(**187**)

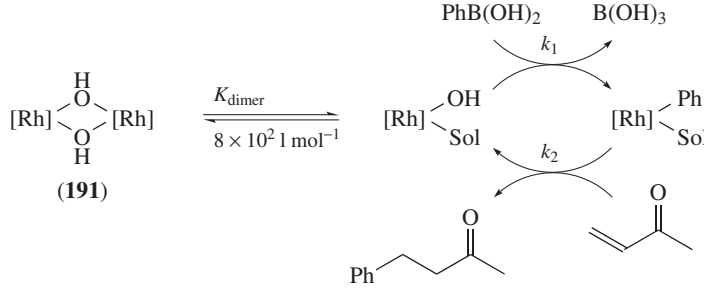


(**188**) (**189**) (**190**)

Alkynes in combination with a catalytic amount of a nickel complex have been found to catalyse the conjugate addition of arylboron reagents to α,β-unsaturated carbonyl compounds.[238]

An efficient cobalt-catalysed conjugate addition of functionalized aryl derivatives ArX (X = Cl, Br, OTf) to Michael acceptors $CH_2{=}CHZ$ (Z = CO_2Et, CN, $CONMe_2$) has been developed, using (2,2′-bipyridine)$CoBr_2$ as a particularly suitable catalyst. This procedure permits the synthesis of compounds resulting from 1,4-addition in good to excellent yields. The versatility of this original process represents a simple alternative to most known methods using organometallic reagents.[239]

A kinetic study of the Rh–BINAP-catalysed 1,4-addition of phenylboronic acid using reaction calorimetry revealed that the catalytically inactive dimeric hydroxo-rhodium complex [Rh(OH){(*R*)-BINAP}]$_2$ (**191**) is the resting state (Scheme 6). A negative non-linear effect in ee_{prod} and an amplified reaction rate were predicted and observed in the present reaction system that is characterized by the preferential formation of the homochiral (**191**) dimer.[240] (*ee*)

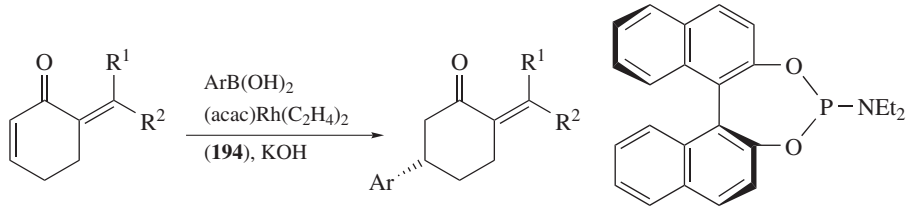


(**191**)

[Rh] = (R)-Binap Rh k_1 = 0.5 mol $l^{-1}s^{-1}$
Sol = Solvent

SCHEME 6

The rhodium-catalysed enantioselective 1,4-addition of arylboronic acids to the bifunctional Michael acceptors (**192**) in the presence of phosphoramidites (**194**) occurs regioselectively at the endocyclic C=C bond and in up to 95% *ee*. The presence of KOH is required to increase the reactivity so that less boronic acid and lower reaction temperatures can be used.[241] (*ee*)

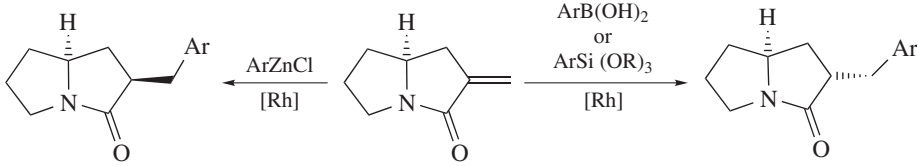


(**192**) (**193**) (**194**)

Asymmetric 1,4-addition of Ar^1ZnCl to (*E*)-3-arylpropenals ($Ar^2CH{=}CHCH{=}O$) proceeded with high enantioselectivity in the presence of Me_3SiCl and [(*R*)-BINAP–RhCl]$_2$ as catalyst in THF at room temperature to afford, after hydrolysis, the corresponding 3,3-diarylpropanals in 98–99% ee. The presence of the chlorosilane is essential to attain high yields (55–80%).[242] (*ee*)

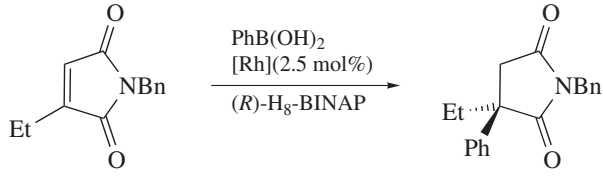
A highly enantioselective 1,4-addition of aryltrialkoxysilanes $ArSi(OR)_3$ to α,β-unsaturated esters and amides RCH=COX (X = OR′, NR′R″) was catalysed by a chiral rhodium complex generated from $[(MeCN)_2Rh(COD)]BF_4$ and (*S*)-BINAP in aqueous dioxane.[243] (*ee*)

The choice of the organometallic nucleophile (Zn, B, or Si) has been shown to facilitate the straightforward conversion of enone (**195**) into the opposite diastereoisomers of 2-substituted pyrrolizidinones (**196**)/(**197**) via the rhodium-catalysed 1,4-addition reaction.[244] (*de*)



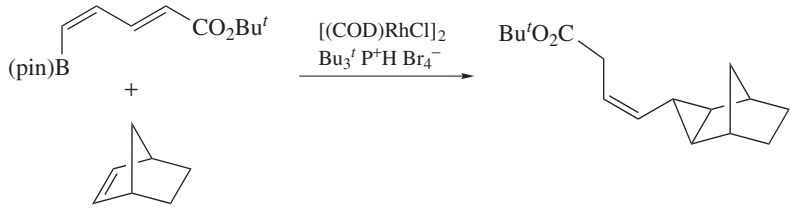
(**196**) (**195**) (**197**)

A rhodium-catalysed asymmetric 1,4-addition of arylboronic acids to substituted maleimides (**198**) has been described. The regioselectivity in this reaction is controlled by the choice of ligand (dienes or bisphosphines); 1,4-adducts with a quaternary stereocentre (**199**) can be obtained with high regioselectivity (87%) and enantioselectivity (≤97% *ee*) when (*R*)-H_8-BINAP is employed as ligand.[245] (*ee*)



(**198**) (**199**)

An unusual rhodium-catalysed addition of a dienylboronate ester to highly strained alkenes, such as norbornene, has been reported, resulting in the formation of vinylcyclopropane-fused tricyclic products (Scheme 7). Preliminary mechanistic studies have been presented.[246]



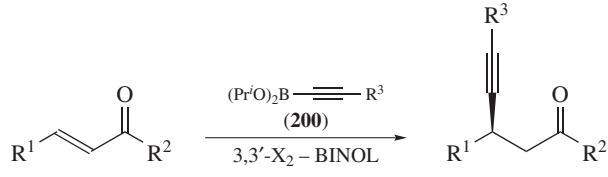
SCHEME 7

A chiral cationic rhodium complex has been shown to catalyse the enantioselective conjugate addition of silyl anion equivalents to cyclic α,β-unsaturated ketones and esters, thus providing a facile access to chiral organosilicon compounds.[247] (*ee*)

The silylformylation of functionalized alk-1-ynes $X(CH_2)_nCR^1R^2C{\equiv}CH$ with $ArMe_2SiH$ and CO, catalysed by $Rh_4(CO)_{12}$, affords the corresponding (*Z*)-β-silylalkenals $X(CH_2)_nCR^1R^2C(CHO){=}CHSiMe_2Ar$ in high yields under mild conditions.[248] (*de*)

The catalytic 1,6-addition of arylboronic acids to electron-deficient dienes, such as (*E*,*E*)-MeCH=CHCH=CHCOMe, was realized by use of an iridium catalyst. High yields of the corresponding δ-arylated carbonyl compounds were obtained with perfect 1,6-selectivity.[249]

The conjugate addition of alkynylboronates (**200**) to enones, catalysed by binaphthol organocatalysts (i.e., in the absence of any metal catalysts), has been studied theoretically with DFT methods. The high reactivity of the alkynylboronate derived from binaphthol seems to arise from electronic effects since its acidic boron atom binds tightly to the enone carbonyl and lowers the activation energy of the alkynylboration step. Steric clashes between the atoms of the ligands on boron and the enone have been invoked to account for the observed facial diastereoselectivity. The competing hetero-Diels–Alder reactions appear to be kinetically disfavoured relative to alkynylborations.[250] (*de*)



Indium(I) iodide has been shown to promote the cleavage of dialkyl disulfides, generating thiolate anions that then undergo facile addition to α,β-unsaturated ketones,

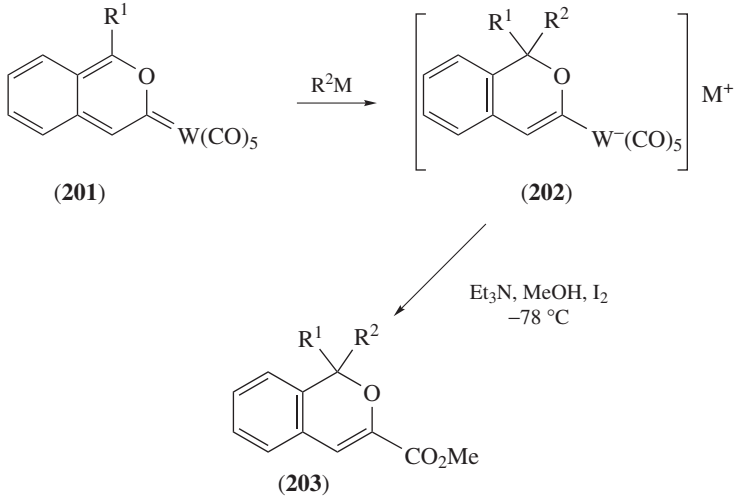
aldehydes, carboxylic esters, and nitriles under neutral conditions, producing the corresponding β-keto sulfides or β-cyano sulfides. This strategy has also been used for the regioselective nucleophilic ring opening of epoxides by thiolate anions in the presence of indium(III) chloride, affording β-hydroxyphenyl sulfides.[251]

An asymmetric synthesis of 1,3-dinitro compounds through Michael addition of nitroalkanes $R^1CH_2NO_2$ to nitroalkenes $R^2CH{=}CHNO_2$, catalysed by C_2-symmetric (*ee*) chiral tridentate bis(oxazoline) and bis(thiazoline) complexes of Et_2Zn, has been reported to occur with high enantioselectivities ($\leq$95% *ee*).[252]

The reaction of cinnamate esters with lithium pentamethylcyclopentadienide in the presence of chlorodiethylaluminium provides the corresponding 1,4-adducts in high yield.[253]

An expedient method for the preparation of isochromene carboxylates (**203**) has been developed, which relies on the regioselective 1,6-addition of various nucleophiles, such as Grignard reagents, alkoxides, and cyanide, to benzopyranylidenetungsten(0) complexes (**201**), followed by iodine oxidation of the addition intermediates (**202**).[254]

DFT calculations have been carried out to rationalize the unusual switch in stereoselectivity, where ynone and ynoate substrates exhibit opposite stereochemical preferences in the stannylcupration.[255]



(**201**) (**202**) (**203**)

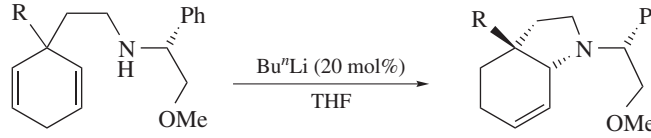
Miscellaneous Nucleophilic Additions

Whereas acid-catalysed cyclization of (**21**) undergoes the 6-*endo-dig* cyclization to afford (**23**), as discussed earlier, application of a base results in the formation of (**22**) as a product of 5-*exo-dig* ring closure.[39]

A dimeric proline-derived diamidobinaphthyl dilithium salt has been introduced as the first example of a chiral main group metal-based catalyst for asymmetric hydroamination–cyclization reactions of aminoalkenes.[256]

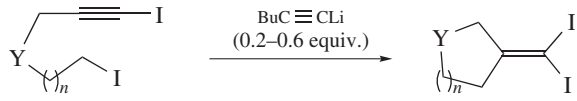
Intramolecular hydroamination of cyclohexa-2,5-dienes (**204**) mediated by Bu^nLi has been reported to produce the corresponding bicyclic allylic amines (**205**) with high

selectivity (≤95%). A mechanistic study has demonstrated that the reaction does not proceed through a direct hydroamination of one of the diastereotopic C=C bonds but more likely involves a diastereoselective protonation of the intermediate pentadienyl anion, followed by addition of a lithium amide across the double bond of the resulting 1,3-diene, and subsequent highly regioselective protonation of the final allylic anion.[257]



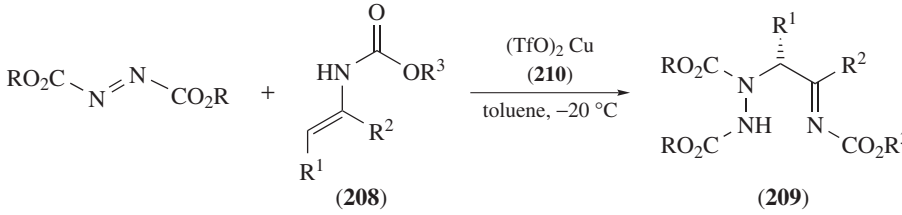
(**204**) (**205**)

In the presence of 1-hexynyllithium (0.2–0.6 equiv.), 1,ω-diiodoalk-1-ynes (**206**); Y = O, CH_2; n = 1, 2) undergo a new type of cyclization reaction with retention of the two iodine atoms to afford (diiodomethylene)cycloalkanes (**207**).[258]

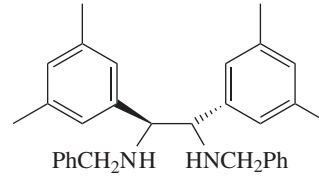


(**206**) (**207**)

A catalytic asymmetric amination of enecarbamates has been attained using a chiral Cu(II) complex of diamine (**210**) as catalyst. Thus, azodicarboxylates have been shown to react with various enecarbamates (**208**) derived from aromatic and aliphatic ketones and aldehydes to provide acylimines (**209**) in good yields with high enantioselectivity (≤99% *ee*). The catalyst loading required for high enantioselectivity was generally low (0.2 mol% in some cases).[259]

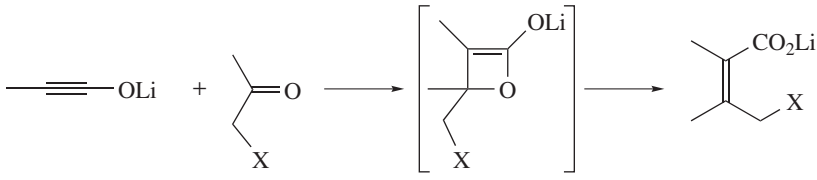


(**208**) (**209**)



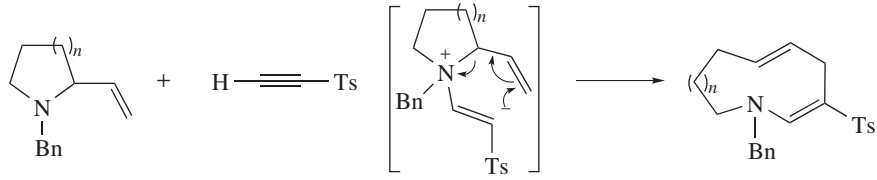
(**210**)

Tetrasubstituted alkenes (**214**) were obtained with high *Z* selectivity (>99:1) by reaction of ynolates (**211**) with α-oxy- and α-amino-ketones (**212**; X = OR, NR_2) (*de*) at room temperature. According to experimental and theoretical studies, the high *Z* selectivity is induced by orbital interactions in the ring opening of the β-lactone enolate intermediate (**213**), rather than by the initially presumed chelation of the lithium atom.[260]



(**211**) (**212**) (**213**) (**214**)

A novel ring-expansion protocol has been developed, based on the conjugate additions of cyclic allylamines (**215**) to (*p*-toluenesulfonyl)ethyne (**216**), followed by aza-Cope rearrangement of the resulting zwitterions (**217**), to afford medium- and large-ring cyclic amines (**218**) under remarkably mild conditions.[261]

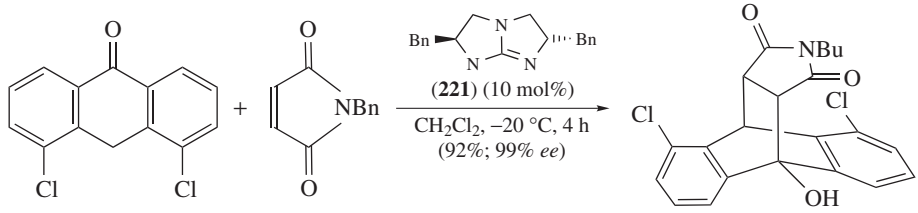


(**215**) (**216**) (**217**) (**218**)

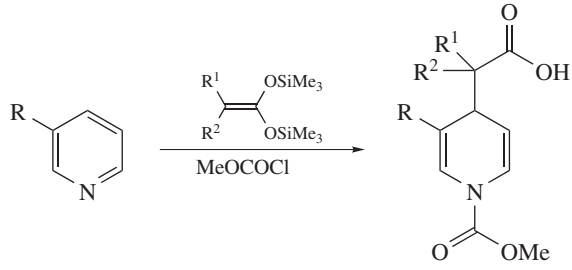
The alkylideneallyl cation, generated from the Lewis acid-mediated ring-opening reaction of alkylidenecyclopropanone acetal, has been employed in the reaction with siloxyalkenes to give 3 + 2-cycloaddition and acyclic addition products. All products resulted from a nucleophilic addition to the sp^2 centre of the alkylideneallyl cation, with no sign of the nucleophilic addition to the *sp* centre. The regioselectivity was found to be independent of the electronic and steric effects of siloxyalkene nucleophiles, and appears compatible with the charge distribution of the allylic cation.[262]

Chiral bicyclic guanidine (**221**) has been identified as an excellent catalyst for reactions between anthrones (**219**) and various dienophiles, such as (**220**). The catalyst can tolerate a range of substituents and substitution patterns, making several anthrone derivatives suitable for this reaction. Both Diels–Alder and Michael adducts were obtained in excellent yields, high regioselectivities, and high enantioselectivities ($\leq$99% *ee*). This is the first case of a highly enantioselective base-catalysed anthrone (*ee*) Diels–Alder reaction.[263]

A nucleophilic addition of bis(TMS) ketene acetals to pyridines (**223**), aided by acylation of the pyridine nitrogen with methyl chloroformate, has been reported to produce the 1,4-adduct (**224**).[264]

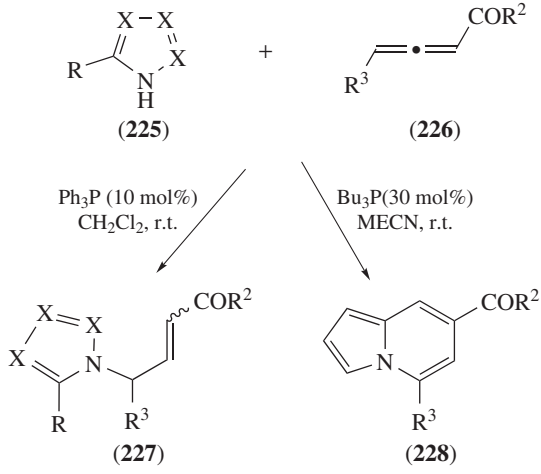


(**219**) (**220**) (**222**)



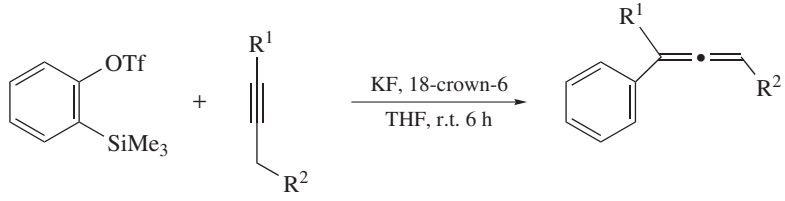
(**223**) (**224**)

Triphenylphosphine was employed as a nucleophilic catalyst for the umpolung addition of azoles (**225**) to the electron-deficient allenes (**226**; $R^1 = H$, $R^2 = OEt$, $R^3 = H$, Et) to afford the addition products (**227**). This organocatalytic methodology has been extended to addition–cyclization reactions between electron-deficient allenes or alkynes and pyrrole-2-carboxaldehyde in the presence of a catalytic amount of tributylphosphine, giving the substituted indolizine-7-carboxylates (**228**; $R^2 = OEt$, Me; $R^3 = H$, Et).[265]



(**225**) (**226**) (**227**) (**228**)

Arynes, generated *in situ* from *o*-silylaryl triflates (**229**), undergo ene reaction with alkynes (**230**) possessing propargylic hydrogen in the presence of KF–18-crown-6 in



(**229**) (**230**) (**231**)

THF at room temperature to produce substituted phenylallenes (**231**). Various arynes and terminal and internal alkynes can be used. The reaction of alkyne without propargylic hydrogen gave an acetylenic C–H addition product (a phenylalkyne) and a dehydro-Diels–Alder product (a phenanthrene).[266]

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CHAPTER 12

Addition Reactions: Cycloaddition

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The thermal intramolecular 2 + 2-cycloaddition of 4,4′-disubstituted-2,2′-bis(phenylethynyl)biphenyls (**1**) yielded the intermediate 1,2-diphenylcyclobuta[1]phenanthrenes (**2**), which could be trapped with 2,3,4,5-tetraphenylcyclopenta-2,4-dione (**3**) to produce the Diels–Alder adduct (**4**). Thermal decarbonylative ring opening of (**4**) gave 9,10,11,12,13,14-hexaphenylcycloocta[1]phenanthrenes (**5**) as the final product in 12–23% yield (Scheme 1).[1]

The reaction of 1-lithiobuta-1,3-dienes with aromatic nitriles produced substituted pyridines, pyrroles, and/or linear butadienylimines in good to excellent yields. The competition between 5-*exo* and 6-*endo* cyclization is responsible for the formation of either pyrroles or pyridines.[2]

The thermal intramolecular cycloaddition of 2-(allenyl)phenylazides furnished C(2)–C(3) and N–C(2) cyclopentannelated indoles via a cascade cyclization sequence involving an initial 3 + 2-cycloaddition, a nitrogen extrusion and a ring formation.[3] The acid-catalysed ring opening of alkylidenecyclopropanone acetal (**6**) produced 1-alkylidene-2-oxyallyl cation (**7**), which reacted with furan to yield both 3 + 2-(**8**) and 4 + 3-(**9**) cycloadducts (Scheme 2).[4] The 1,3-dipolar cycloaddition of azomethine ylides from sarcosine, with (*E*)-3-furfurylindene-4-chromanone and (*E*)-furfurylidene-1-tetralone, formed spiropyrrolidines which undergo Diels–Alder addition with DMAD to give dispiropyrrolobicyclo[2.2.1]heptanes in good yields.[5]

The tandem double intramolecular 4 + 3/3 + 2-cycloaddition of the nitroalkene (**10**) produced the nitroso acetal (**11**) in 77% yield. Further functional group manipulations allowed for the conversion to the partial core (**12**) of the complex polycyclic alkaloid daphnilactone B in high yield (Scheme 3).[6] The tandem intramolecular 4 + 2/3 + 2-cycloaddition cascade of 1,3,4-oxadiazoles (**13**) to polycyclic adducts (**14**) was investigated by considering the tethered initiating dienophile, the tethered dipolarophile, the 1,3,4-oxadiazole C(2) and C(5) substituents, the tether lengths and sites, and the central heterocycle (Scheme 4).[7]

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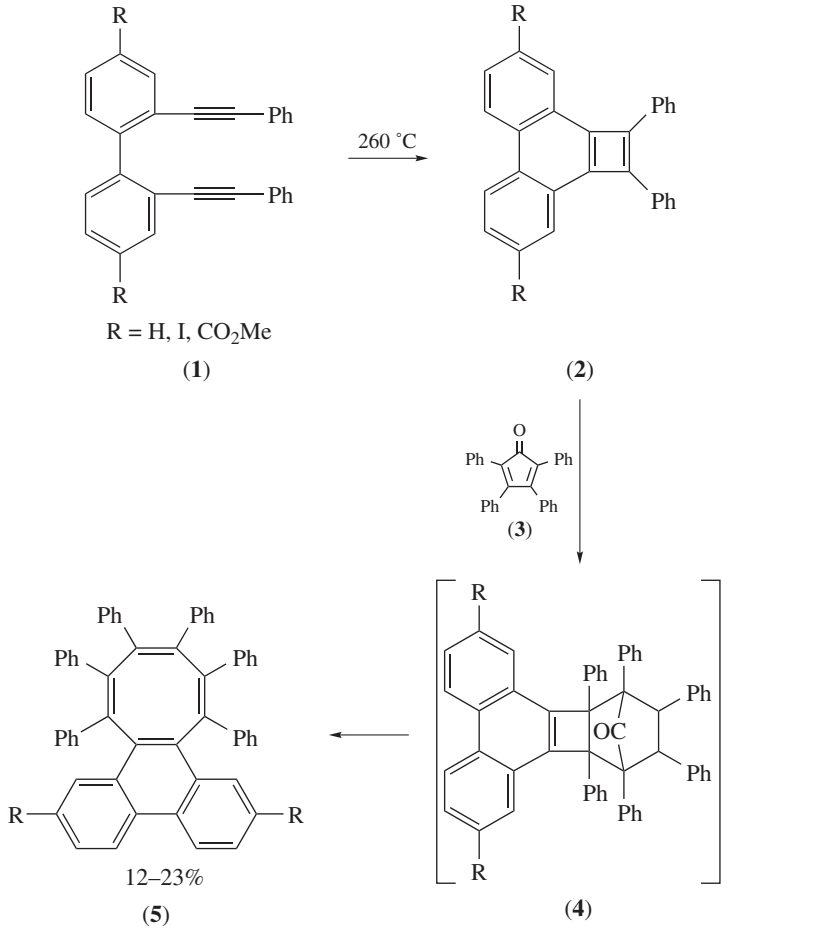
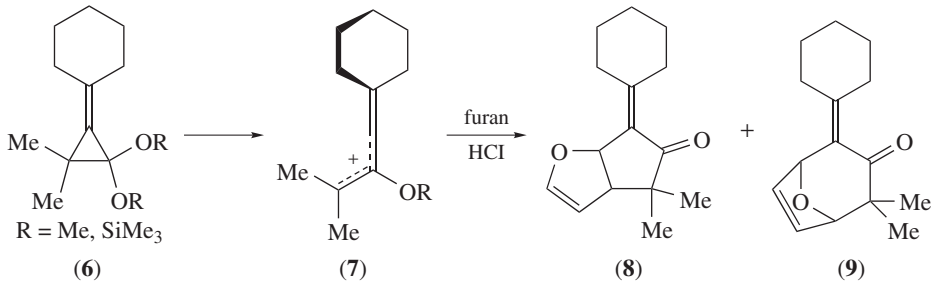
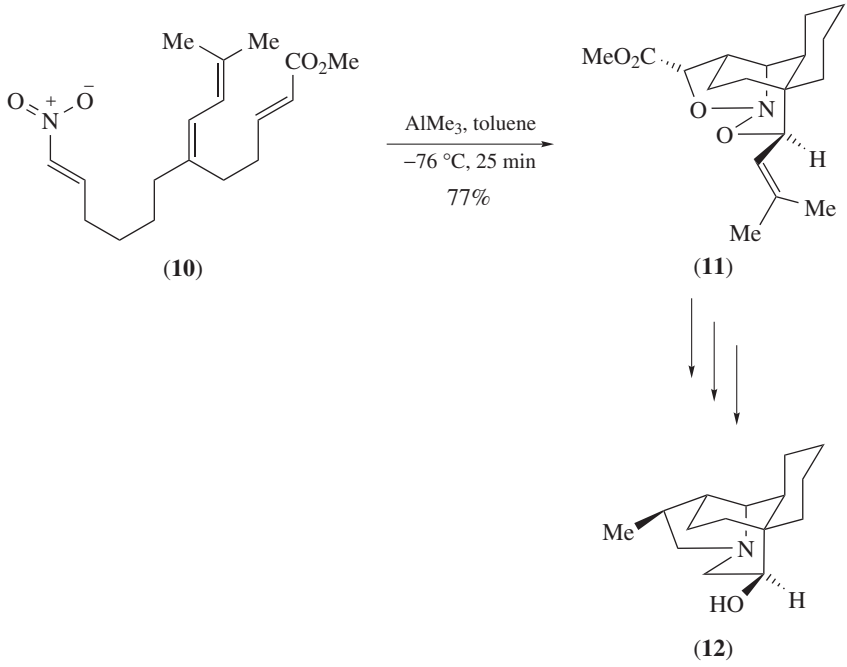


SCHEME 1

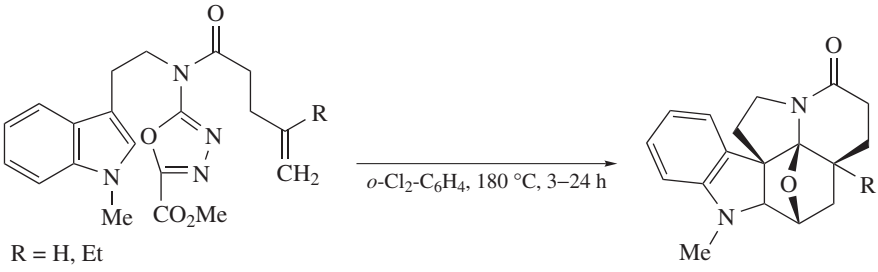


SCHEME 2



(**10**) (**11**) (**12**)

SCHEME 3



(**13**) (**14**)

SCHEME 4

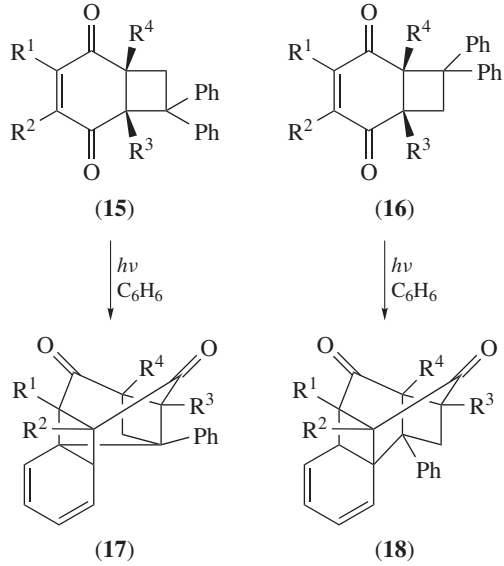
The [Rh(NHC)Cl(COD)]/$AgSbF_6$-catalysed intramolecular 4 + 2-cycloaddition of dienynes and the intramolecular 5 + 2-cycloaddition of alkyne vinylcyclopropanes formed the corresponding bicyclic cycloadducts in 91–99% yields within 10 min.[8]

2 + 2-Cycloaddition

CR-CCSD(T) calculations of the 2 + 2-cycloaddition of cyclopentyne to ethylene indicate a highly exothermic ($\Delta G_r^{298} = -68$ kcal mol^{-1}) reaction and a predominately

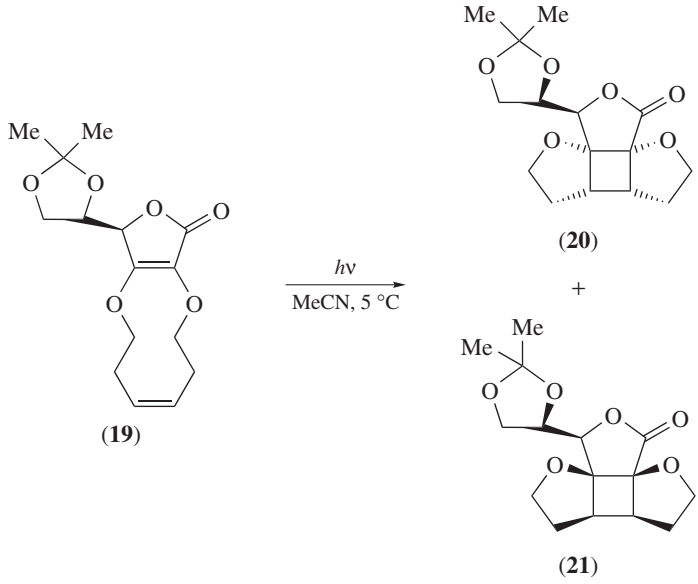
concerted process with a relatively low activation barrier.[9] Triflic imide (Tf_2NH) promoted the 2 + 2-cycloaddition of allylsilanes with electron-deficient alkenes leading to substituted cyclobutanes. Silyl triflic imide acts as the actual catalyst in this reaction.[10] The first linear free energy relationship for the thermal cyclodimerization of aromatic trifluorovinyl ethers to 1,2-disubstituted perfluorocyclobutyl compounds has been reported.[11] The thermal intramolecular 2 + 2-cycloadditions of fuller-1,6-enynes in toluene produce fused cyclobutenes as stable solids in very high yields.[12] ^{3}H NMR spectroscopy has been used successfully to determine the regioselectivity of the 2 + 2-photocycloaddition of enones to fullerene, C_{70}. The major method of photocycloaddition involves addition to the C(1)–C(2) bond of the ovoid fullerene.[13] The intramolecular 2 + 2-cycloadditions of α-substituted enones are solvent controlled. In aprotic solvents, 2′-hydroxyenones underwent cycloaddition in a manner consistent with the presence of an intramolecular H-bond between the carbonyl group and the tether's hydroxyl group. In protic solvents, the disruption of the intramolecular H-bond produced products with complementary diastereoselectivity.[14]

The photochemical intramolecular 2 + 2-cycloaddition of diphenylbicyclo[3.2.0]oct-3-ene-2,5-diones (**15**, **16**) produced pentacyclotetradeca-10,12-diene-2,7-diones (**17**, **18**), respectively. These reactions involve a triplet 1,4-biradical intermediate derived from the spin-inverted excited triplet state of the primary 1:1 adducts (Scheme 5).[15] Photoinduced 2 + 2-cycloadditions of *N*-methylnaphthalene-1,8-dicarboximide with alkynes take place at the naphthalene C(1)=C(2) bond to give cyclobutane adducts. Experiments show that these reactions proceed from the $\pi\pi^*$ singlet excited state



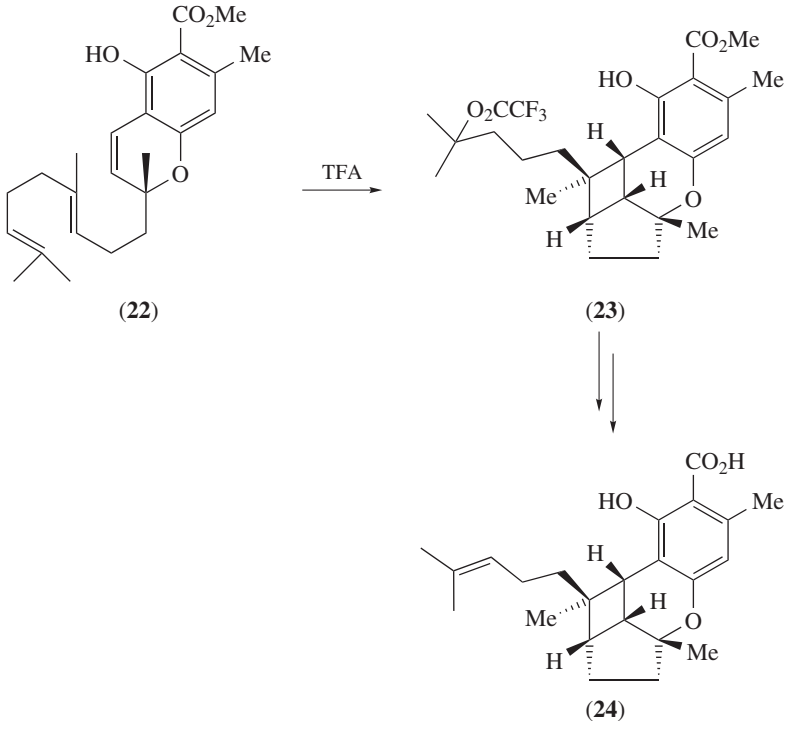
SCHEME 5

of the naphthalene.[16] Direct excitation of stilbenes and the selective excitation of the charge-transfer (CT) complex at various temperatures succeeded in diastereodifferentiating the 2 + 2-photocycloadditions of (*E*)- and (*Z*)-stilbenes to bis[(*R*)-1-methylpropyl]fumarate to produce *p*-truxinates.[17] The diastereoselective transannular 2 + 2-photocycloaddition of ascorbic acid derivatives (**19**) produced polyoxacyclic structures (**20**, **21**) in high yields with high diastereocontrol. The adducts will be tested as chiral ligands for enantioselective reactions (Scheme 6).[18]



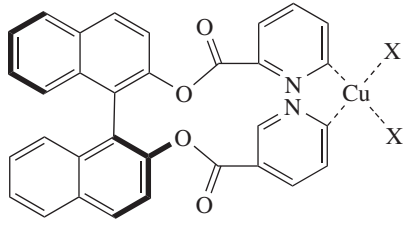
SCHEME 6

The TFA treatment of daurichromenic acid ester (**22**) produced the cyclobutane (**23**) as the major product via a Gassman-like cationic 2 + 2-cycloaddition. Further manipulation of adduct (**23**) yielded rhododaurichromanic acid A (**24**) (Scheme 7).[19] Ruthenium-catalysed 2 + 2-cycloadditions of norbornenes with alkynes produced the corresponding *exo*-cyclobutenes in good yields. Regioselectivity was observed with various substituents on the C(2) position of the norbornenes.[20,21] The chiral Rh-catalysed enantioselective 2 + 2-cycloaddition of alkynyl esters with norbornene yielded chiral tri- and tetra-cyclic cyclobutenes in moderate to high *ee*.[22] The bis(imino) pyridine iron bis(dinitrogen) complex catalysed the 2 + 2-cycloaddition of α,ω-dienes to produce the corresponding bicyclo[3.2.0] ring compounds. The redox activity of the bis(imino)pyridine ligand to maintain the ferrous oxidation state throughout the catalytic cycle has been shown to be important for reaction.[23] Ruthenium-catalysed 2 + 2-cycloaddition of C(1)-substituted 7-oxanorbornadienes with alkynes at 65 °C produced cyclobutene cycloadducts in moderate to good yields.[24–26] A new chiral copper



(**22**) (**23**) (**24**)

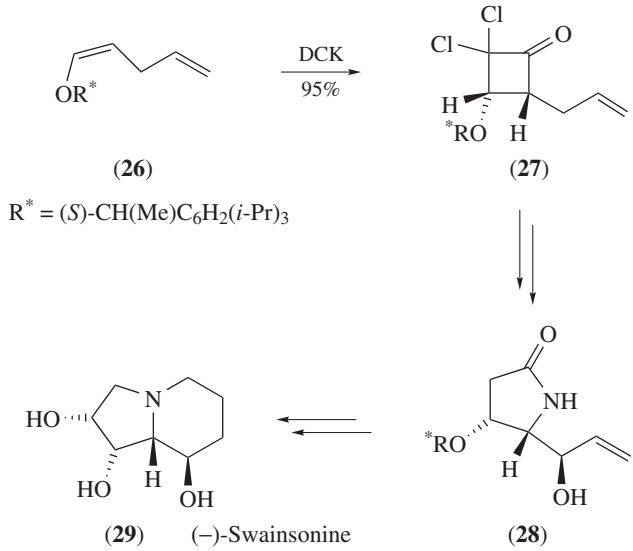
SCHEME 7



(**25**)

catalyst (**25**) promotes the 2 + 2-cycloaddition of 2-methoxycarbonylcyclopent-2-en-1-one with thioalkynes to produce substituted bicyclo[3.2.0]hept-6-enes in 67% yield and 73% *ee*. This catalytic system was applied to the enantioselective total synthesis (*ee*) of the marine prostanoid tricycloclavulone.[27]

An *ab initio* study of the 2 + 2-cycloadditions of allene to isocyanic acid and ketene to vinylimine found the reactions to be concerted and mostly asynchronous.[28,29] The diastereoselective 2 + 2-cycloaddition of dichloroketene with a chiral enol ether (**26**) produced the cyclobutanone (**27**), which leads to a key intermediate (**28**) in (*de*) the total synthesis of the natural alkaloid (−)-Swainsonine (**29**) (Scheme 8).[30] The

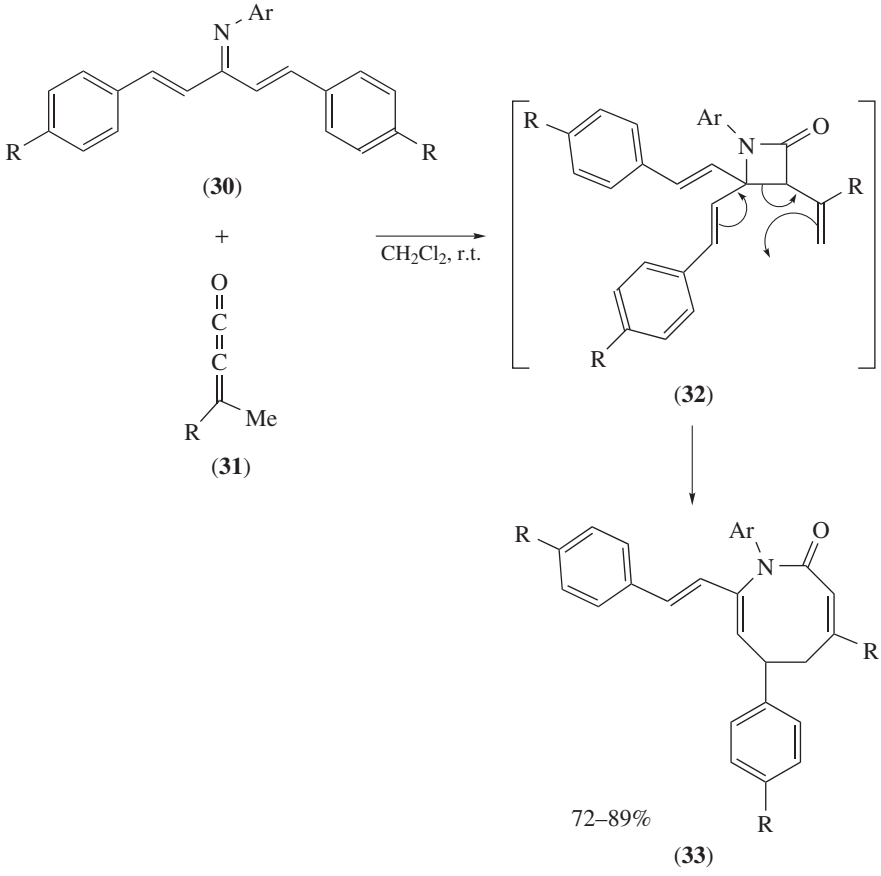


SCHEME 8

repeated 2 + 2-cycloaddition of benzyne with ketene silyl acetals provided a route to polyoxygenated tricyclobutabenzenes, e.g. tetraketone.[31] The reaction of cross-conjugated azatrienes (**30**) with conjugated ketenes (**31**) produced the intermediate 2 + 2-cycloadducts (3,4,4-trisubstituted-2-azetidinones) (**32**), which readily underwent Cope rearrangement to substituted 5,6-dihydro-1*H*-azocinones (**33**) in high yields (Scheme 9).[32] The origin of the relative stereoselectivity of the β-lactam formation in the Staudinger reaction has been investigated by using detailed Hammett analyses. The stereoselectivity is generated as a result of the competition between the direct ring closure and the isomerization of the imine moiety in the zwitterionic intermediate.[33]

(*R*)-2,2-Diphenylcyclopentanol has been used as a successful chiral auxiliary in the 2 + 2-cycloaddition of dichloroketene with acyclic enoxy-lactones.[34] The 2 + 2-cycloaddition of ynamides with ketenes produced a variety of substituted 3-amino-cyclobut-2-en-1-ones in good yields.[35] Mesoionic 1,3-dioxolium-4-olates (**34**) readily ring open to acyloxyphenylketenes (**35**), which can be trapped with ketenophiles (dihydrofuran, carbodiimides, and imines) to yield 2 + 2-cycloadducts [e.g. (**36**), (**37**)] (Scheme 10).[36] The 2 + 2-cycloaddition of four-membered endocyclic enamides (azetidines) to dichloroketene provides a new synthesis of substituted azetidine-3-carboxylic acid derivatives of interest in biological chemistry.[37]

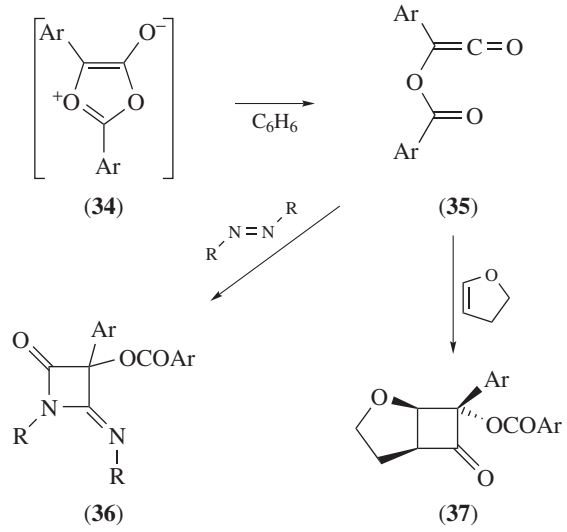
The reaction of 2-(phenylamino)- and 2-(dimethylamino)-thiazoles (**38**) with DMAD produced dimethyl 6-(phenylamino)- and 6-(dimethylamino)-3,4-pyridinedicarboxylates exclusively. The intermediate 2 + 2-cycloadduct (**39**) undergoes ring opening, 6π-electrocyclization with the extrusion of sulfur to produce the final pyridine derivatives (**40**) (Scheme 11).[38]



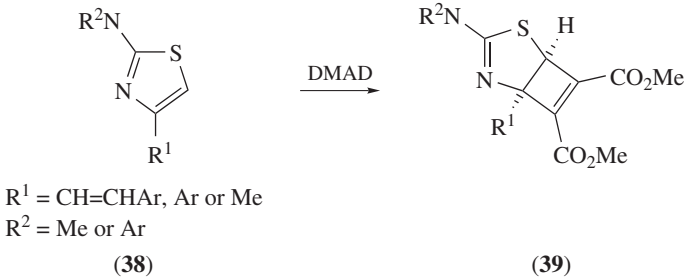
SCHEME 9

2 + 3-Cycloaddition

SCS-MP2 and the new perturbative B2-PLYP density functional methods provide accurate reaction barriers and outperform MP2 and B3-LYP methods when applied to the 1,3-dipolar cycloaddition reactions of ethylene and acetylene.[39] Phosphepine has been shown to catalyse the asymmetric 3 + 2-cycloaddition of allenes with a variety of enones (e.g. chalcones) to produce highly functionalized cyclopentenes with good enantiomeric excess.[40] The $AuPPh_3SbF_6$ complex catalysed the intramolecular 3 + 2-cycloaddition of unactivated arenyne- (or enyne)-yne functionalities under ambient conditions.[41] A review of the use of Rh(I)-catalysed 3 + 2-cycloadditions of diaryl- and arylalkyl-cyclopropenones and aryl-, heteroaryl-, and dialkyl-substituted alkynes to synthesise cyclopentadienones for use in the synthesis of natural products, polymers, dendrimers, and antigen-presenting scaffolds has been presented.[42]



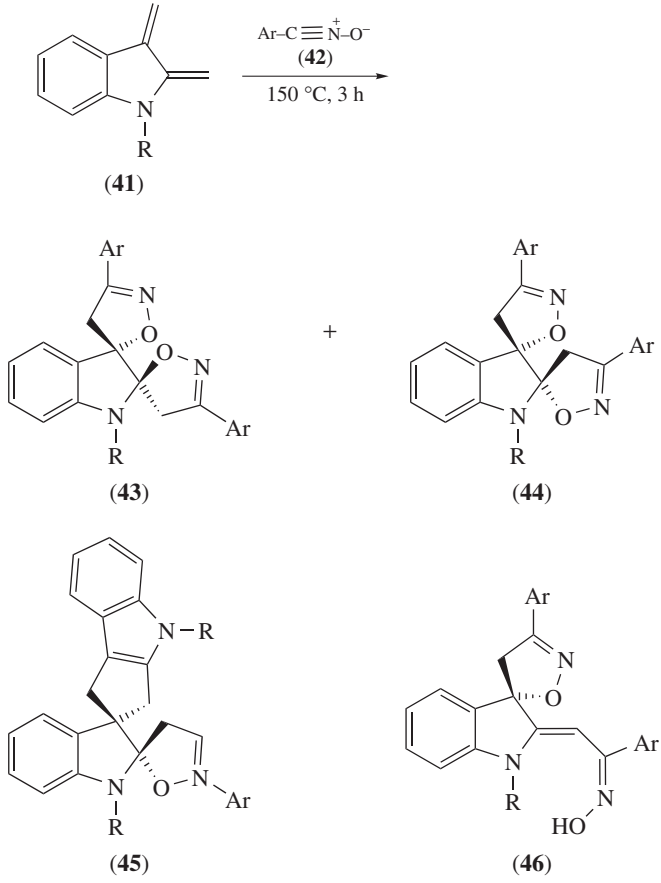
SCHEME 10



SCHEME 11

In the absence of a Lewis acid promoter, the 2 + 3-reaction between *p*-quinone monoimide and azadienes, e.g. α,β-unsaturated hydrazones yielded 2,3-dihydrobenzofurans in moderate to excellent yields when the dienophile was maintained at low concentration.[43]

A DFT study of the 1,3-dipolar cycloaddition of benzonitrile *N*-oxides with 9-methylenephthalimidines showed a concerted reaction with highly asynchronous transition states.[44] The 3 + 2-cycloaddition of aryl nitrile oxides with acetyl- and benzyl-protected *exo*-glucals or benzoylated β-D-glucopyranosyl cyanide produced glucose-derived spiroisoxazolines and 3-aryl-5-*C*-glucosyl-1,2,4-oxadiazoles. The removal of the protecting groups provided water-soluble products, which were evaluated as glycogen phosphorylase inhibitors.[45] The 1,3-dipolar cycloaddition of pentafluorophenyl-substituted imines with nitrile oxides formed pentafluoro-1,2,4-oxadiazoles in moderate to good yields.[46] The 1,3-dipolar cycloadditions of stable nitrile oxides (**42**) with indole *o*-quinodimethanes (**41**) produced the *exo-anti*-dispiroisoxazolines (**43**–**46**) in (*de*)



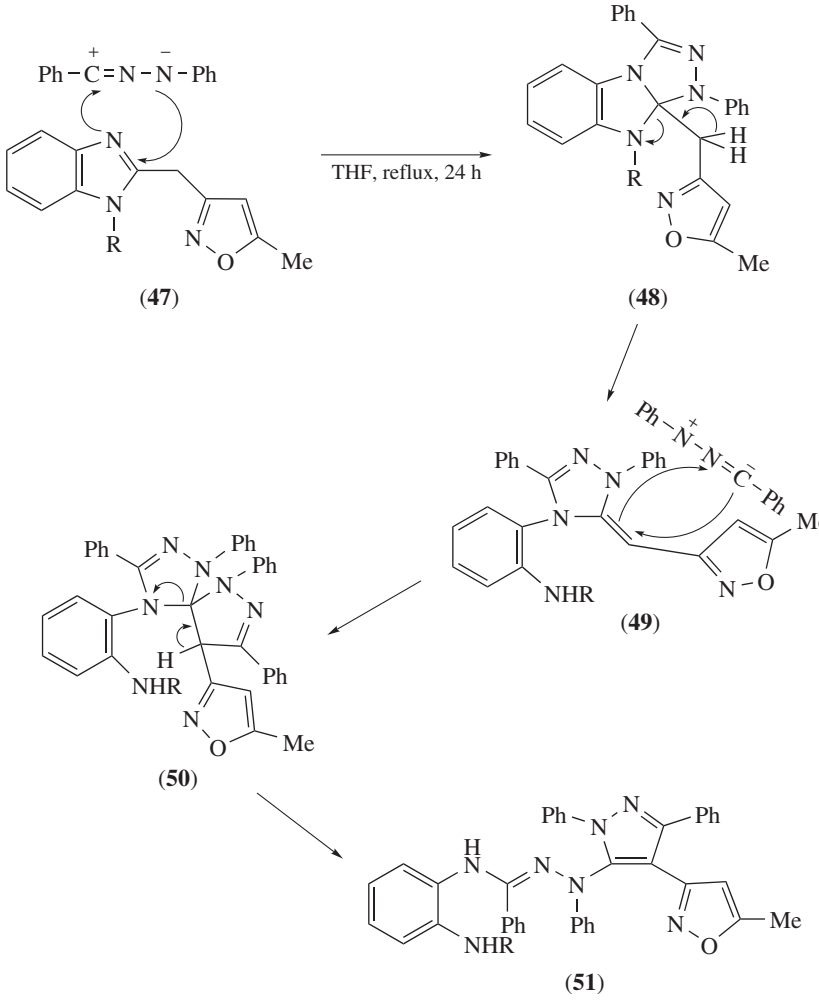
SCHEME 12

moderate to good yields (25–47%) (Scheme 12).[47] The intramolecular 1,3-dipolar cycloaddition of nitrile oxides, nitrones, and nitrile imines provided a synthesis of tetrahydroisoxazolo-, dihydroisoxazolo-, and dihydropyrazolo-fused pyrano[2,3-*b*] quinolines.[48] The thermal and microwave 1,3-dipolar cycloaddition of adamantylidenefulvene with aryl- and alkyl-nitrile oxides gave 1:1 cycloadducts, as major adducts, and four other 1:2 minor cycloadducts. The use of cyclodextrins was shown to enhance the regio- and stereo-selectivity of the cycloadditions.[49]

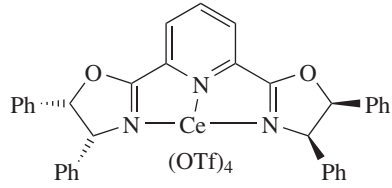
The intramolecular 1,3-dipolar cycloadditions of homochiral nitrilimines derived from methyl esters of glycine, L-alanine, L-phenylalanine, and (*S*)-2-phenylglycine produced enantiopure 2,3,3*a*,4,5,6-hexahydropyrrolo[3,4-*c*]pyrazoles in fair to good overall product yields.[50] The thermal reaction of diphenylnitrilimine with *N*-substituted benzimidazoles (**47**) produced *N*,*N*′-disubstituted *o*-phenylenediamines (**51**). The reaction involved two 1,3-dipolar cycloadditions with two nitrilimine moieties yielding adducts (**48**–**50**), followed by a ring opening of the azolic ring of (**50**) (Scheme 13).[51]

The chemo-, regio-, and stereo-selective 1,3-dipolar cycloaddition of *C*-aryl-*N*-phenylnitrones with 3,5-bis(arylidine)-1-methylpiperidin-4-ones produced mono- and bis-spiroisoxazolidines, with the former predominating.[52] The 1,3-dipolar cycloaddition of five-membered cyclic nitrones with α,β-unsaturated γ-lactones provides an interesting example of a double asymmetric induction.[53] $Eu(fod)_3$ catalysed the (ee) 1,3-dipolar cycloaddition of α-alkoxycarbonylnitrones with vinyl ethers to give *trans*-isoxazolidines in a highly stereoselective manner.[54] The bis(oxazolinyl)pyridine–cerium(IV) triflate complex (**52**) catalysed the enantioselective nitrone cycloaddition of β-substituted α,β-unsaturated 2-acylimidazoles to produce isoxazolidines products which can be effectively converted to β'-hydroxy-β-amino acid derivatives.[55] The intramolecular nitrone–alkene cycloaddition of nitrones (**53**) derived from hept-6-enoses produced fused isoxazolidines (**54**) (Scheme 14). The effect of blocking groups, the stereochemistry of the substituents and the reaction solvent on the regio- and stereo-selectivity of the cycloadditions has been investigated.[56] The 1,3-dipolar cycloaddition of cyclic nitrones with free and Pt-bound nitriles has been investigated by theoretical methods at different levels of theory. The coordination of an RCN to a Pt centre provides an even higher activation effect upon cycloaddition in comparison with the introduction of a strong electron accepting group R such as CF_3.[57]

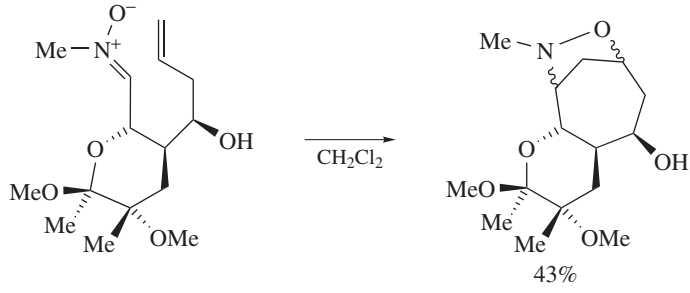
3-Substituted 1,2-diphenylcyclopropenes and 3,3-disubstituted cyclopropenes reacted with carbonyl ylides, derived by dirhodium tetraacetate-catalysed decomposition of diazocarbonyl precursors, to produce 8-azatricyclo[3.2.1.$0^{2,4}$]octanes and 9-oxatricyclo[3.3.1.$0^{2,4}$]nonanes.[58] Chiral 5-ethoxy-3-*p*-tolylsulfinylfuran-2(5*H*)-ones (**55**) reacted with 2-benzopyrylium-4-olate (**56**) to give 4,10-epoxybenzo[4,5]cyclohepta[1,2-*c*]furan-3,9-diones (**57**, **58**) in good to moderate yields with high regioselectivity (Scheme 15).[59] 2,6-Bis(oxazolinyl)pyridine–lanthanoid complexes catalysed the asymmetric 3 + 2-cycloaddition reactions of 2-benzopyrilium-4-olates with 3-(alk-2-enoyl)-2-oxazolidinones to yield cycloadducts, substituted (2-oxazolidinoyl)carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-ones with high enantioselectivity (96% *ee*) and (ee) *endo* selectivity (>99:1).[60] The 3 + 2-cycloaddition of mesoionic acyclic C-nucleoside (de) 1,3-thiazolium-4-olates (**59**), derived from δ-gluconolactone, with acetylenic (**60**) and



SCHEME 13

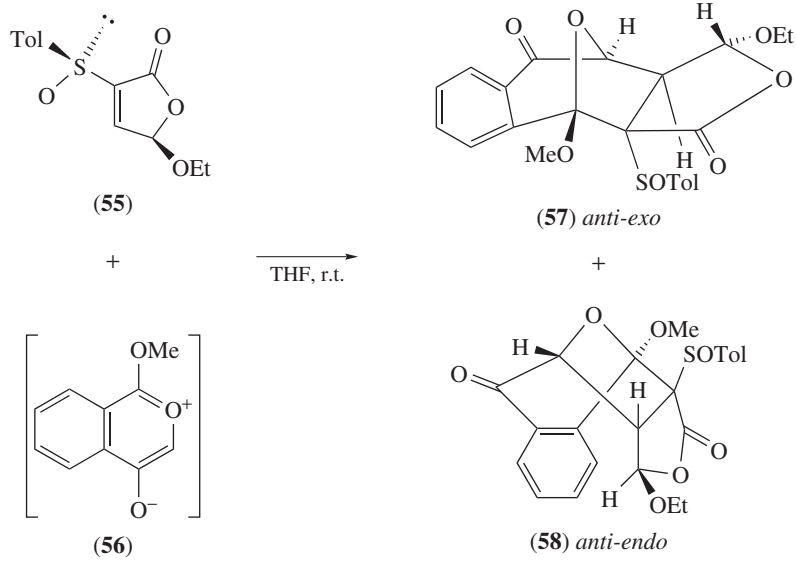


(**52**)



(**53**) (**54**)

SCHEME 14



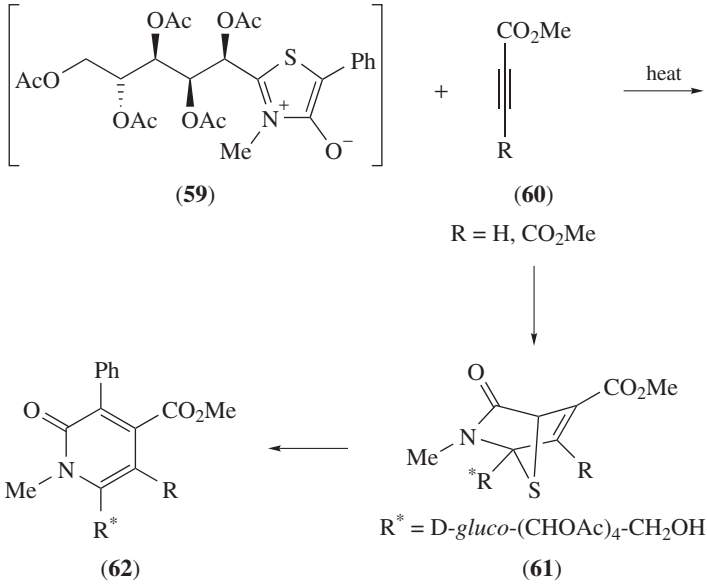
(**55**) + (**56**)

(**57**) *anti-exo* + (**58**) *anti-endo*

SCHEME 15

olefinic dipolarophiles produced substituted 2-aza-7-thiabicyclo[2.2.1]heptenes (**61**) and heptanes. On sulfur extrusion, the cycloadducts formed enantiomerically pure acyclic C-nucleosides (**62**) containing a pyridin-2-one moiety. These cycloadditions proved to be regioselective but showed no facial selectivity (Scheme 16).[61]

The palladium-catalysed intramolecular 3 + 2-cycloaddition of alk-5-enylidenecyclopropanes produced a variety of bicyclo[3.3.0]octane systems with up to three stereocentres.[62] The oxidative addition of cyclopropyl phenyl ketone to $Ni(Pcy_3)$ gave nickeladihydropyran, which is a key intermediate in the Ni(0)-catalysed homo-

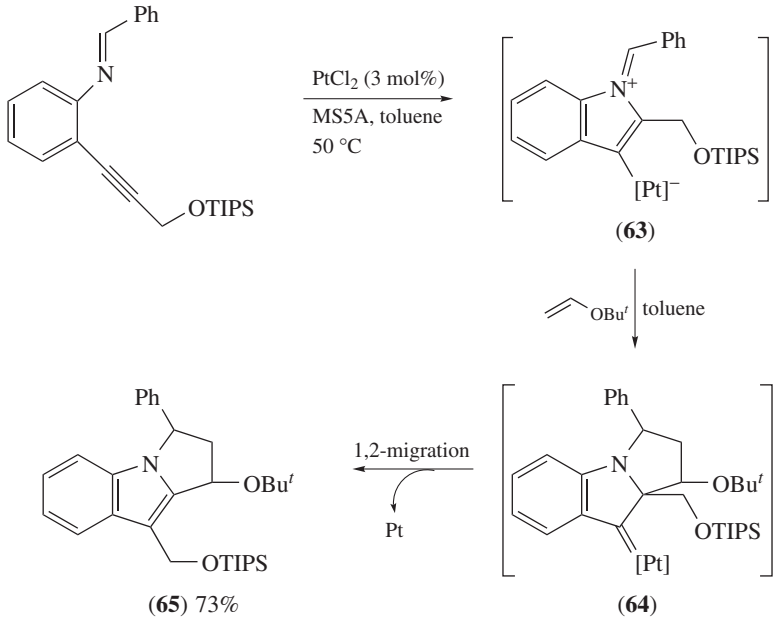


Scheme 16

or hetero-cycloaddition to give substituted cyclopentanes having two carbonyl substituents at the 1,3-position.[63] The palladium-catalysed asymmetric 3 + 2-trimethylenemethane cycloaddition of 3-acetoxy-2-trimethylsilylmethylprop-1-ene with di- and tri-substituted alkenes produced *exo*-methylenecyclopentanes in 59–99% yields and (*ee*) enantiomeric excesses from 58 to 92% *ee*.[64]

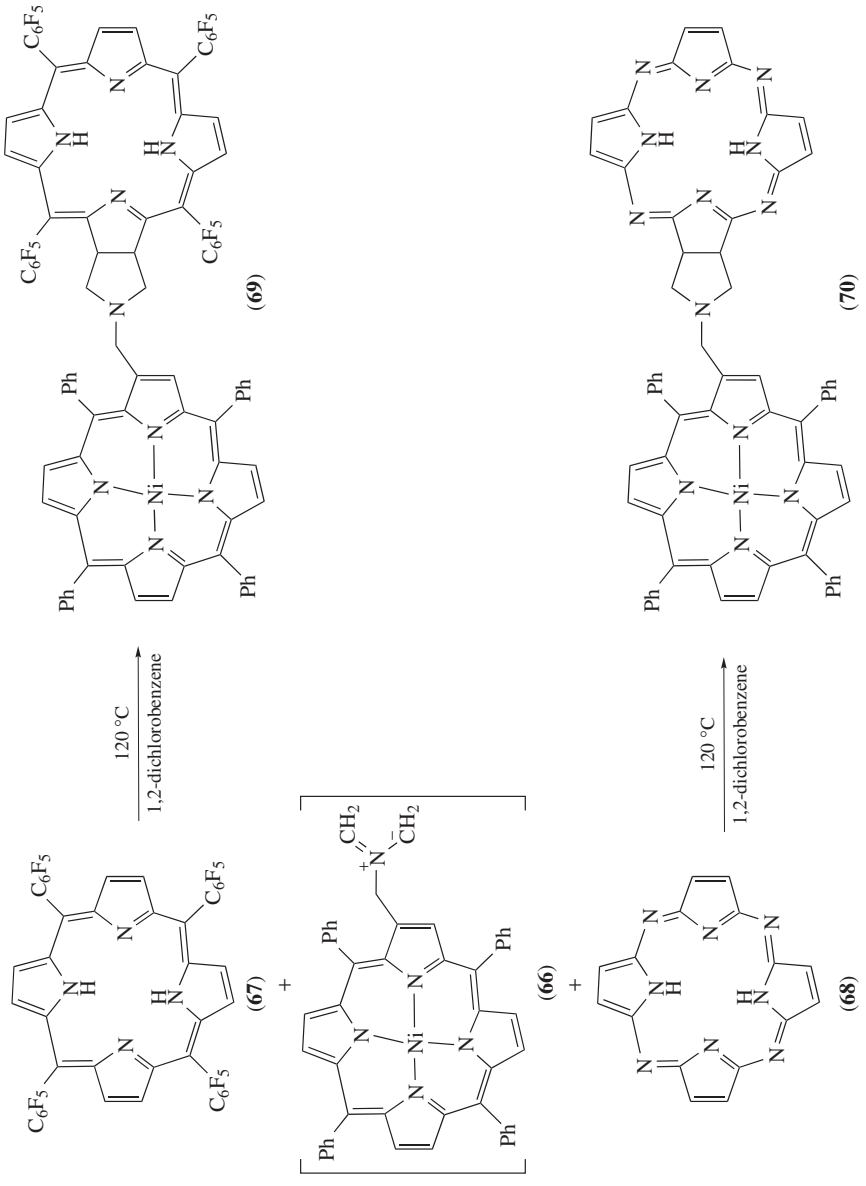
In the absence of organic solvents, $Sc(OTf)_3$ catalysed the cycloaddition of aziridines to nitriles to produce substituted imidazolines in good to excellent yields at room temperature and in an air atmosphere. The reaction is believed to progress through a highly reactive cationic intermediate in which the aziridine nitrogen is coordinated to $Sc(OTf)_3$.[65] The phosphine-catalysed enantioselective 3 + 2-cycloaddition of buta-2,3-dienoates with arylimines yielded 2-aryl-3-pyrrolidines with 64% *ee*.[66] (*ee*)

Supercritical carbon dioxide with a minute co-solvent addition is an effective medium for the 1,3-dipolar cycloaddition of azomethine ylides with DMAD to produce substituted pyrroles.[67] The 1,3-dipolar cycloaddition of nitrile ylides [e.g. benzonitrile (4-nitrobenzylide) and 4-nitrobenzonitrile(benzylide)] with acrylamides provided a synthesis of 3,4-dihydro-2*H*-pyrroles with moderate to good yields.[68] The Pt(II)- or Au(III)-catalysed 3 + 2-cycloaddition of the transition metal-containing azomethine ylide (**63**) with electron-rich alkenes provided a carbene complex (**64**), which yields tricyclic indoles (**65**) having a substituent at 3-position (Scheme 17).[69] The 1,3-dipolar cycloadditions of azomethine ylides with aryl vinyl sulfones are catalysed by (*de*) $Cu(MeCN)_4ClO_4$–Taniaphos with nearly complete *exo*- selectivity and enantioselectivities up to 85% *ee*.[70] The 3 + 2-cycloaddition of benzo[*b*]thiophene 1,1-dioxide (*ee*)

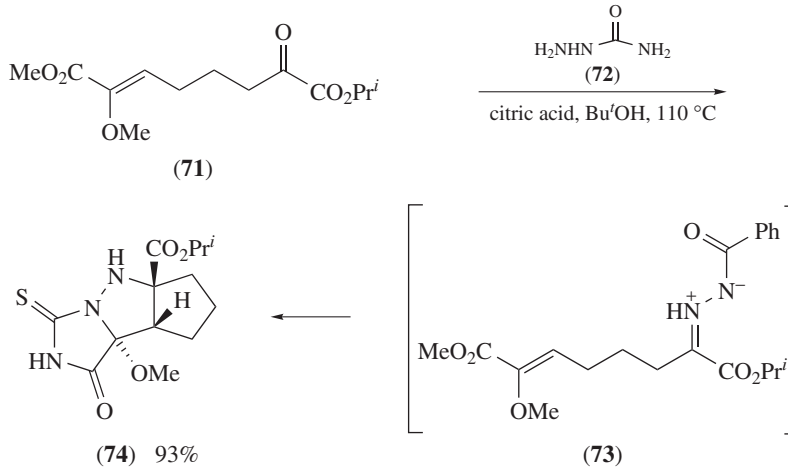


SCHEME 17

with stabilized and non-stabilized azomethine ylides yielded new pyrrolo derivatives of benzo[*b*]thiophene 1,1-dioxide.[71] 3-Methylsulfanyl-2-arylazo-3-(pyrrolidin-1-yl)acrylonitriles reacted with *N*-substituted maleimides to form 3 + 2-cycloadducts, 3-methylenepyrrolizidines, via pyrrolidine-derived azomethine ylides.[72] *N*-(Porphyrin-2-ylmethyl)glycine is a precursor of the azomethine ylide (**66**), which underwent 3 + 2-cycloaddition with *meso*-tetrakis(pentafluorophenyl)porphyrin (**67**) and tetraazaporphine (**68**) to yield porphyrin–chlorin (**69**) and porphyrin–tetraazachlorin (**70**) dyads, respectively (Scheme 18).[73] The reaction of alkene-tethered α-ketocarboxylic acid derivatives (**71**) with monosubstituted hydrazines (**72**) produced azomethine imines (**73**). These dipoles underwent thermal or Lewis acid-catalysed intramolecular 1,3-diploar cycloaddition to produce highly substituted *cis*-cyclopentapyrazolidines (**74**). This work was directed towards the total synthesis of the diguanidine alkaloid massadine (Scheme 19).[74] For the first time, the Cu(I)-catalysed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with nitroalkenes has been reported. By using electron-rich or electron-deficient aryl groups on the P atom of the chiral *P*,*N*-ferrocenyl ligands, high yields of either *exo*- or *endo*-adducts can be obtained, respectively.[75] The 1,3-dipolar cycloadditions of the imines of 2-amino-γ-lactones and thiolactones are catalysed by a mixture of AgOAc or Ag_2O and NEt_3 or DBU to produce spiro-lactone/thiolactone cycloadducts as single cycloadducts in good yields. In all cases, the imines generated the corresponding metallo-azomethine ylide stereoselectively.[76]


120 °C
1,2-dichlorobenzene
(67)
(66)
(68)
(69)
(70)
120 °C
1,2-dichlorobenzene

SCHEME 18

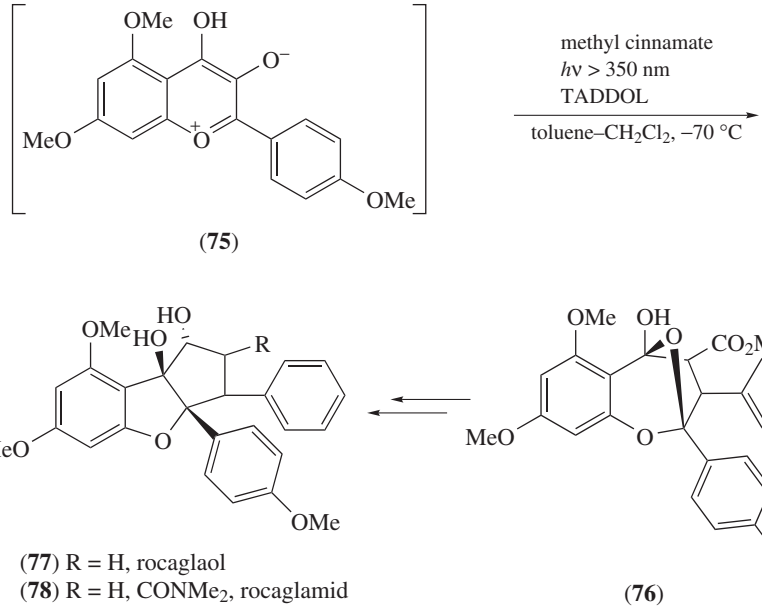


SCHEME 19

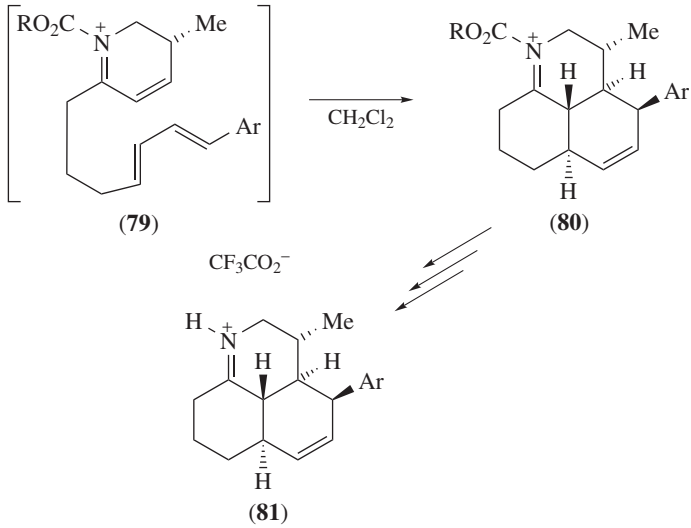
The 1,3-dipolar cycloaddition of homochiral 1-benzyl-2-phenyl-3-oxidopyridinium betaine with electron-withdrawing alkenes produced 8-azabicyclo[3.2.1]oct-3-en-2-ones. Excellent diastereofacial selectivity was exhibited for the major 6-*exo* cycloadducts.[77] The enantioselective 1,3-dipolar cycloaddition of the 3-oxidopyrylium betaine (**75**) with methyl cinnamate in the presence of a Brønsted acid, TADDOL, produced the key intermediate cycloadduct (**76**). Further elaboration of the intermediate (**76**) achieved the synthesis of the natural products rocaglaol (**77**) and rocaglamide (**78**) in good yields and high *ee* (Scheme 20).[78] The intramolecular Diels–Alder reaction of *N*-alkoxycarbonyl-2,3-dihydropyridinium cation (**79**) gave exclusively the *endo*-adduct (**80**), which could be converted to the tricyclic compound (**81**) possessing symbioimine stereochemistry (Scheme 21).[79]

It has been reported that the cycloaddition of arylimines with nitrosoalkenes proceeds in a 3 + 2-manner, whereas alkylimines cycloadd to nitrosoalkenes in a competitive 3 + 2- and 4 + 2-manner.[80] The alkylative 3 + 2-cycloaddition of nitrosoarenes with alkynes, phenylacetylene and methyl propiolate, in the presence of K_2CO_3–Me_2SO_4 produced *N*-methoxyindoles in high yields. This procedure has been used to prepare the Wasabi phytoalexins, 3-carboxy-*N*-alkoxyindoles.[81]

A kinetic study of the primary 1,3-dipolar cycloaddition of *meta*- and *para*-substituted diphenyldiazomethanes with fullerenes C_{60} and C_{70}, showed that fullerene C_{60} was ca 1.5 times more reactive than C_{70}.[82] The copper-catalysed 3 + 2-cycloaddition of *N*-benzyl-*N*-tosylynamides with azides yielded 1-substituted 4-amino-1,2,3-triazoles in high yields and high regioselectivity.[83] The $CuSO_4.5H_2O$-catalysed 3 + 2-cycloadducts of benzyl azide with terminal di-, tri-, and tetra-ynes produced 4-alkynyl, 4-butadiynyl-, and 4-hexatriynyl-triazoles in good yields. No evidence of multiple addition to the polyyne framework was observed.[84] The $Cp^*RuCl(PPh_3)_2$-catalysed 3 + 2-cycloaddition of azides to unsymmetrical internal alkynes in refluxing benzene formed 1,4,5-trisubstituted-1,2,3-triazoles in good yields.[85] A titanium



SCHEME 20



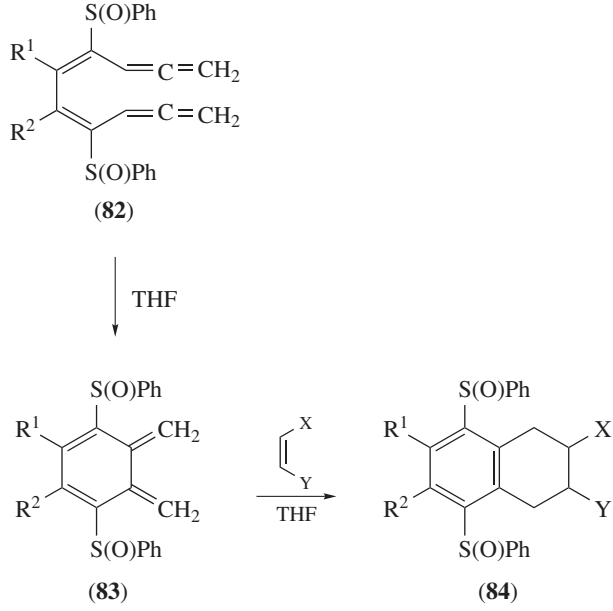
SCHEME 21

BINOL-catalysed enantioselective 1,3-dipolar cycloaddition between α-substituted acroleins and alkyl diazoacetates yielded chiral 2-pyrazolines with 95% *ee*. This methodology has been used to synthesise manzacidin A.[86] (*ee*)

2 + 4-Cycloaddition

The activation enthalpies for the Diels–Alder reactions of cyclopentadiene and 9,10-dimethylanthracene with cyanoalkenes have been computed by the Hartree–Fock quantum method and a variety of density functionals (B3LYP, BPW91, and WPW1K) and compared with experimental data. This work identified significant errors in B3LYP activation enthalpies involving cyano groups, whereas HF and WPW1K reproduce substituent effects fairly accurately.[87] The halogenation of dienes is beneficial in Diels–Alder reactions, increasing both the rates and yields of these reactions. The trifluoromethyl group shows comparable effects to halogen at the 2-position of furan.[88] Also, the incorporation of a halogen in the 3- or 5-position of *N*-alkenyl-substituted furanylamides increased the reaction rate of the intramolecular Diels–Alder reactions.[89]

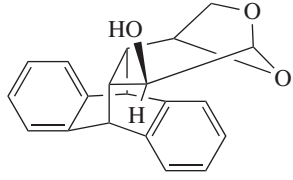
In a recent re-examination of the thermolysis of benzocyclobutenes for the *in situ* generation of *o*-quinodimethanes, the resultant IMDA diastereoselectivity was highly dependent on the nature of the hydroxyl protective group.[90] The intramolecular 4 + 2-cycloaddition of *o*-quinodimethanes (**83**), derived from ene-bis(sulfinylallenes) (**82**), with electron-deficient and electron-rich alkenes produced the corresponding polycyclic aromatic compounds (**84**) (Scheme 22).[91] The enantioselective Diels–Alder (*de*)



Scheme 22

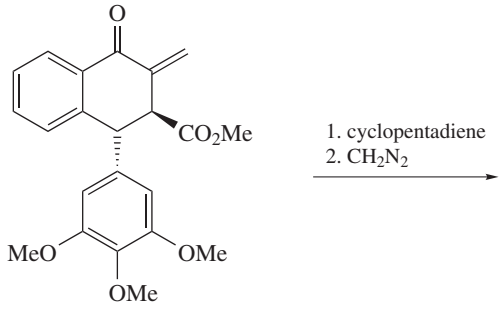
reaction of *o*-quinodimethanes with fumaric acid esters was achieved by utilizing (ee) diisopropyl (*R*,*R*)-tartrate as a chiral auxiliary.[92]

DFT studies have been used to investigate the 4 + 2-cycloaddition of ethyl 3,3-difluoro-2-(*N*,*N*-diethylcarbamoyloxy)prop-2-enoate with furan and substituted furans in the presence of tin(IV) catalyst. In the presence of $SnCl_4$ and polar solvents, a two-step reaction was predicted.[93] The catalytic effect of Lewis acids in the Diels–Alder reaction between methylacrolein derivatives and cyclopentadiene can be explained through the analysis of the electrophilicity effect of the regents and the molecular structure of the corresponding transition structures.[94] The chiral auxiliary (**85**), derived from levoglucosenone, has been used as a chiral template in the Diels–Alder reaction of the corresponding acrylic ester derivative with cyclopentadiene. The reaction showed excellent diastereoselective excess with Et_2AlCl even at room temperature.[95] (de) The Diels–Alder reactions of 3-phosphonopropenoyl derivatives of 1,3-oxazolidin-2-ones with cyclic and acyclic dienes are highly stereoselective.[96] The Diels–Alder cycloadditions of the natural cyclolignins thuriferic acid and epithuriferic acid with cyclopentadiene have been reinvestigated. In the case of thuriferic acid (**86**), all four possible α,β-isomers (**87**–**90**) were isolated and characterized, while with epithuriferic acid only the β-isomers were isolated and identified (Scheme 23).[97] The cycloaddition of zirconacyclopentadienes to *p*-quinones in the presence of CuCl–*p*-chloranil produced higher *p*-dihydroquinones in high yields (65–79%).[98] The intramolecular 4 + 2-cycloaddition of reactions of *N*-(*o*-ethynyl)phenylynamides with arylynamides yielded carbazoles and benzannulated and heteroannulated carbazoles in moderate to good yields.[99] Aromatic ketones have been used as photosensitizers in the Diels–Alder reactions between indoles and cyclohexa-1,3-dienes (CHD). Theoretical calculations support a stepwise mechanism involving a triplet ternary complex arising from a nearly barrierless reaction between CHD and the exciplex.[100]

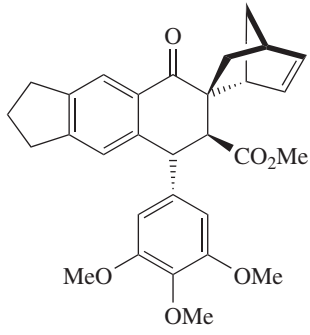


(**85**)

The influence of Lewis acids on the 4 + 2-cycloaddition of (2*R*,2′*R*)-*N*,*N*′-fumaroylbis[fenchane-8,2-sultam] with cyclopentadiene and cyclohexadiene was investigated by IR studies of the sultam compexes with various Lewis acids.[101] The first enantioselective silicon Lewis acid catalyst (**91**) catalysed the Diels–Alder cycloaddition of methacrolein and cyclopentadiene with 94% *ee*.[102] [$AlCl_3$ + 2THF] is a new and efficient catalytic system for the Diels–Alder cycloaddition of α,β-unsaturated carbonyl compounds with dienes under solvent-free conditions.[103] Dendritic copper(II) triflate catalysts with a 2,2′-bipyridine core (**92**) increased the chemical yields of Diels–Alder adducts.[104] (ee)

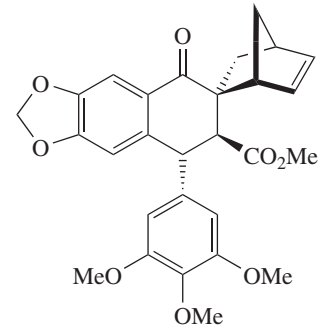


(**86**)

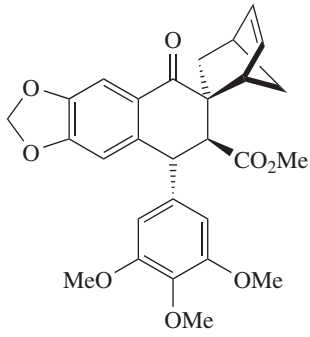


(**87**) *α-exo*

+

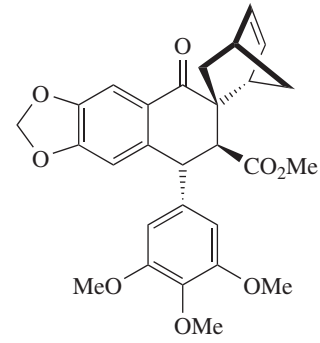


(**88**) *β-exo*



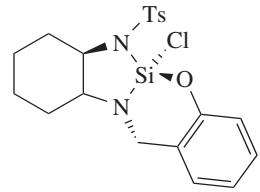
(**89**) *β-endo*

+

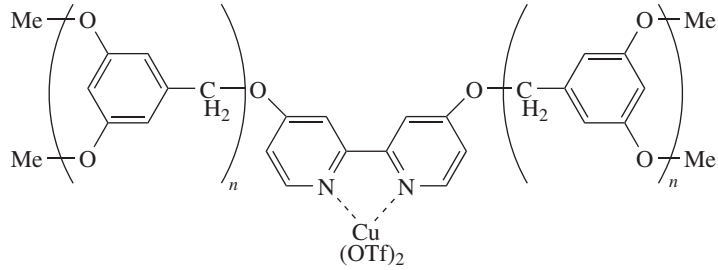


(**90**) *α-endo*

SCHEME 23



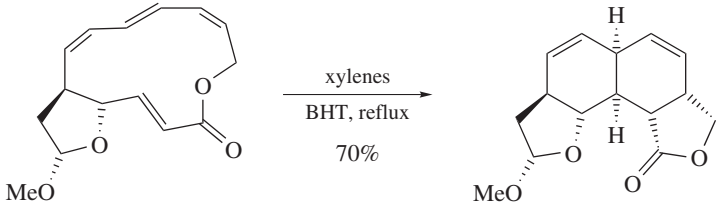
(**91**)



$n = 1, 2, 3$

(**92**)

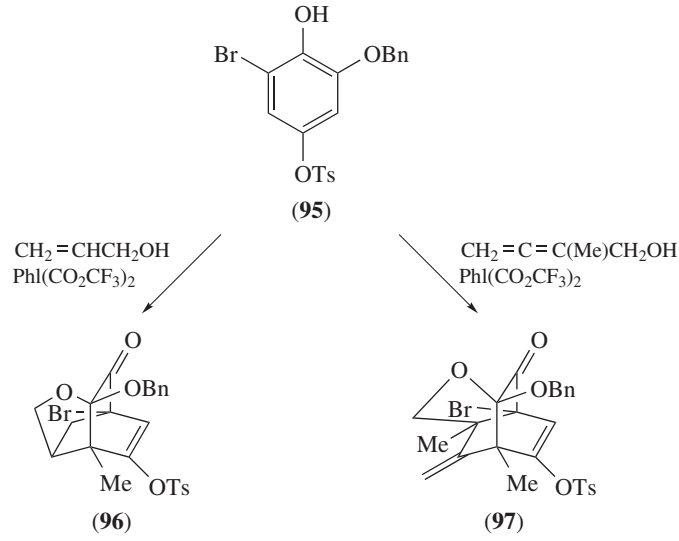
The key intermediate (**94**), in the projected synthesis of the antibiotic branimycin, was prepared by the transannular Diels–Alder reaction of the macrocyclic tetraene (**93**) in 70% yield (Scheme 24).[105] The hypervalent iodine-mediated oxidative dearomatization–Diels–Alder cascade was investigated as a means of preparing the [2.2.2]bicyclic core of the natural product tashironin. Trapping of allyl alcohols during the oxidative dearomatization of phenol (**95**) produced the desired five-membered acetal (**96**), whereas trapping of the allenyl alcohols resulted in the undesired six-membered acetal (**97**) (Scheme 25).[106] The configuration of the stereogenic C(3) centre bearing the protected hydroxyl group is crucial to the diastereoselectivity in the IMDA reaction (*de*) of (*E*,*E*,*E*)-nona-1,6,8-trienes leading to products containing the bicyclo[4.3.0]non-2-ene carbon skeleton.[107] A DFT study of the intramolecular Diels–Alder reaction of vinyloxocarbenium ions has shown that torsional steering is responsible for the stereoselectivity exhibited during cycloaddition.[108]



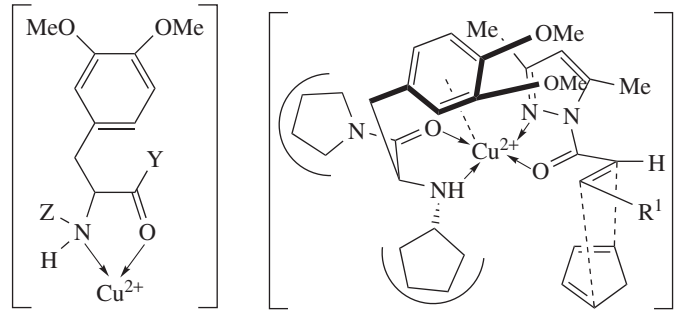
(**93**) (**94**)

SCHEME 24

Binuclear complexes with calixarene-like [$M_2(\mu\text{-}L')$ (L^1)] structures have been used to accelerate the Diels–Alder reaction between sorbic acid and acrylonitrile. The reaction between the coordinated sorbinate co-ligand and acrylonitrile is controlled by the binding cavity of the complexes and is highly regioselective.[109] Treating serum albumins, BSA or HAS, with phthalocyanine–Cu(II) complexes produced Lewis acid cat- (*ee*) alysts for highly enantioselective Diels–Alder reactions of azalactones with cyclopentadiene in aqueous medium.[110] The L-DOPA-derived monopeptide (Y = NR_2)–Cu(II) complex (**98**) catalysed the enantioselective Diels–Alder reaction of α,β-unsaturated (*ee*)



SCHEME 25



1-acyl-3,5-dimethylpyrazoles with cyclopentadiene. A transition-state assembly (**99**) has been proposed based on the crystal structure of known bis(L-tyrosino)–Cu(II) complex.[111] A chiral Sn(IV) aryl oxide has been designed as a mild Lewis acid catalyst for enantioselective Diels–Alder reactions of cyclopentadiene with α,β-unsaturated aldehydes.[112] (*ee*)

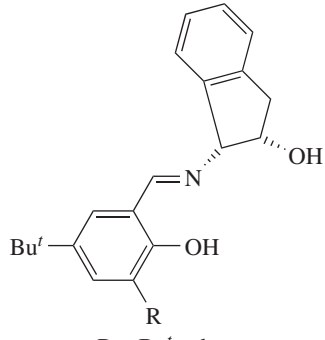
The hyperbaric 4 + 2-cycloaddition of 1,2,4-trioxegenated 1,3-dienes with dienophiles, *N*-phenylmaleimide, and methyl and phenyl acrylates produced the expected *endo*-cycloadducts with excellent stereo- and regio-control.[113] The high-pressure Diels–Alder reactions of 3-substituted coumarins with methylbuta-1,3-dienes in water formed tetrahydro-6*H*-benzo[*c*]chromen-6-ones in high yields (85–95%).[114] (*de*)

Hydrophobic effects have been shown to dominate the geometries of the transition states for the simple Diels–Alder reactions of cyclopentadiene and methyl acrylates (*de*)

in water.[115] In salt solutions, hydrophobic effects are dominant over secondary orbital interactions for Diels–Alder reactions between cyclopentadiene and methyl *trans*-crotonate.[116] Protic imidazolium ionic liquids have been used as reaction media for the Diels–Alder reaction of cyclopentadiene with dimethyl maleate and methyl acrylate.[117]

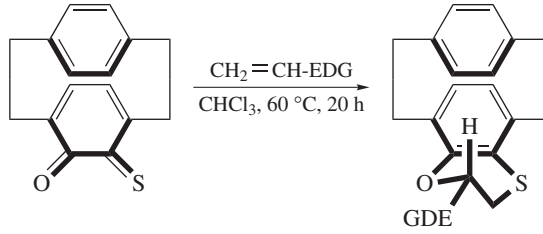
The AuCl-catalysed 4 + 2-cycloaddition of benzyne with *o*-alkynyl(oxo)benzenes produced anthracene derivatives having a ketone in the 9-position, in good to high yields under mild conditions.[118] Hypervalent iodine compounds, [5-acyl-2-(trimethylsilyl)]iodonium triflates, readily yielded acylbenzynes which could be trapped with furan.[119] Both DMAD and benzyne reacted with borabenzene to yield substituted borabarrelenes and borabenzobarrelenes, respectively.[120]

A DFT study of the Lewis acid-catalysed hetero-Diels–Alder reaction of vinylallenes with aldehydes found that the reaction proceeds via a highly asynchronous polar transition state; *endo–exo* mixtures were obtained in all cases.[121] A computational study at the B3LYP/TZVP//B3LYP6–31G* level of the hetero-cycloadditions of *o*-thioquinones with 1,3-dienes has been published. The 2 + 4-cycloadditions are favoured kinetically, whereas the 4 + 2-cycloadditions are favoured thermodynamically.[122] Hetero-Diels–Alder reactions, e.g. between Danishefsky's diene and benzaldehyde, are effectively catalysed by cage-shaped borate esters, although open-shaped borates are not catalytic.[123] The chiral copper(II) Schiff base complexes (**100**) catalysed the enantio- and diastereo-selective hetero-Diels–Alder reactions of Brassard diene with aldehydes to produce 5-methyl-containing α,β-unsaturated δ-lactones in moderate yields, high enantioselectivites (>99% *ee*) and excellent diastereoselectivities (99:1 *anti*:*syn*).[124] The TADDOL-catalysed enantioselective oxa-Diels–Alder reaction of Danishefsky's diene with benzaldehyde produced 2-phenyl-2,3-dihydro-4*H*-pyran-4-one, through hydrogen-bonding activation, in moderate yield and good enantioselectivity. Calculations at the B3LYP/31G*:PM3 level indicated that this reaction proceeds through a concerted method via an asynchronous and zwitterionic TS.[125] The chiral *N*-heterocyclic carbene-catalysed 1-oxadiene Diels–Alder reaction of unsaturated α-keto esters with dienes derived from α-chloroaldehydes formed 3,4,6-trisubstituted dihydropyran-2-ones in 70–95% yields and up to 99% *ee*. The reaction conditions are mild using 1 mol% *N*-mesityltriazolium salt as precatalyst in EtOAc



R = Bu^t, adam

(**100**)



(**101**) (**102**)

SCHEME 26

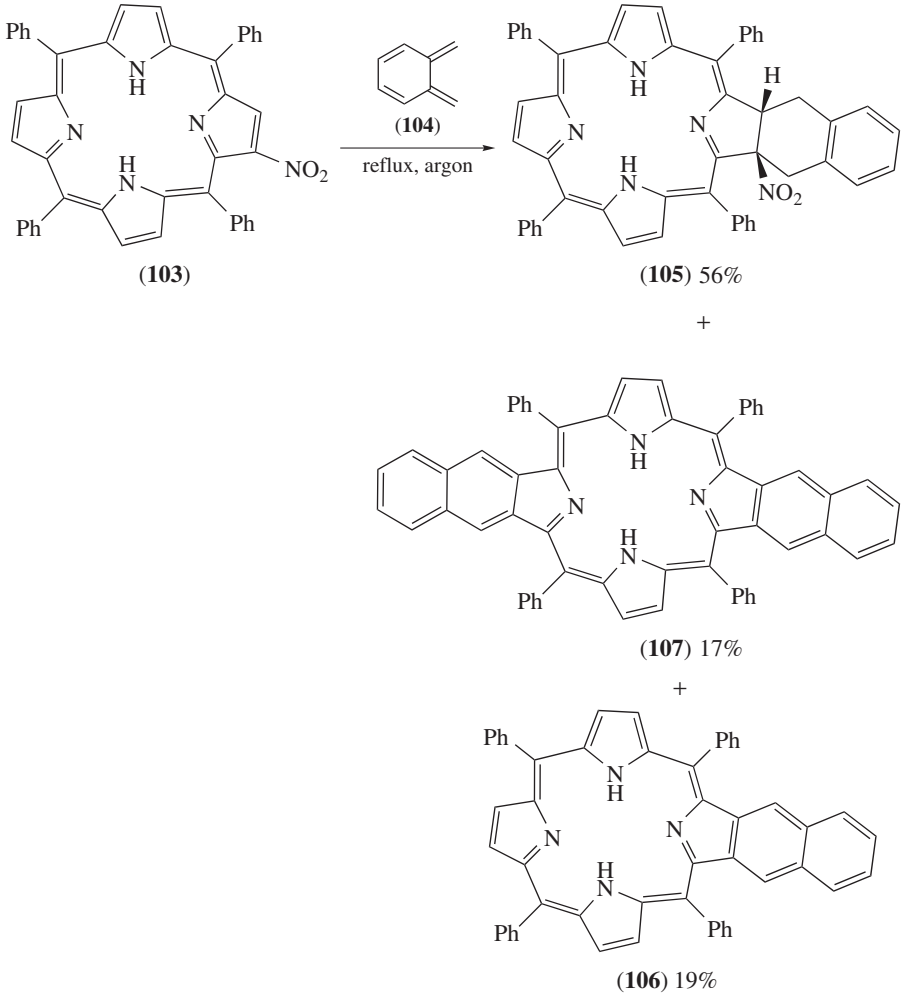
at room temperature.[126] The inverse-electron-demand hetero-Diels–Alder reaction of paracyclophane-*o*-thioquinone (**101**) with electron-rich alkenes produced the expected benzoxathiin cycloadducts (**102**) with complete control of regio- and stereo-chemistry (Scheme 26).[127] (*de*)

The hetero-Diels–Alder reaction between 1-aza-3-siloxybuta-1,3-dienes, including α,β-unsaturated oximes and hydrazones, with electron-deficient alkynes yielded tri- and tetra-substituted pyridines containing a C(3) oxygen functionality. These investigations were directed towards the total synthesis of nosiheptide.[128] A highly regio-, diastereo-, and enantio-selective aza hetero-Diels–Alder reaction has been developed using 2-azopyridine and silver(I)–BINAP (2:1) catalyst to produce a number of chiral 1,4-diamines of pharmaceutical importance.[129] A detailed study of the diastereoselective Diels–Alder reactions of *N*-sulfonyl-1-azabuta-1,3-dienes with optically active enol ethers has highlighted a number of previously unexplored asymmetric auxiliaries for use in the 1-azadiene Diels–Alder reaction.[130] (*de*) (*ee*) (*de*)

DFT and *ab initio* studies of the cycloaddition reaction between methyleneketene and cyclopentadiene indicated that the norbornene adduct is the primary reaction product from a 1,2-addition.[131] The thermal 4 + 2-cycloaddition of *o*-xylylenes (**104**) with β-nitro-*meso*-tetraphenylporphyrin (**103**) produced a high yield of the chlorin (**105**) together with low yields of the naphthoporphyrin (**106**) and the bis-naphthoporphyrin (**107**). These reactions allow access to chlorins, bacteriochlorins, and isobacteriochlorins having biological activity (Scheme 27).[132] The key marine metabolite oroidin (**108**) underwent Diels–Alder cycloaddition with electron-poor dienophiles, maleimide, and *N*-phenylmaleimide (**109**), to form cycloadducts (**110**) in good yields (54% and 45%, respectively) (Scheme 28).[133]

The normally sluggish Diels–Alder cycloaddition between cyclohexa-1,3-diene and various enones and enals can be activated by precoordination of the diene to a π-basic molybdenum complex [TpMo(NO)MeIm(η-cyclohexadiene)].[134] The 4 + 2-cycloaddition of cyclohexa-2,4-dienones with electron-deficient 2π-dienophiles produced bridged bicyclo[2.2.2]octenones. Triplet-sensitized irradiation of these bridged bicyclooctenones produced bicyclo[3.3.0]octanoids, whereas direct irradiation yielded bicyclo[4.2.0]octanes.[135]

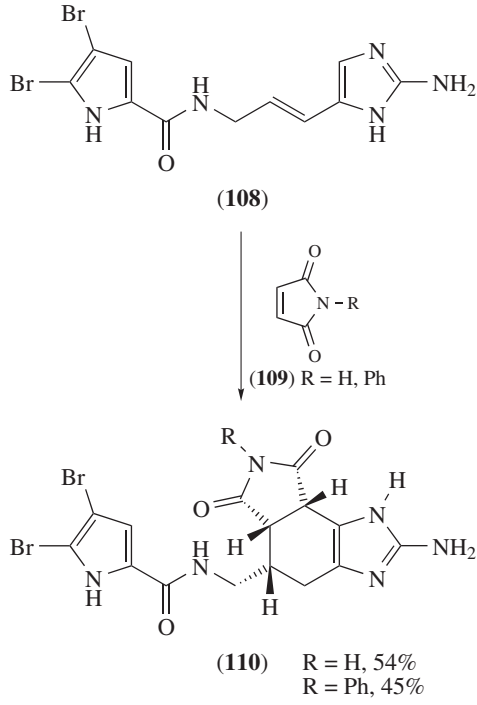
Cinchona alkaloid derivatives catalysed the enantioselective 4 + 2-cycloaddition of *o*-quinones with ketene enolates to produce chiral *o*-quinone cycloadducts in high *ee* (*ee*)



SCHEME 27

and good to excellent yields. The cycloadducts can be readily converted into optically active α-hydroxy esters in the presence of ceric ammonium nitrate.[136] Lewis acid co-catalysts [$Zn(OTf)_2$–$Sc(OTf)_3$] are extremely effective in catalysing the enantioselective inverse-electron-demand hetero-Diels–Alder reaction of ketene enolates with *o*-benzoquinonediimides to give biologically active quinoxalinones in high yields and >99% *ee*.[137] The 4 + 2-cycloaddition of *o*-quinone methides with substituted 2-aminooxazoles produced a variety of benzopyrans.[138]

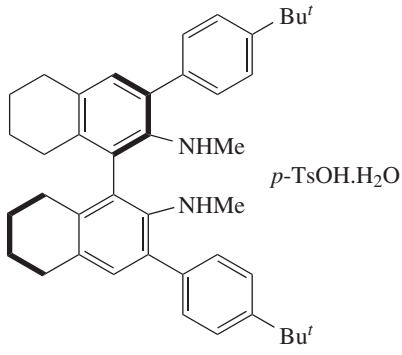
DFT has been used to investigate the Diels–Alder reactions of cyclopentadiene with α,β-unsaturated aldehydes and ketones organocatalysed by MacMillan's chiral



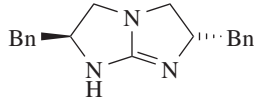
SCHEME 28

imidazolidinones.[139] A DFT study of the Diels–Alder reaction of 2-methylacrolein and cyclopentadiene catalysed by cationic oxazaborolidine Lewis acids showed that the reaction is stepwise and not concerted as exhibited in the absence of the catalyst.[140] Binaphthyl-based diamine salts (**111**) are organocatalysts in the Diels–Alder reaction between cinnamaldehyde and cyclopentadiene producing the corresponding *exo*-cycloadduct as the major isomer with 92% *ee*.[141] Aziridin-2-ylmethanol salts are effective organocatalysts for the Diels–Alder reactions of *N*-methylpyrrole and *N*-methylindole with *ee*s ranging from 10 to 66%.[142] The chiral bicyclic guanidine (**112**) catalysed the Diels–Alder reaction between substituted anthrones and dienophiles, e.g. maleimides, to form cycloadducts in excellent yields, with high regioselectivities and high enantioselectivities.[143] Phosphonium salts derived from dioxaphosphacycles behaved as organocatalysts in the Diels–Alder reaction of cyclopentadiene with dienophiles.[144] A chiral indium(III) complex in [hmim][PF_6^-] ionic liquid catalysed the enantioselective Diels–Alder reactions of 2-methacrolein and 2-bromoacrolein with dienes to produce cycloadducts in good yields and high enantioselectivities.[145] In the presence of chiral 1,1′-binaphthyl-2,2′-diammonium salt catalysts in EtCN at $-75\,^{\circ}C$, the Diels–Alder reaction of α-(cyclohexanecarbonyloxy)acrolein with cyclopentadiene produced the cycloadducts in 88% yield with 92% *exo*-isomer and 91% *ee*.[146]

(*de*) (*ee*) (*ee*) (*ee*) (*ee*)



(**111**)



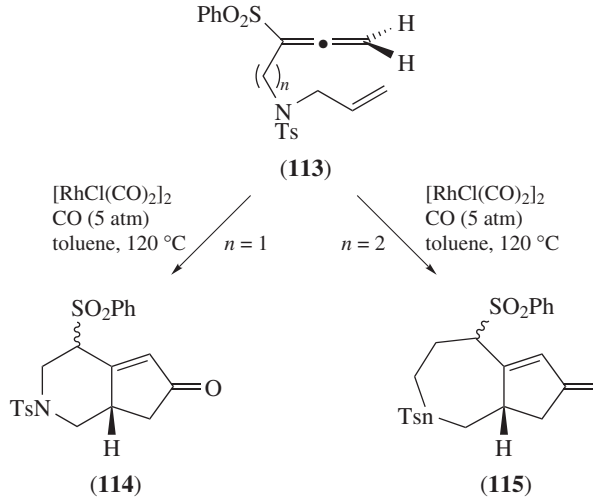
(**112**)

A phosphoric acid diester, derived from (*R*)-BINOL, catalysed the inverse-electron-demand aza-Diels–Alder reaction of aldimines with enol ethers to produce tetrahydroquinoline derivatives with excellent enantioselectivity.[147] The aza hetero-Diels–Alder reaction of aromatic aldimines with cyclohexenones in the presence of a chiral phosphoric acid, derived from 3,3-di(4-chlorophenyl)-H$_8$-BINOL, proceeded with good yields and enantioselectivity.[148] TMBOTf catalysed the aza-Diels–Alder reactions of sulfinimines with Rawal diene to produce enantiomerically enriched dihydropyridones with *ee* up to 90%.[149] Triflic imide catalysed the Diels–Alder reaction of 2-siloxydienes to aldimines to produce substituted piperidin-4-ones.[150] The CAN-initiated aza-Diels–Alder reaction of *N*-arylimines with *N*-vinylpyrrolid-2-one or *N*-methyl-*N*-vinylacetamide formed the corresponding 2,4-*cis*-4-amido-*N*-yl tetrahydroquinoline derivatives in good yields.[151] A DFT investigation of the Diels–Alder reactions of substituted triazolo[3,2-*d*][1,4,2]diazaphospholes with buta-1,3-diene and isoprene revealed concerted mechanisms via asynchronous transition states.[152] The inverse-electron-demand Diels–Alder reactions of 3-methylsulfinyl-6-methylthio-1,2,4,5-tetrazine and 3-(benzyloxycarbonyl)amino-6-methylsulfinyl-1,2,4,5-tetrazine are regioselective, producing a single cycloadduct in each case.[153] Allenyltrimethylsilylthioketenes undergo 4 + 2-cycloaddition with imines to produce the corresponding δ-thiolactones, which can be converted into (±)-lupinine in six steps.[154]

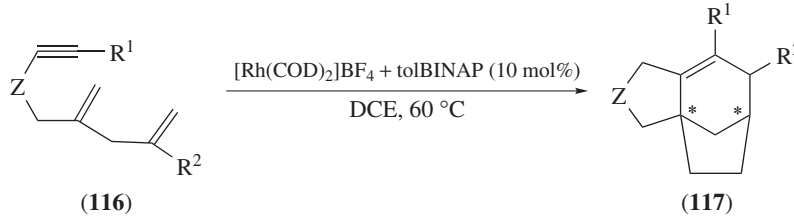
(*de*) (*ee*) (*ee*) (*ee*)

Miscellaneous Cycloadditions

The [RhCl(CO)$_2$]$_2$-catalysed intramolecular 2 + 2 + 1-cycloaddition of allenes (**113**) produced bicyclo[4.3.0]non-1(9)-en-8-ones (**114**) and also the bicyclo[5.3.0]dec-1(10)-en-9-ones (**115**) (Scheme 29).[155]

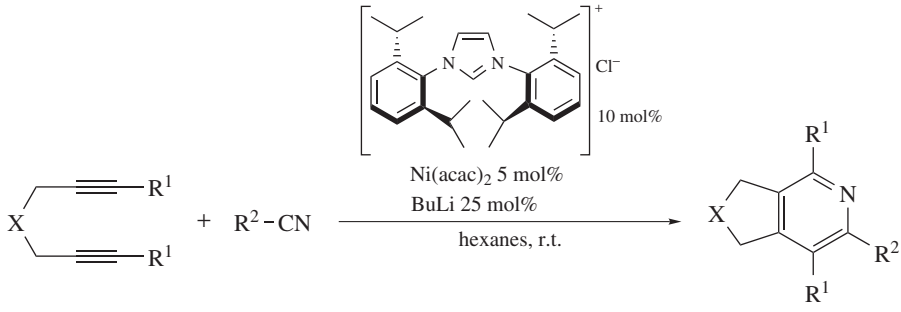


SCHEME 29



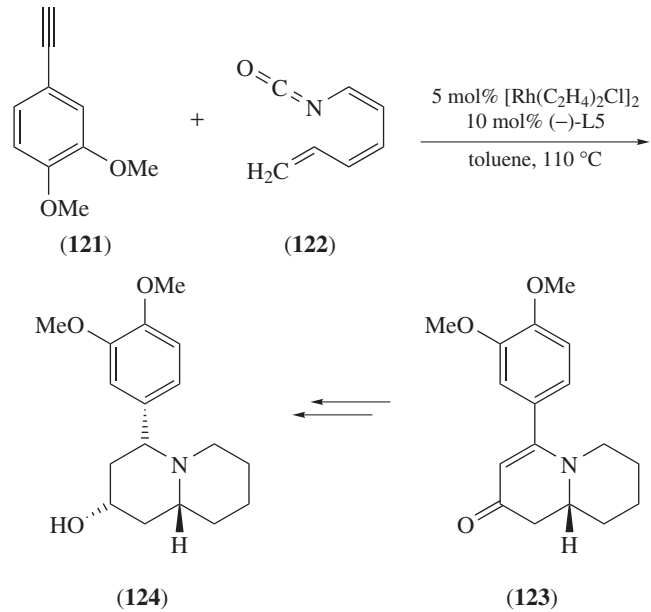
SCHEME 30

The enantioselective Rh-catalysed intramolecular 2 + 2 + 2-cycloaddition reaction of 1,4-dienynes (**116**) yielded strained multicyclic compounds (**117**) with quaternary carbon stereocentres in high enantiomeric excess (Scheme 30).[156] Again, the rhodium-catalysed double 2 + 2 + 2-cycloaddition of ether-linked tetraynes produced tetra-*ortho*-substituted axially chiral biaryls with up to 99% *ee*.[157] $[Ir(cod)Cl]_2$–DPPE is an effective catalyst for the 2 + 2 + 2-cycloaddition of α,ω-diynes with monoynes to give polysubstituted benzene derivatives.[158,159] However, a rhodium-catalysed enantioselective intermolecular 2 + 2 + 2-cycloaddition of 1,6-diynes with trimethylsilylynamides readily yielded axially chiral anilides with 98% *ee*.[160] The nickel-mediated regioselective 2 + 2 + 2-cycloaddition reaction of carboryne with alkenes produced highly substituted benzocarboranes via the Ni–carboryne intermediate $[(\eta^2\text{-}C_2B_{10}H_{10})Ni(PPh_3)_2]$.[161] The Ni(0)–NHC-catalysed intermolecular 2 + 2 + 2-cycloaddition of diynes (**118**) with nitriles (**119**) formed pyridines (**120**) in reasonable yields (up to 100%) (Scheme 31).[162] The $Ni(0)L_n$-catalysed 2 + 2 + 2-cycloaddition of one alkyne and two isocyanates formed pyrimidinediones in appreciable amounts.[163] The regio- and enantio-selective rhodium-catalysed 2 + 2 + 2-cycloaddition of alkenyl



(**118**) (**119**) (**120**)

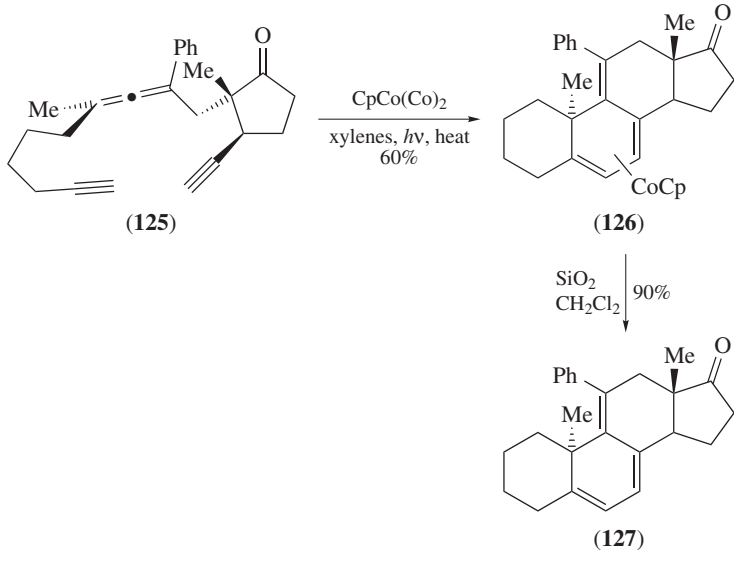
SCHEME 31



(**121**) (**122**) (**124**) (**123**)

SCHEME 32

isocyanates (**122**) with terminal alkynes (**121**) produced quinazolinones (**123**), which are key intermediates in the total synthesis of the alkaloid (+)-lasubine II (**124**) (Scheme 32).[164,165] The enantioselective [Rh(cod){(*S*)-xylyl-binap}]BF_4-catalysed 2 + 2 + 2-cycloaddition of 1,6-diynes with α-methylene lactones and cyclic ketones formed chiral spirocyclic compounds.[166] Mono- and di-nuclear titanium complexes of *p-t*-butylthiacalix[4]arene are efficient catalysts for the 2 + 2 + 2-cyclotrimerization of terminal alkynes to produce 1,3,5-trisubstituted benzenes regioselectively.[167] The diastereoselective cobalt(I)-mediated 2 + 2 + 2-cycloaddition of allenediynes (**125**) with a pre-existing D-ring led to cycloadducts (**126**) possessing the skeletons of 11-aryl steroids (**127**) (Scheme 33).[168]



(**125**) (**126**) (**127**)

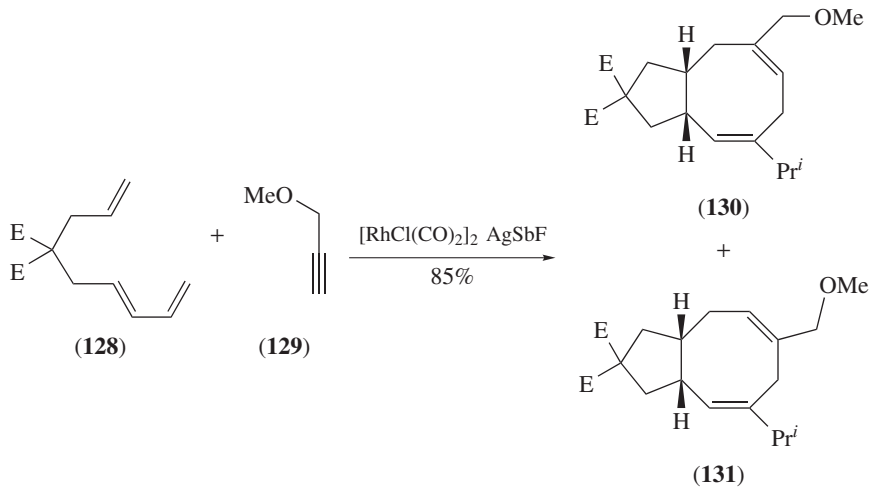
SCHEME 33

The nickel-catalysed 3 + 1 + 1-cycloaddition of alkenyl Fischer carbene complexes with methylenecyclopropanes produced the methylenecyclopentanone in high yields.[169] The nickel-catalysed three-component 3 + 2 + 2-cocyclization of ethyl cyclopropylideneacetate with two alkynes gave cycloheptadienes in good yields and high chemo- and regio-selectivity.[170]

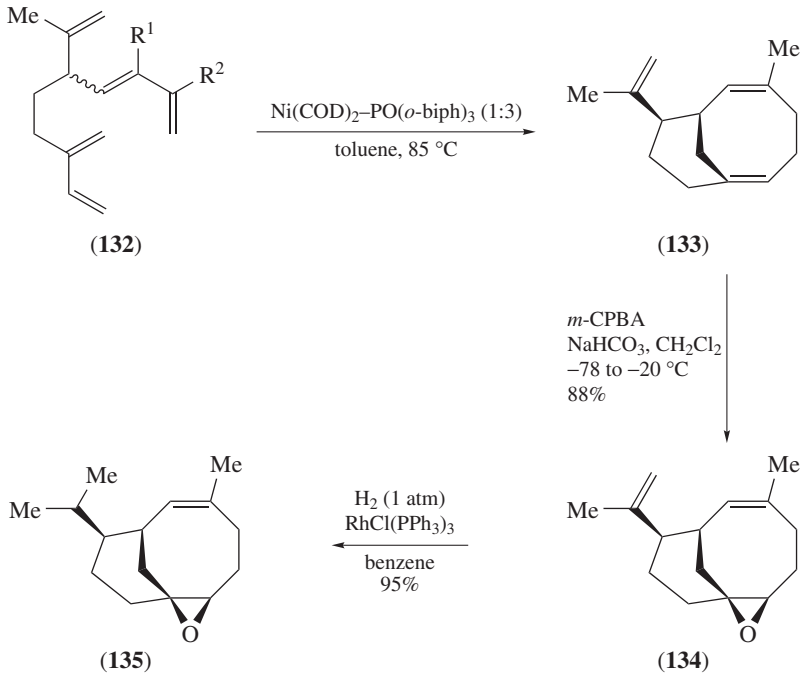
The palladium [$Pd(Ph_3)_4$]-catalysed 3 + 3-cycloaddition of trimethylenemethane with azomethineimines produced hexahydropyridazine derivatives under mild conditions (40 °C).[171] The Lewis acid-catalysed formal oxa-[3 + 3]-cycloaddition of α,β-unsaturated aldehydes with 6-methyl-4-hydroxy-2-pyrone, 1,3-diketones, and vinylogous silyl esters yielded a variety of pyrones at room temperature.[172] Crotonaldehyde has been converted to 6-hydroxy-4-methylcyclohex-1-enecarboxaldehyde by an enantioselective 3 + 3-cycloaddition catalysed by proline. This methodology was (*ee*) used in the synthesis of (−)-isopulegol hydrate, (−)-cubebaol, and (−)-6-hydroxy-4-methylcyclohex-1-ene-1-methanol acetate, an intermediate in the total synthesis of the alkaloid magellanine.[173]

The $Ni(COD)_2$-catalysed 4 + 2 + 1-cycloaddition of (trimethylsilyl)diazomethane with dienynes readily produced carbo-, oxa-, and aza-cyclic adducts. Evidence has been supplied for a mechanism involving a 3 + 3-sigmatropic rearrangement of intermediate divinylcyclopropanes.[174] The rhodium(I)-catalysed 4 + 2 + 2-cycloaddition of diene-enes (**128**) and alkynes (**129**) resulted in the preparation of cyclooctadienes (**130**, **131**) in high yields (Scheme 34).[175] The Ni(0)-catalysed intermolecular formal 4 + 2 + 2-annulation of cyclobutanones with 1,6- and 1,7-diynes gave bicyclic eight-membered ring ketones via a β-elimination for ring expansion.[176]

The Lewis acid-catalysed 4 + 3-cycloaddition of furan with chiral allylic dioxolans (*de*) produced cycloadducts with high diastereoselectivity.[177] Theoretical calculations have



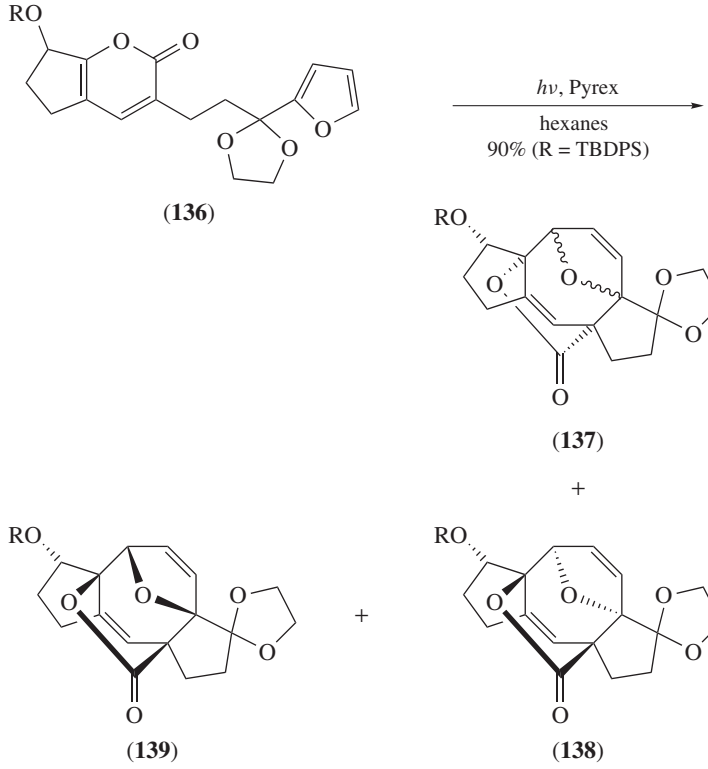
SCHEME 34



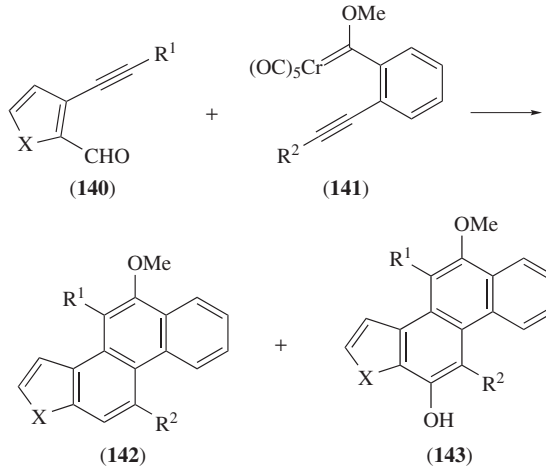
SCHEME 35

shown that the key 4 + 4-cycloaddition in the biosynthesis of epoxytwinol A consists of three consecutive steps involving biradical intermediates. The first step is the formation of the C(8)–C(8′) bond generating a biradical intermediate. Next, rotation about the C(8)–C(8′) bond occurs, and finally the C(1)–C(1′) bond is formed.[178] A novel type of nickel(0)-catalysed intramolecular 4 + 4-cycloaddition of the (*Z*)-bis-diene (**132**) yielded the cyclooctadiene cycloadduct (**133**), which was converted to the tricyclic sesquiterpene (±)-salsolene oxide (**135**) in two chemoselective steps via intermediate (**134**) (Scheme 35).[179] The photochemical diastereoselective 4 + 4-cycloaddition of the fused bicyclic pyran-2-ones (**136**), with pendant furan side-chains and a stereogenic centre adjacent to the pyranone ring oxygen, furnished the corresponding lactone bridged 5–8–5 cycloadducts (**137**–**139**) in good yields. These cycloadducts are suitable intermediates in the total synthesis of traversianal and related fusicoccin fungal metabolites (Scheme 36).[180] The photocycloaddition of anthracene derivatives to anthracene produced only 4 + 4-cross-cyclomer adducts under selective excitation conditions.[181]

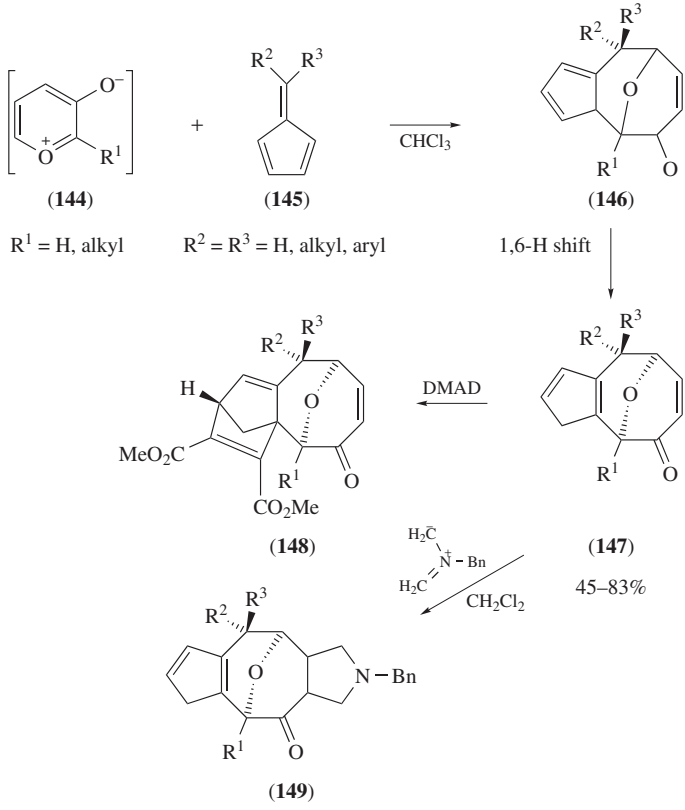
The intermolecular 1,5-dipolar cycloaddition of tungsten-containing vinylazomethine ylides with ketene acetals produced azepino[1,2-*a*]indole derivatives in good



SCHEME 36



SCHEME 37



SCHEME 38

yields.[182] [{(*R*)-BINAP}Rh]$^+SbF_6^-$ catalysed the intramolecular 5 + 2-cycloaddition of vinylcyclopropanes with π-systems to produce bicyclic cycloadducts in high yields (*ee*) and high enantioselectivities.[183] Alkynylphenylcarbene complexes (**141**) and alkynyl-heteroaromatic carboxaldehydes (**140**) underwent net 5 + 5-cycloaddition to form heterocycle-annulated phenanthrenes (**142**, **143**) (Scheme 37).[184]

The cobalt(I)-catalysed 6 + 2-cycloadditions of cyclooctatetraene with monosubstituted alkynes produced monosubstituted bicyclo[4.2.2]deca-2,4,7,8-tetraenes in good yields.[185] The 6 + 3-cycloaddition of fulvenes (**145**) with 3-oxidopyrylium betaines (**144**) formed 5–8 fused oxa-bridged cyclooctanoids (**146**, **147**), which can be manipulated by cycloaddition reactions to produce key intermediates (**148**, **149**) for the synthesis of fused cyclooctanoid natural products e.g. lancifodilactones (Scheme 38).[186,187]

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CHAPTER 13

Molecular Rearrangements: Part 1. Pericyclic Reactions

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A new type of rearrangement, dubbed 'hiscotropic', has been predicted by DFT calculations to occur, albeit with a high energy barrier. The reaction has been described as a fusion of a two-electron electrocyclic ring opening and a [1,2]-hydrogen shift to an adjacent carbocation, and the calculations have shown that the two processes occur in an asynchronous, concerted fashion, and share a *p*-type orbital in the single transition state.[1]

The aromaticities of symmetry-allowed and -forbidden transition states for electrocyclic reactions and sigmatropic rearrangements involving two, four, and six π-electrons, and Diels–Alder cycloadditions, have been investigated by *ab initio* CASSCF calculations and analysis based on an index of deviation from aromaticity. The order of the aromaticity levels was found to correspond to the energy barriers for some of the reactions studied, and also to the 'allowed' or 'forbidden' nature of the transition states.[2] The uses of catalytic metal vinylidene complexes in electrocyclization, [1,5]-hydrogen shift reactions, and 2 + 2-cycloadditions, and the mechanisms of these transformations, have been reviewed.[3]

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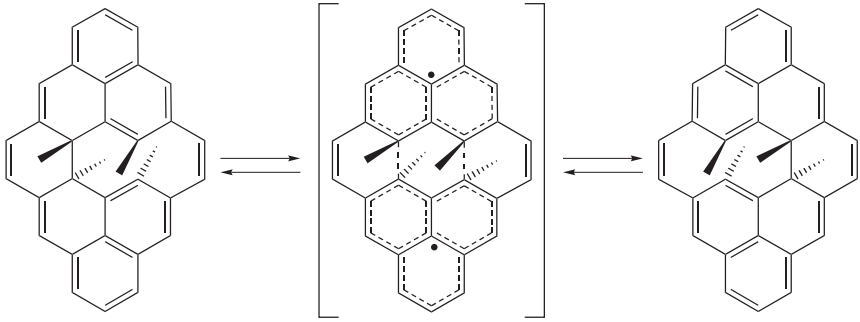
[3,3]-Sigmatropic Rearrangements

A review of the use of Pd(II) catalysis for the acceleration of the Cope, Claisen, and aza-Claisen rearrangements has focused on the mechanism of catalysis, stereochemical (*de*) outcome and synthetic applications of these reactions.[4]

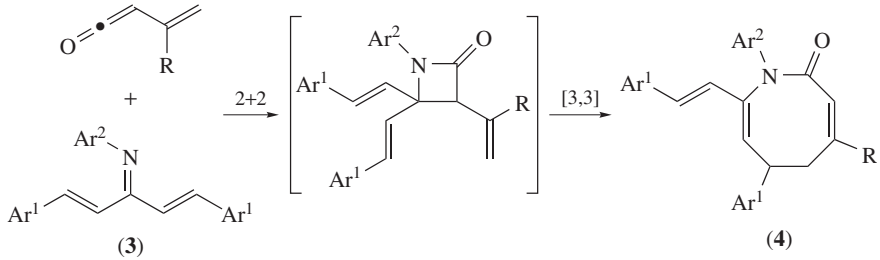
All-carbon Pericyclic Systems

The Cope rearrangements of a series of 1(5)-monosubstituted and 1,5-disubstituted semibullvalenes have been investigated by *ab initio* quantum methods. In the monosubstituted series, the results were found to be in accordance with Hoffmann's predictions, depending on the electronic nature of the substituents. In the disubstituted series, rearrangement barriers have been shown to be lowered by π-donor groups, and the position of equilibrium was found to correlate with the BCO stabilization effects of the substituents.[5] A DFT investigation of the Cope rearrangement of the cyclobiphenalenyl (**1**) has shown it to occur via the unusual diradical (**2**), stabilized by π-dimerization, and having an unusually long inter-phenalenyl distance (comparable to the inter-allyl distance in a classical Cope rearrangement) of ~2.8 Å.[6]



(**1**) (**2**)

Calculations of the interactions between matured catalytic antibody AZ28 and the different conformers and enantiomers of 2,5-diaryl-hexa-1,5-dien-3-ol, allowing for the flexibility of the antibody, have reproduced, qualitatively only, the observed selectivity of the antibody for the *S*,equatorial substrate.[7] Doubly α,β-unsaturated *N*-arylimines (**3**) have been shown to react with α,β-unsaturated ketenes to give azocinones (**4**),



(**3**) (**4**)

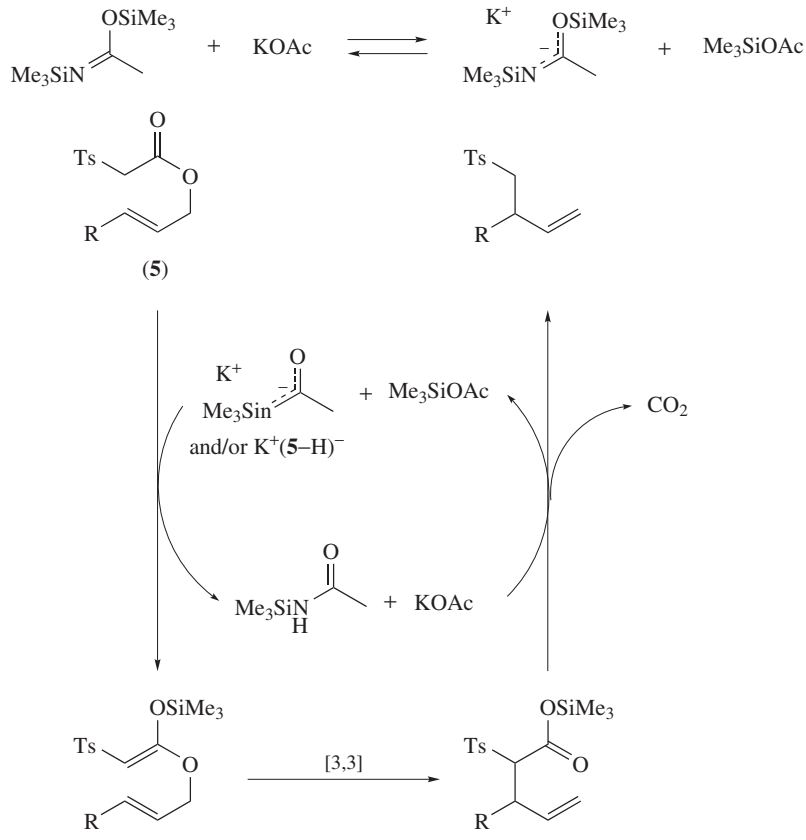
in which any aromatic ring(s) may bear a *para*-substituent. The mechanism shown, involving 2 + 2-cycloaddition followed by a facile ring-expanding Cope rearrangement, has been supported by AM1 calculations.[8]

One Heteroatom

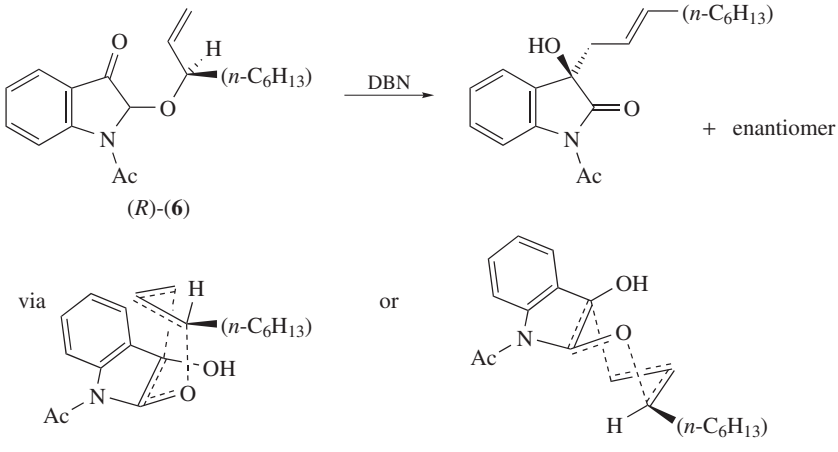
The Claisen rearrangement of allyl vinyl ether has been studied using a combination of spin-coupled modern valence bond theory and DFT. These calculations have suggested a non-synchronous, concerted, homolytic mechanism in which aromaticity is achieved but not at the transition state.[9] A range of 3-alkylidene-2-oxabicyclo[2.2.2]oct-5-ene derivatives has been shown to undergo thermal or Lewis acid-catalysed Claisen rearrangement giving bicyclo[4.2.0]oct-5-en-2-one derivatives. The rate of rearrangement was found to correlate qualitatively with the electron donor ability of an aromatic substituent on the *exo*-methylene group. The related 3-dichloromethylene-2-oxabicyclo[2.2.1]hept-5-ene could not be isolated, the observed product of its attempted synthesis by elimination being 3,3-dichlorobicyclo[3.2.0]hept-5-ene-2-one. These results are consistent with the related Claisen rearrangement believed to follow 4 + 2-cycloaddition of ketene derivatives to cyclopentadiene, the sequence leading to the observed products of this cycloaddition, the bicyclo[3.2.0]hept-5-en-2-one derivatives.[10]

The decarboxylative Claisen rearrangement of allylic tosylacetate (**5**) and methyl tosylmalonate derivatives has been extensively studied. In the tosylacetate series, it has been found that acetate ions, base and a silylating agent, preferably *N*,*O*-bis(trimethylsilyl)acetamide (BSA), are all necessary, but in only catalytic quantities provided that BSA is used. Potassium acetate has been shown to be a suitable base. In the absence of acetate ion, ketene acetal formation and Claisen rearrangement have been found to proceed, but without the final decarboxylation. These findings have been interpreted in terms of a proposed catalytic cycle (Scheme 1). By contrast, in the methyl tosylmalonate series, rapid room temperature rearrangement and decarboxylation have been shown to occur using either BSA–KOAc or DBU–TMSOTf reagent systems, but a stoichiometric amount of silylating agent has been found to be necessary. In this case, it has been proposed that decarboxylative silatropic retro-ene rearrangement can occur without the need for the acetate catalyst.[11]

Bismuth triflate has been shown to be an effective catalyst for the Claisen rearrangement of allyl naphthyl ether derivatives in refluxing acetonitrile, giving exclusively *o*-allylnaphthol derivatives. Vinylic substitution has been found to cause competing [1,3]-sigmatropic migration of the allyl group. Although 1,4-diallyloxynaphthalene has been shown to undergo Claisen rearrangement of both substituents, this did not occur cleanly for either 1,5- or 2,5-diallylnaphthol, where single rearrangement was found to compete. Clean double [3,3]-sigmatropic rearrangement to give *p*-allylnaphthol derivatives was found to occur, as expected, with 2-substituted 1-allylnaphthol derivatives.[12] The asymmetric Claisen rearrangement of 2-allyloxyindolin-3-one derivative (**6**) has been investigated. Treatment with a weak base such as DBN has been found to give only (*ee*) modest enantioselectivity; this has been attributed to competition between chair-like and boat-like transition states as shown in Scheme 2. By contrast, the corresponding



SCHEME 1



SCHEME 2

TMS enol ether has been shown to rearrange with good enantioselectivity, presumably because the boat-shaped transition state is sterically disfavoured. Rearrangement of (*ee*) the enantiomeric starting material has been used as a key step in a total synthesis of (+)-alline.[13]

Ring-expanding Claisen rearrangements of some 1-vinyl-5-methylene-glucose and -mannose derivatives have been found to occur either on strong heating or, in one case, by Lewis acid treatment, to give protected 2,3,4-trioxygenated cyclooct-5-en-1-ones. Since the Lewis acid used was TRIBAL, this rearrangement was found to be accompanied by stereoselective reduction to the corresponding cyclooctenol.[14] Total diastereoselectivity has been found to occur in an Mg(II)-promoted Claisen (*de*) rearrangement of some sugar-derived enol ethers. Treatment of 2-substituted 1-chloro-1-isopropoxycarbonyl epoxides (**7**) with MgI_2–Mg followed by allyl bromide–HMPA was found to generate a mixture of allyl enol ethers (**9**), α-keto esters (**10**), and β-allyl α-keto esters (**11**), formed as single diastereomers from sugar derivatives (**7a**) or (**7b**). Although esters (**11**) could be derived by *C*-allylation of magnesium enolates (**8**), these have previously been shown to undergo exclusively *O*-allylation. This, and the total stereoselectivity of the reaction, have led to a proposed mechanism involving *O*-allylation followed by Claisen rearrangement with a chair-shaped transition state having the Mg-coordinated ring oxygen, and the allyl group, both avoiding close contact with the isopropylidene protecting group(s) on the sugar moiety R, as shown in Scheme 3.[15]

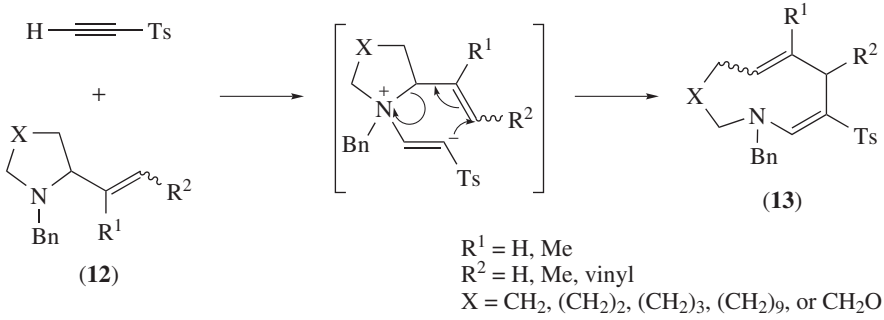
Ireland–Claisen ester enolate rearrangements have been shown to occur readily in conjugated dienes bearing an internal acetoxymethylene substituent, giving conjugated dienes bearing an internal $CH_2CH_2CO_2H$ or $CH_2CH_2CO_2Me$ substituent. A wide range of initial diene substitution patterns has been found to be compatible with the rearrangement. With an enantiomerically enriched starting material, however, some loss of chirality has been observed, and attributed to competing chair- and boat-like transition states.[16]

Tertiary cyclic α-vinylamines (**12**) have been shown to undergo four-atom ring expansion on treatment with alkynyl *p*-toluenesulfonate, giving medium- or large-ring amines (**13**). The reaction, which has been found to be generally stereoselective, although the alkene stereochemistry could not always be determined, has been presumed to occur by nucleophilic addition followed by a rapid zwitterionic formal [3,3]-sigmatropic rearrangement as shown in Scheme 4, although no intermediates could be trapped or detected, so it remains unclear whether the rearrangement is concerted.[17]

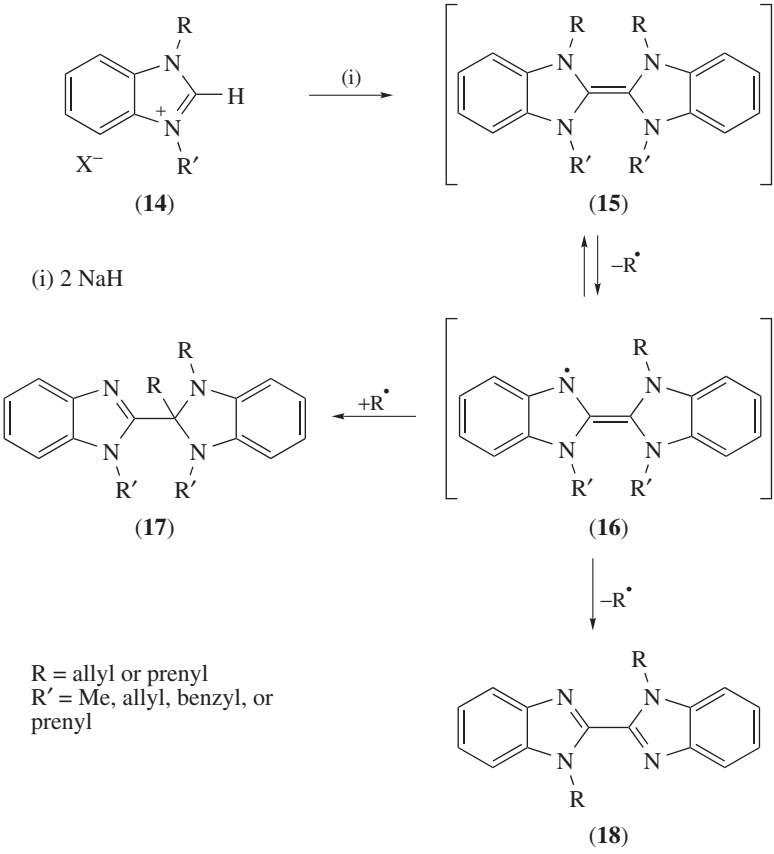
The rearrangements of some di- and tetra-*N*-allyldibenzotetraazafulvalenes (**15**), generated *in situ* by deprotonation of *N*-allylbenzimidazolium halides (**14**), have been investigated experimentally and by DFT calculations. Deprotonation of *N*,*N*′-diallylbenzimidazolium and *N*-allyl-*N*′-methylbenzimidazolium halides (**14**) has been found to give a mixture of rearrangement products (**17**) and deallylation products (**18**), whereas with *N*-allyl-*N*′-benzylbenzimidazolium and *N*,*N*′-diprenylbenzimidazolium ions only the debenzylation or deprenylation products (**18**) have been observed. DFT calculations have suggested that all these reactions occur by radical mechanisms via intermediates (**16**) as shown in Scheme 5, unlike the corresponding rearrangements

(i)
(ii)
(iii)
(iii)
(iii)
(7)
(8)
(9)
(10)
(11)
a; R =
b; R =
c; R = $(Me)_2CH$
(i) Mg/MgI_2 (1 equiv. of each), Et_2O
(ii) allyl bromide, HMPA
(both in excess)
(iii) H_2O

SCHEME 3



SCHEME 4



SCHEME 5

of non-benzannulated tetraazafulvalenes, which are believed to involve pericyclic Claisen-like rearrangements.[18]

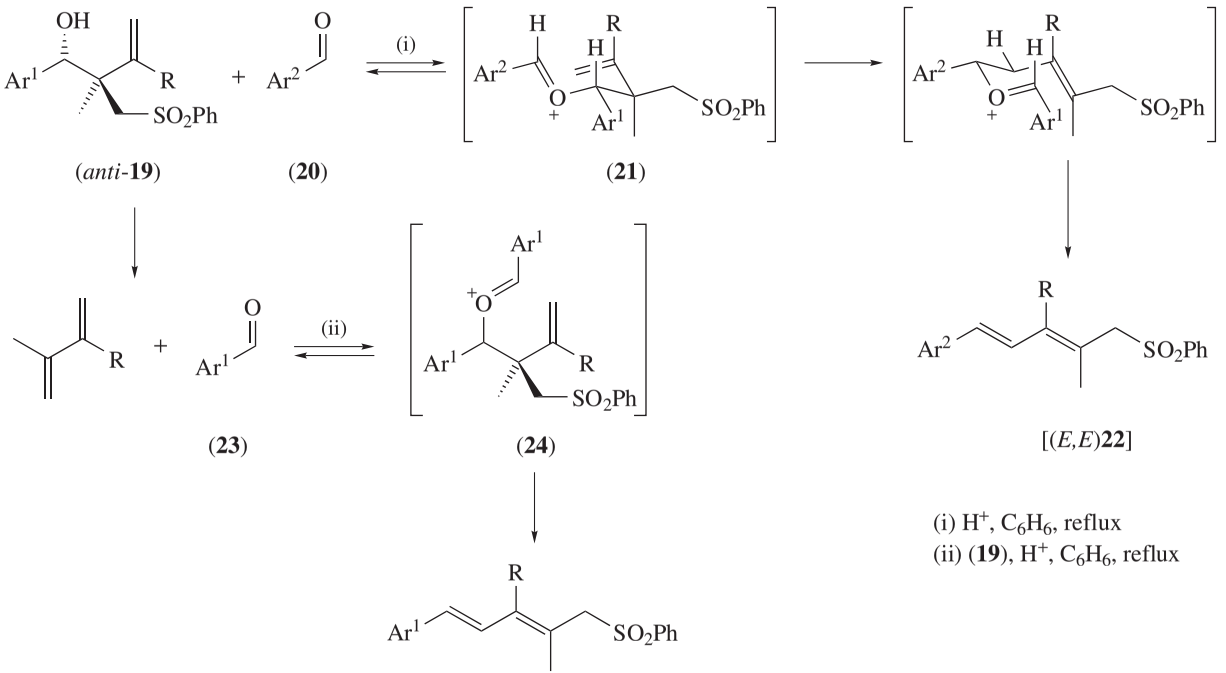
Homoallylic alcohols (**19**), which are also homoallylic sulfones, have been shown to react with aldehydes (**20**) under acidic conditions to produce dienes (**22**), which are allylic sulfones, via an oxonia-Cope rearrangement and elimination of the resulting oxonium ion. The rearrangement has often been found to proceed with excellent diastereoselectivity, which has been accounted for with a chair-like transition state. (de) Thus *anti*-alcohols (**19**) have been shown to give (all-*E*)-sulfones (**22**), whereas *syn*-(**19**) has been found to give (2*Z*,4*E*)-sulfones (**22**). Some erosion of stereoselectivity has been observed, however, from starting materials having a vinyl substituent and a tertiary allylic centre. Although the aldehyde appears mechanistically to be a catalyst, higher yields have been obtained using stoichiometric amounts. Further studies have revealed that the electronic nature of aldehyde (**20**), and of the aromatic ring adjacent to the alcohol in (**19**), influence the course of the reaction, with the more electron rich of the two being incorporated into the product. This has been attributed to a combination of fragmentation of alcohol (**19**), generating the corresponding benzaldehyde derivative (**23**) as shown in Scheme 6, and the relative abilities of the two aldehyde moieties to stabilize the adjacent oxonium ion in intermediates (**21**) and (**24**). The fragmentation has been supported by the recovery of more than the starting amount of aldehyde in some cases, when $Ar^1 = Ar^2$.[19]

A new mechanism for loss of optical purity in Prins cyclizations has been elucidated using ^2H and ^{13}C labelling, supported by structural modification and calculations. The mechanism involves 2-oxonia-Cope rearrangements via (*Z*)-oxocarbenium ion intermediates, as shown in Scheme 7. It has been shown that racemization can be suppressed by conditions or structural features which slow the Cope rearrangement in either forward or reverse directions, since the [3,3]-sigmatropic rearrangement must occur many times before reaction via the less favoured (*Z*)-oxocarbenium ion becomes important.[20]

Two or More Heteroatoms

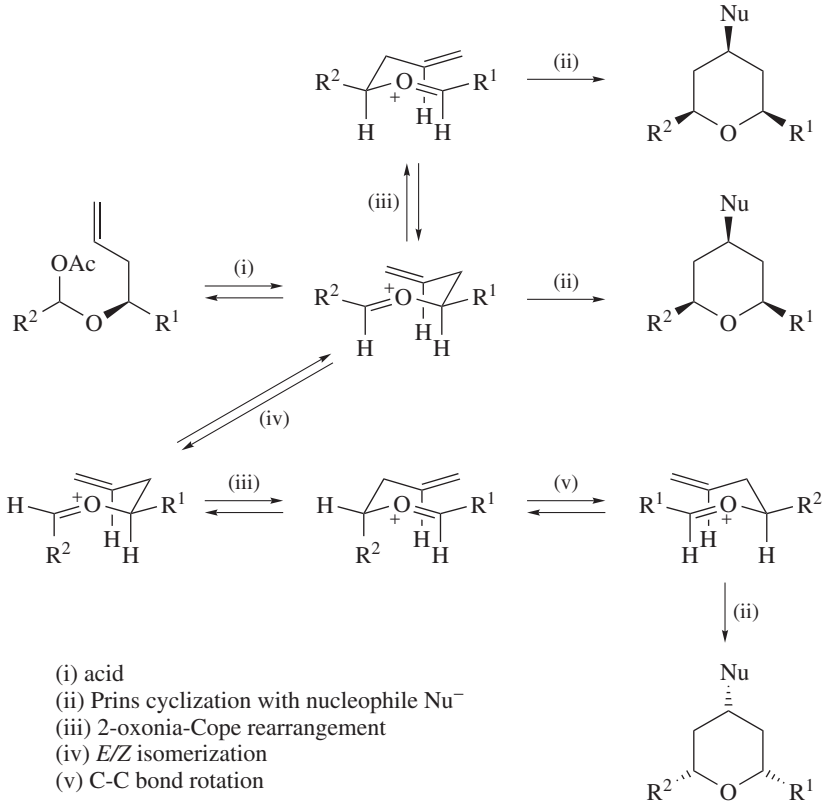
Arylpropargyl acetates have been shown to produce indenyl acetates on treatment with $AgBF_4$ and an AuCl complex of a sterically demanding *N*-heterocyclic carbene ligand. In view of the occasional observation of allene by-products, and of various regioisomeric byproducts, a mechanism has been proposed involving Au coordination to the alkyne, rearrangement to an allene by acetate migration, and hydroarylation of the gold-coordinated allene. The acetate migration may formally occur by either two [1,2]-migrations with a vinyl acetate intermediate or a single [1,3]- or [3,3]-rearrangement.[21]

The synthesis of *N*-arylindoles from *N*,*N*-diaryl-*N*′-trifluoroacetyl enehydrazines, a process analogous to the Fischer indole synthesis, has been studied in various solvents, including water, and in solvent-free conditions. Solvent polarity, or presence, appears to have had little influence on the reaction course. The *N*-TFA group has been found to be necessary for efficient reaction, with less electron-withdrawing substituents giving slower reactions, and triflyl diverting the reaction course after the



(i) H^+, C_6H_6, reflux
(ii) (**19**), H^+, C_6H_6, reflux

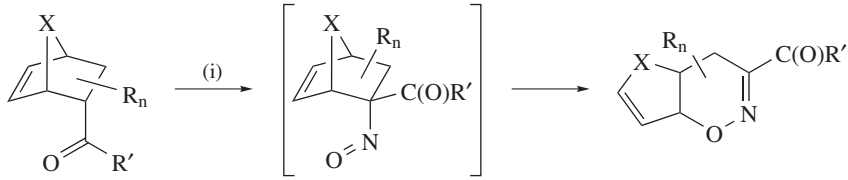
SCHEME 6



SCHEME 7

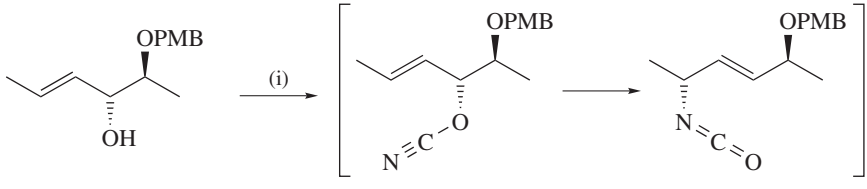
initial [3,3]-sigmatropic rearrangement. Formation of *N*-arylindoles has been shown to occur readily when the *N*-vinyl group of the starting enehydrazine was acyclic or part of a six-membered ring, but required higher temperatures when it was in a five-membered ring. In these cases, it was found possible to isolate instead the indoline intermediates, prior to elimination of trifluoroacetamide. Indole formation has been shown to be accelerated by an electron-donating *N*-aryl substituent, and retarded by an electron-withdrawing one. With *ortho*- and *meta*-substituents, the reaction has been found generally to lack regioselectivity, although electron-deficient *ortho*-substituted starting materials have unexpectedly been found to give only 7-substituted indoline products. Product distributions observed with electron-rich *ortho*-substituents have been attributed to competing chair- and boat-like transition states for the initial [3,3]-sigmatropic rearrangement.[22]

Some ester- or aldehyde-substituted bicyclo[2.2.2]oct-2-ene and bicyclo[2.2.1]hept-2-ene systems (**25**) have been shown to undergo nitrosation adjacent to the carbonyl group followed by [3,3]-sigmatropic rearrangement to give oxazine products (**26**).[23] Stereodefined monoprotected allylic 1,2-diol (**27**) and its diastereomer have been converted into stereodefined propenylimidazolidinone (**30**) and its diastereomer by



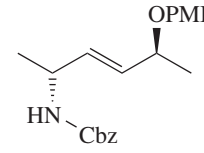
(**25**) (**26**)

(i) 1. Base, Me_3SiCl; 2. *i*-$C_5H_{11}ONO$, $TiCl_4$ X = CH_2, $(CH_2)_2$



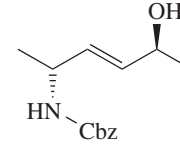
(**27**) (**28**)

(i) 1. CCl_3CONCO, CH_2Cl_2;
2. K_2CO_3, MeOH;
3. PPh_3, CBr_4, Et_3N, CH_2Cl_2
(ii) $PhCH_2OH$, Bu_3SnOCH_2Ph
(iii) DDQ, CH_2Cl_2, H_2O

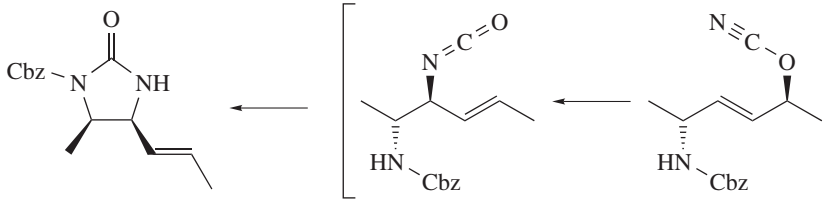


(ii)

(iii)



(i)

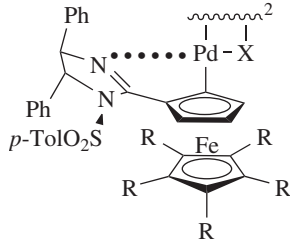


(**30**) (**29**)

successive diastereoselective [3,3]-sigmatropic rearrangements of the initially formed allylic cyanates (**28**), (**29**), or their diastereomers as shown.[24]

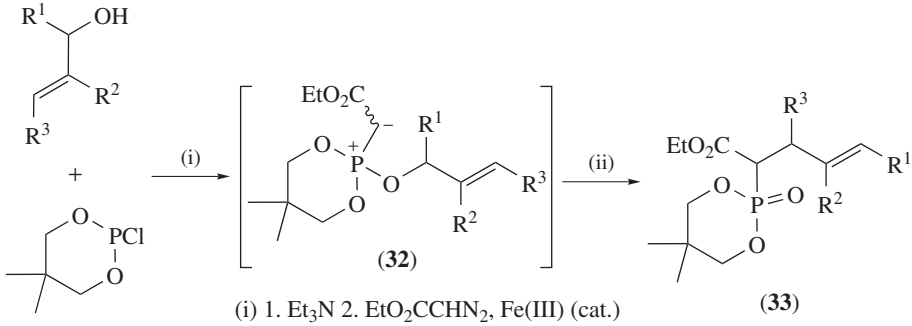
The stereoselectivity of the MOM ether-directed, transition metal-catalysed aza-Claisen rearrangement of *O*-(4-methoxymethoxypent-2-en-1-yl) trichloroacetimidate to *N*-(4-methoxymethoxypent-1-en-3-yl) trichloroacetimidate has been studied under various conditions. A range of Pd(II) and Pt(II) catalysts have all been shown to give ~10:1 diastereoselectivity, whereas Ni(II), Ru(II) and Hg(II) complexes have been (*de*) shown to have no catalytic activity. An Au(II) catalyst gave lower selectivity, whereas thermal reaction has been shown to give very little selectivity. Solvent polarity and metal-coordinating ability have been found to have a greater effect on reaction stereoselectivity, with toluene giving greatest selectivity and an ionic liquid least, which is consistent with selectivity being largely influenced by coordination of the metal to the alkene and the ether oxygen.[25] Similarly, use of toluene as solvent has been found to give good diastereoselectivities in the rearrangements of trichloroacetimidates of 4-alkyl-(2*E*,4*S*,5*R*)-5-methoxymethoxyhex-2-en-1-ol. In these cases, the more remote (*de*) MOM ether has been found to give little or no Pd coordination and diastereoselectivity in THF, with the low selectivities observed being attributed to allylic strain from the closer chiral centre.[26]

A Pd(II)-catalysed formal [3,3]-sigmatropic rearrangement has been used to convert 4-THP protected, 3-substituted but-2-en-1,4-diols, via their *N*-PMP trifluoroacetimidate derivatives, into THP-protected, 2-substituted *N*-*p*-methoxyphenyl-*N*-trifluoroacetyl-2-aminobut-3-en-1-ols, which are quaternary α-vinylglycine precursors, usually in excellent yields.[27] Enantioselective aza-Claisen rearrangement of *N*-*p*-methoxyphenyl trifluoroacetimidates has been shown to be catalysed by ferrocenyl–Pd(II) complexes (**31**). It has been found that the catalysts may be optimized to suit the alkene geometry in the substrate by varying the ferrocenyl substituent R; best results have been obtained using *E*-substrates and the pentaphenylcyclopentadienyl-derived catalyst.[28]



(**31**)

Allyloxyphosphonium ylids (**32**), generated *in situ*, have been shown to undergo [3,3]-sigmatropic rearrangements readily on heating to give phosphonate derivatives (**33**) in good yields. Diastereoselectivity has been found to be low; following DFT cal- (*de*) culations, this has been attributed to the small energy gap between axial and equatorial ylid substituents, because of the long P–C ylid bond.[29]



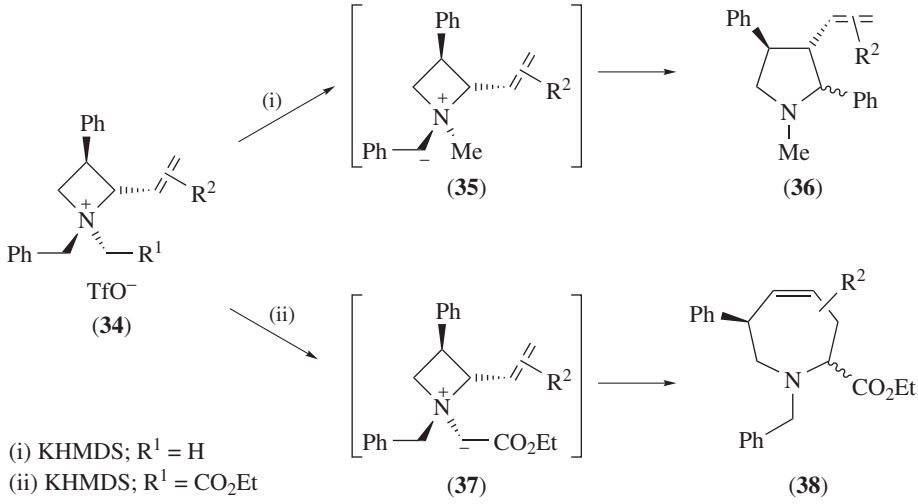
(i) 1. Et_3N 2. EtO_2CCHN_2, Fe(III) (cat.)
(ii) heat

[2,3]-Sigmatropic Rearrangements

The [2,3]-Wittig rearrangements of cinnamyloxyacetone and various analogues into *syn*-4-hydroxy-3-phenylhex-1-en-5-one and analogues has been shown to be catalysed by pyrrolidine, allowing the rearrangements to be carried out at or well below room temperature, provided that methanol is used as solvent. A range of substitution patterns has been found to be tolerated, and chirality transfer from an α-chiral ether starting material was found to be effectively complete. A chiral pyrrolidine (*ee*) derivative has been shown to give moderate enantiomeric induction. In contrast to reactions in other solvents, the rearrangements have been found to be *syn* selective in (*de*) every case, except for rearrangement of 5-triisopropylsilylpent-4-yn-2-enyloxyacetone, which was not diastereoselective. A possible catalytic cycle and transition-state model have been proposed, in which the sigmatropic rearrangement occurs from an enamine, with hydrogen bonding from the ether to the methanolic solvent playing an important rôle in determining transition-state geometry.[30]

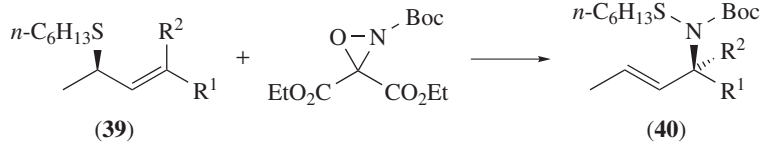
Vinyl epoxide derivatives have been shown to undergo ring expansion to 3,6-dihydropyran-2-carboxylates on treatment with diazoacetate esters and a Cu(II) catalyst, presumably by [2,3]-sigmatropic rearrangement of the resulting oxonium ylids. 1,2-*trans*-Disubstituted epoxides have been found to give exclusively 2,6-*trans*-disubstituted dihydropyrans, but it has been shown that only 1,2-*trans*-divinyl-substituted epoxides gave useful yields of the dihydropyran products; with other substituents, deoxygenation to penta-1,3-dienes was found to compete. These results are consistent with [2,3]-sigmatropic rearrangement of the initally formed oxonium ylid via a boat-shaped transition state, with a requirement for a vinyl substituent *cis* to the alkoxycarbonylmethyne substituent on the epoxide.[31]

Ring expansions of ylids (**35**) or (**37**), generated by deprotonation of alk-2-enylazetidinium salts (**34**), to alk-3-enylpyrrolidines (**36**) or azepanes (**38**) respectively, have been investigated. KHMDS treatment of *N*-benzyl-*N*-methylalk-2-enyl-3-phenylazetidinium triflates (**34**; $R^1 = H$) has been found to give *N*-methylalk-3-enyl-2,4-diphenylpyrrolidines (**36**) in good to excellent yields but with very variable stereoselectivity, via a [1,2]-Stevens rearrangement. By contrast, KHMDS treatment of *N*-benzyl-*N*-ethoxycarbonylmethylalk-2-enyl-3-phenylazetidinium salts (**34**; $R^1 = CO_2Et$) has (*de*) been shown to give *N*-benzyl-2-ethoxycarbonyl-6-phenylazepane derivatives (**38**),



again with variable stereoselectivity, by a [2,3]-sigmatropic rearrangement of the intermediate ylid (**37**). The contrasting behaviour of these two groups of substrates has been attributed to the *cis* or *trans* relationship between the anion and the vinyl group in the ylids (**35**) and (**37**).[32]

A DFT study of the [2,3]-sigmatropic rearrangements of some hydrogen and alkyl prop-3-enyl sulfoxides to the corresponding prop-3-enyl sulfenates has found the rearrangements to be concerted, with the competing *exo* and *endo* transition states very close in energy.[33] Enantiomerically pure branched allylic alkyl sulfides (**39**) (*ee*) have been shown to give *N*-allylic-*N*-Boc-sulfimides (**40**) via a [2,3]-sigmatropic rearrangement, with essentially complete transfer of chirality, on treatment with *N*-Boc-3,3-di(ethoxycarbonyl)oxaziridine.[34]



A mild method for thiol allylation has been developed based on the [2,3]-sigmatropic rearrangement of allylic disulfides. Treatment of a thiol, which may be sugar-derived or a protected or unprotected cysteine-containing peptide, with an allylic pyridyl or benzothiazolyl disulfide, followed by a thiophilic phosphine, has been shown to result in transfer of the allylic group to the thiol with allylic transposition.[35] The analogous [2,3]-rearrangement of allylic selenosulfides has also been shown to be a suitable method for the same conversions. In these cases, with *Se*-allylic selenium Bunte salts such as allyl–Se–SO_3K as the allylic reagents, the allylic transposition has been found to occur slowly but spontaneously at room temperature even in the absence

of the phosphine.[36] It has further been shown that the allyl sulfides resulting from these two rearrangements, which have usually been cysteine-derived, react with diazo compounds in the presence of catalytic amounts of $Rh_2(OAc)_4$ by a further [2,3]-sigmatropic sulfonium ylid rearrangement to give α-substituted homoallylic sulfides in moderate yields. The reaction has been shown to be compatible with peptides bearing allyl sulfides, and with diazo compounds derived from fatty acids or mono- or di-saccharides, but not with tryptophan, as the indole system apparently competes with the sulfide for the carbenoid moiety.[37]

Other [*n*,*m*]-Sigmatropic Rearrangements

It has been shown that a single *ortho* or *meta* substituent on either aromatic ring can suppress formation of byproducts in the [5,5]-sigmatropic rearrangements of aryl hydrazides (readily prepared by Pd-catalysed coupling reactions), allowing clean formation of benzidine derivatives. The reaction has been shown to be extendible to double and triple [5,5]-sigmatropic rearrangements.[38]

[1,*n*]-Sigmatropic Rearrangements

An asymmetric [1,2]-Wagner–Meerwein shift has been achieved under Pd catalysis, allowing ring expansion of 1-(alkyloxyallenyl)cyclobutanol and simple derivatives to (*ee*) 2-alkyloxy-2-vinylcyclopentanones. A mechanistic rationale for the high *ee* values observed has been proposed, based on the C_2-symmetry of the chiral ligands used.[39] A dynamic NMR study of the stepwise, cationic [1,2]-migrations of differently substituted vinyl groups on 9,10-dimethyl-9-vinylphenanthrenium derivatives has found that prop-2-enyl and *trans*-but-2-en-2-yl groups migrate at comparable rates, but, unexpectedly, nearly 10^5 times more slowly than vinyl or *cis*-but-2-en-2-yl groups. This slow migration has not been explained.[40]

[1,3]-Sigmatropic migrations of the nitroso group in the systems ON–X–CH=X (X = O, S, Se, NH, CH_2) have been studied by DFT methods.[41]

Treatment of silyl ethers of allyl alcohol, and some simple derivatives, with *t*-BuLi in THF–HMPA, followed by a suitable electrophile, has been shown to give the 1,4-retro-Brook rearrangement products, which are ethers, carbonates or carbamates of 3-trialkylsilylprop-1-en-1-ol. With Et_3Si as the migrating group, it has been found necessary to use *t*-$BuMe_2SiOTf$ as electrophile to suppress 1,2-silyl migration, but with *t*-$BuPh_2Si$ or *t*-BuPh(MeO)Si as migrating groups a wider range of electrophiles has been shown to be suitable, with no competing 1,2-rearrangement observed. In the last case, rearrangement has been shown to proceed with retention of configuration at (*ee*) Si, although only moderate asymmetric induction to an adjacent chiral carbon could be achieved. A possible transition state has been proposed.[42]

It has been shown that treatment of α-benzyloxyallyltrimethylsilane with strong base (*s*-BuLi) at low temperatures results in exclusive formation of the [1,4]-Wittig rearrangement product, the enolate of 4-phenylbutanoyltrimethylsilane, which can be protonated or trapped with a range of electrophiles. By contrast, when weaker bases

needing higher temperatures for complete deprotonation were used, a [1,2]-Wittig rearrangement has been found to compete. This has been interpreted as evidence for the [1,4]-rearrangement occuring via a concerted pathway.[43] A DFT study on thermal aryl migration in two aryliodonium ylids has suggested that the mechanism in each case is a concerted, single-step process involving a five-membered cyclic transition state, FMO controlled by an intramolecular HOMO–LUMO interaction. The ylids studied were the phenyliodonium ylids of cyclohexane-1,3-dione and 2-amino-1,4-diquinone; the lower energy barrier calculated for the latter is in line with previous experimental observations.[44]

DFT studies on [1,5]-hydrogen shifts in cyclopentadiene and 2-fluorocyclopentadiene have suggested that the reactions may be enhanced in polar solvents.[45] Kinetic studies of the [1,5]-hydrogen shift in deuterated 2-methyl-10-methylenebicyclo[4.4.0]dec-1-ene, a cisoid-locked (*Z*)-penta-1,3-diene, have allowed calculations of deuterium kinetic isotope effects and Arrhenius parameters for this reaction, but little or no evidence for any influence of tunnelling has been obtained.[46] A kinetic study of gas-phase thermal [1,5]-hydrogen shifts in monodeuterated *cis*,*cis*-cyclonona-1,3-dienes has allowed calculation of activation parameters. A parallel DFT study, which has given excellent agreement with the experimental results, has highlighted the importance of conformational flexibility in this complex system.[47]

Contrasting [1,5]-sigmatropic rearrangements have been observed on heating 4-*t*-butyl-2,7-dimethoxy-2*H*-azepine and 4-*t*-butyl-7-methoxy-2-propylthio-2*H*-azepine. In the former case, an equilibrium mixture of 4- and 5-*t*-butyl-2,7-dimethoxy-3*H*-azepines has been found to be formed rapidly. This has been attributed to a [1,5]-hydrogen shift followed by a very rapid second [1,5]-hydrogen shift. In the latter case, a 1:1 mixture of 3- and 7-propylthio-5-*t*-butyl-2-methoxy-3*H*-azepines has been observed, and attributed to competing [1,5]-hydrogen and [1,5]-propylthio sigmatropic shifts. Further studies have shown the rates of these competing reactions to be little affected by changes in solvent polarity, and the activation parameters to be similar, and consistent with concerted pericyclic mechanisms. The figures have been qualitatively supported by DFT analysis, which has also shown a much higher activation energy for [1,5]-methoxy shift (which has not been observed). It has therefore been concluded that both [1,5]-hydrogen and [1,5]-propylthio shifts are pericyclic in nature. This is apparently the first such [1,5]-alkylthio migration.[48]

NMR and DFT methods have been used to study [1,5]-silatropic shifts in 1,3- and 1,1-bis(trialkylsilyl)indene derivatives, and to compare these with silyl migration in 1-trimethylsilylindene. In the last compound, the apparent [1,3]-trimethylsilyl migration is known to occur by two sequential [1,5]-migrations, with an unstable 2-trimethylsilylisoindene intermediate. Further silyl substitution has been found to destabilize this intermediate, slowing the overall migration considerably. In addition, replacement of trimethylsilyl by either allyldimethylsilyl or hex-5-enyldimethylsilyl groups has been shown both to slow the rearrangement and to reduce the proportion of the 1,1-disilylindene derivative in the equilibrium mixture. Curiously, silyl migration has not been observed in 1-(pent-5-enyl)-3-allyldimethylsilylindene, so a still higher energy barrier to silyl migration has been presumed in this case.[49]

Vinylcyclopropane–Cyclopentene, Bergman, Di-π-methane, and Related Diradical Rearrangements

The evidence behind a proposed possible mechanism for a new dihalocyclopropane–(dihalomethyl)vinyl rearrangement has been reviewed.[50] 1-Chloro-1-fluoro-2-vinylcyclopropane and its 2-methyl derivative have been shown to give a mixture of butadiene derivatives as well as 4-chloro-4-fluorocyclopentene, or its 1-methyl derivative, on pyrolysis. The product mixture has been attributed to competition between homolytic C(1)–C(2) cleavage, leading to the cyclopentene products, and C(2)–C(3) cleavage, with concerted or subsequent [1,2]-chloro migration, leading to the butadiene products. The various possible butadiene products are themselves interconvertible by [1,3]- and [1,5]-chloro migrations. The competition between ring-opening modes has been attributed to the contrast between the ability of Cl to stabilize an adjacent radical, and the ability of F to destabilize the bond opposite it in a three-membererd ring.[51]

The vinylcyclobutane–cyclohexene rearrangement has been studied using DFT and CASSCF methods. The rearrangement has been found to proceed via diradical species on an almost flat potential energy surface. Although the lowest energy pathway has been shown to be the symmetry-allowed suprafacial route with inversion of configuration at C(4), stationary points for other possible pathways have been found to be only slightly higher in energy, explaining the formation of other products; these include butadiene and ethene, because of a merger of the potential surface with that for the stepwise cycloaddition of those two molecules.[52]

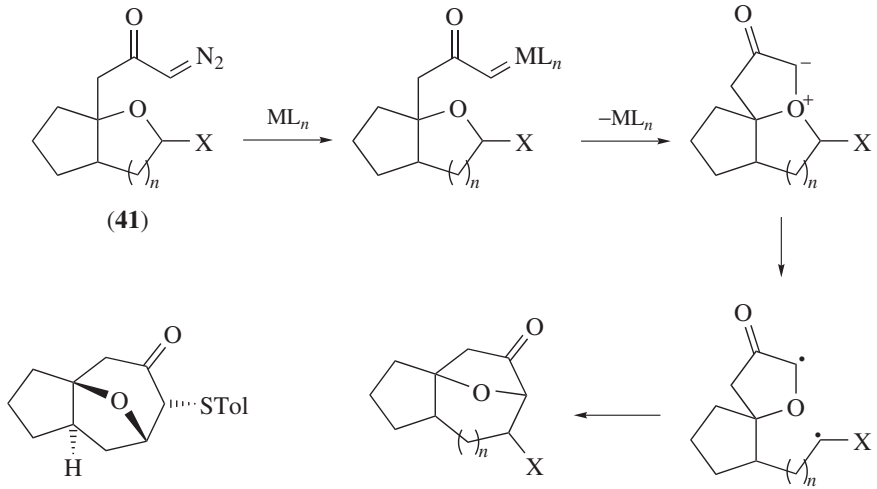
An extensive kinetic study of the evolution of four enantiomerically pure Δ^2-thujenes, *cis*- and *trans*-1-isopropyl-4-methylbicyclo[3.1.0]hex-2-enes and *exo*- and *endo*-3-iso-propyl-6-methylbicyclo[3.1.0]hex-2-enes, into optically pure *trans*-3-isopropyl-5-vinylcyclopentene, has allowed the calculation of 12 specific rate constants, and a greater understanding of the diradical caldera involved in these transformations.[53] Rate constants for thermal isomerizations of [2-^{2}H]-1-(*E*)-propenylcyclobutanes to [4-^{2}H]-3-methylcyclohexenes have been measured, and compared with those of related systems.[54] A modern re-evaluation of stereochemical and mechanistic aspects of the thermal stereomutations and [1,3]-carbon sigmatropic shifts of ^{2}H-labelled (*Z*)-ethylidene-2-methylcyclobutanes has been performed.[55] Kinetic studies on the thermal conversion of ^{2}H-labelled bicyclo[4.2.2]oct-2-ene to norbornene have found reaction to occur largely by homolysis of the C(1)–C(8) bond in the four-membered ring. This contrasts with the homolysis of the ring fusion bond observed in bicyclo[3.2.0]hept-2-ene.[56]

Kinetic and DFT studies have found that the rapid cycloaromatization of 2,3-diethynyl-1-methoxybenzene compared with 1,2-diethynylbenzene can be attributed to intramolecular hydrogen abstraction by the *p*-benzyne diradical intermediate from the OMe substituent. This has been shown to render the cyclization effectively irreversible by leading to a more stable diradical, and may have significant implications for the action of therapeutic enediynes.[57] In general, the Bergman cycloaromatizations of 1-substituted 2,3-diethynylbenzenes have been found to be highly sensitive to the nature of the *ortho*-substituent, but the measurements and even the relative trends

have been found to be highly dependent on the experimental method used for the assessment. DFT and Møller–Plesset second-order perturbation theory calculations have been used to support the experimentally obtained rate constants and activation energies.[58]

DFT studies on heteroatom diallenes have found, in line with previous experimental data, that biradical cyclization to a five-membered heteroaromatic ring is the preferred reaction pathway, although protonation of the heteroatom has been found to promote a competing cyclization to a six-membered, initially biradical, ring.[59]

Fused bicyclic (thio)acetals (**41**) having a pendant diazo ketone have been shown to rearrange to ether-bridged tricyclic ketones (**42**) on treatment with $Cu(hfacac)_2$ by oxonium ylid formation and [1,2]-Stevens rearrangement as shown in Scheme 8. In the six-membered ring series, where only *endo* starting materials were available, the rearrangement has been found to be clean and usually totally stereoselective. In the five-membered ring *endo* compounds, stereoselectivity has been found to be significantly reduced, whereas in the five-membered ring *exo*-thioacetals, sulfonium ylid formation has been shown to compete, giving additional products (**43**) in varying amounts. Several possible explanations for the variation in stereoselectivity have been proposed, including involvement of the copper catalyst in the migration; slow cyclization with the [3.2.1] bridged system as compared with the [4.2.1] case, allowing more bond rotation; and greater ring strain release from the [3.3.0] ylids than from the [4.3.0] ylids, again allowing more bond rotation.[60]



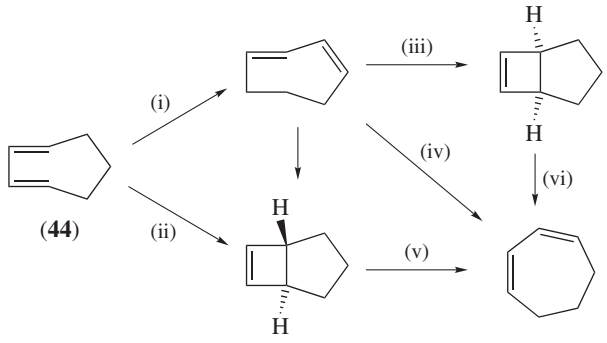
(**41**) (**43**) (**42**)

X = OMe, STol n = 1 or 2

SCHEME 8

Electrocyclic Rearrangements

The potential energy surfaces for the four-electron electrocyclizations of vinylallene and bisallene have been investigated by *ab initio* CASSCF calculations and CiLC-IRC analysis. The orthogonality of the allene π systems has been found to break down near the transition state, allowing considerable interactions between the formally orthogonal orbitals. The energy barriers for both reactions have been found to be significantly lower than for the cyclization of butadiene, which has been attributed to these interactions, but like butadiene, conrotatory pathways have been found for these reactions.[61] The isomers of cycloheptadiene and bicyclo[2.2.0]hept-6-ene and their interconversion pathways have been investigated by multireference SCF methods. (*E*,*E*)-Cyclohepta-1,3-diene (**44**) has been found to occupy a shallow potential well, and to be barely conjugated. The calculated energy barriers, in kcal mol^{-1}, are summarized in Scheme 9.[62]



SCHEME 9

The ring opening of *cis*-bicyclo[4.2.0]oct-7-ene to *cis*,*cis*-cycloocta-1,3-diene has been found to occur by a symmetry-allowed conrotatory ring opening followed by double bond isomerization, using an apparently highly accurate combination of DFT, CASSCF, coupled cluster and multi-reference Møller–Plesset calculations.[63] DFT studies on Nazarov reactions in which one alkene forms part of a six-membered carbo- or oxa-cycle have demonstrated the role of the ring oxygen atom in stabilizing the cationic transition state. The reactions have been further found to occur preferentially via a twist-boat conformation of the developing five-membered ring, and the observed 2,5-*trans* selectivity has been explained by the torquoselectivity associated with the twist-boat shaped transition state.[64] The aza-Nazarov cyclization of 1-azapenta-1,4-dien-3-ones has been studied both by G3 level calculations and experimentally. 1-Amino- and 1-alkoxy-substituted derivatives, including some with extended conjugation, have been shown to cyclize readily to 1-amino- or 1-alkoxy-3-

hydroxypyrrole derivatives, and both theoretical and NMR studies have supported a cationic aza-Nazarov mechanism.[65]

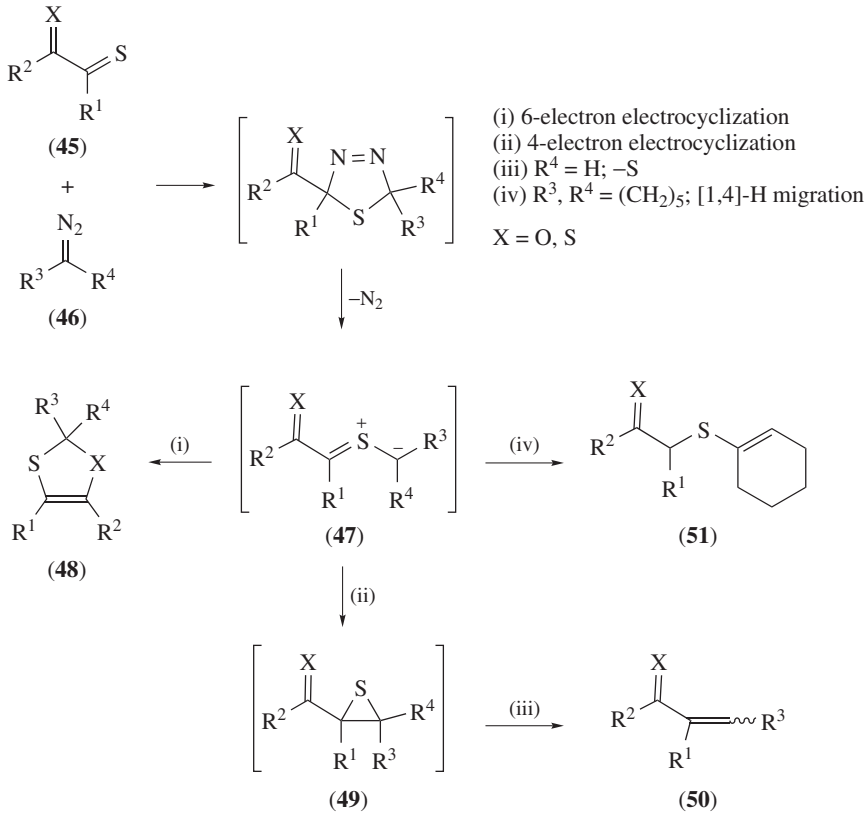
The electron localization function has been used in a further attempt to distinguish pericyclic and pseudopericyclic reactions, the latter having been defined as having significant discontinuities in electron density around the cyclic transition state. These calculations have shown the pericyclic nature of butadiene ring closure, a Claisen rearrangement, and ring closure of hepta-1,3,5,6-tetraene, and the pseudopericyclic nature of the cycloaddition of acetylketene to acetone and of two electrocyclic processes. The controversial ring closures of hexa-2,4,5-trienal and its imine have by this analysis been found to be pseudopericyclic reactions.[66]

Diazo compounds (**46**) have been shown to react with α-thioxo ketones (**45**; X = O) and α-thioxothioamides (**45**; X = S, $R^2 = NMe_2$) to give unstable α-(thio)carbonyl thiocarbonyl ylids (**47**), which can cyclize by either four- or six-electron electrocyclization. 1,5-Dipolar (six-electron) electrocyclization has been found to be the major or exclusive pathway, giving either 1,3-oxathioles (**48**; X = O) or 1,3-dithioles (**48**; X = S). Except with diazo(diphenyl)methane (**46**; $R^3 = R^4 = Ph$), 1,3-dipolar (4-electron) electrocyclization has been shown to compete, giving alkenes (**50**) by sulfur extrusion from the initially formed thiiranes (**49**). When diazacyclohexane [**46**; $R^3 = R^4 = (CH_2)_5$] was used, however, neither electrocyclization pathway was observed. Instead, the products have been found to be thioethers (**51**), arising from [1,4]-hydrogen migration in thiocarbonyl ylids (**47**).[67]

Significant torquoselectivity has been observed in the six-electron electrocyclization of 1-azatrienes prepared *in situ* from a chiral crotonaldehyde derivative and a β-amino α,β-unsaturated carbonyl compound, and so having chiral centre(s) outside the pericyclic system at the C-terminus. Equilibration studies have suggested that although the cyclization may be reversible under the reaction conditions, the torquoselectivity is probably mainly kinetic in origin, and a transition-state model has been proposed to account for the observed selectivity, based on steric interactions between the nitrogen substituent and the groups at the chiral centre(s).[68] Various α,β-unsaturated esters (**52**) have been shown to react with dimethyl diazomalonate in the presence of $Cu(acac)_2$ to give a variety of γ-lactone derivatives by [1,5]-electrocyclization of the initially formed α,β-unsaturated carbonyl ylid (**53**). The immediate ring closure products (**54**) have been found to suffer a range of fates, including hydration, hydrolysis, and capture by a second equivalent of carbenoid, some of which are outlined in Scheme 10.[69]

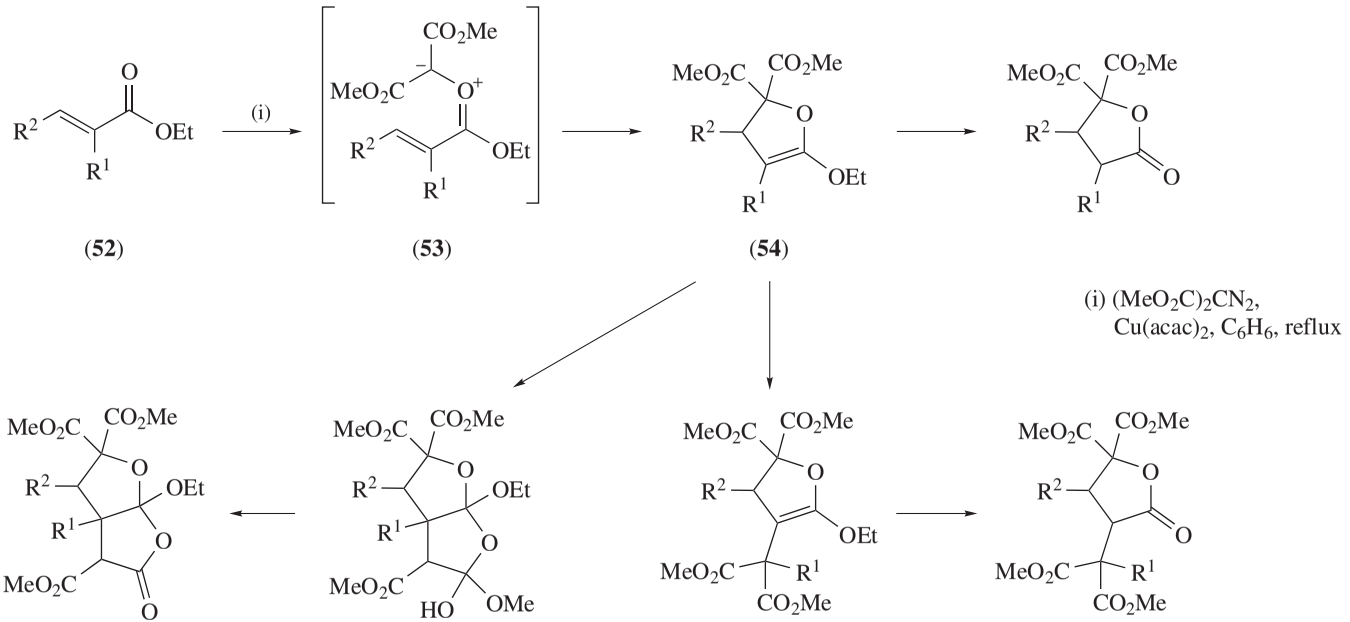
(de)

Using DFT calculations and natural bond orbital analysis, it has been shown that in substituted oxazoles, a C(2)-amino substituent and a C(5)-alkoxy substituent interact independently with orthogonal orbital systems to reduce the energy barrier to ring opening of the oxazole to a carbonyl-substituted nitrile ylid. Thus the lone pair on a C(2)-amino group has been found to conjugate in the plane of the ring with C(2) and with lone pairs on the ring N and O atoms. By contrast, a C(5)-alkoxy substituent has been shown to donate its lone pair to the π system orthogonal to the opening ring. The two effects on the transition state and product energies have been found to be almost additive.[70]

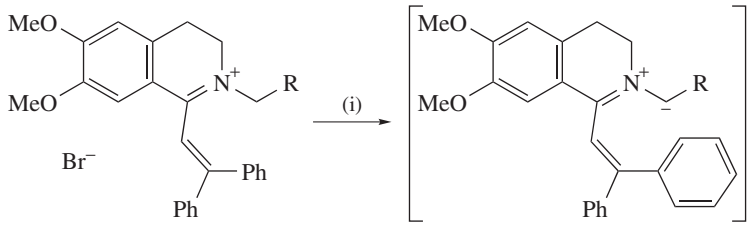


DFT studies have highlighted the rôle which can be played by a molecular container in the eight-electron electrocyclic ring expansion of bicyclo[4.1.0]heptatriene to cyclohepta-1,2,4,6-tetraene.[71] Azomethine ylids (**56**) generated from isoquinolinium salts (**55**) bearing a diphenylvinyl substituent in the 2-position have been shown to form tetrahydro[5,6]azepino[2,1-*a*]isoquinolines (**57**) by a [1,7]-electrocyclization, followed by either a [1,5]-prototropic shift, or proton migration under the prevailing basic conditions. The sequence has been found to give good yields in general, but has been shown to be blocked if the side-chain is unable to adopt a suitable conformation, as for example with a naphthalene side-chain.[72]

2-Bromo-3-(*o*-styryl)cyclopentenone (**58**) and various derivatives and analogues have been shown to react with base in trifluoroethanol to produce tricyclic products (**60**) by electrocyclization of antiaromatic cyclopentadienone intermediates (**59**) as shown. The loss of antiaromaticity as the transition state develops has been confirmed by DFT calculations, which have also suggested that the regioisomeric ring closure on to C(2) of the enone, which has not been observed, would be associated with an increase in antiaromaticity going into the transition state.[73]

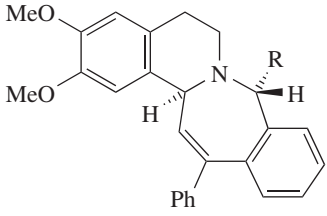


SCHEME 10

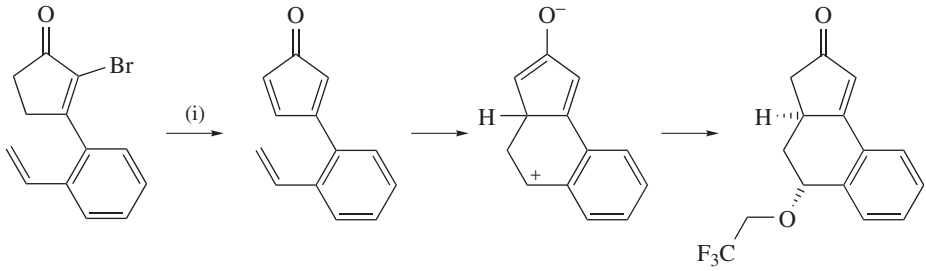


(**55**) (**56**)

(i) Et_3N, MeOH



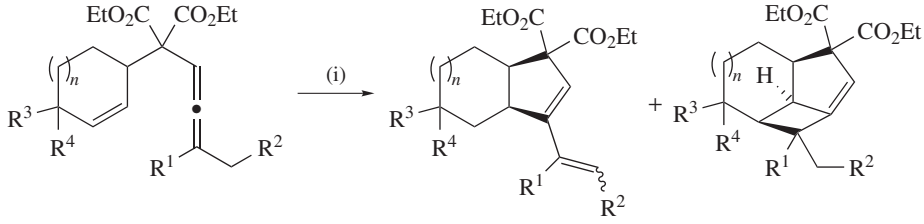
(**57**)



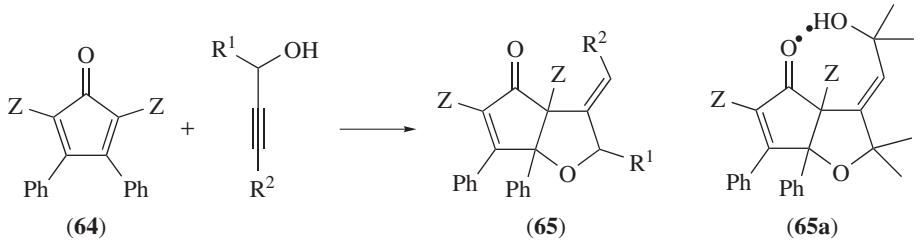
(**58**) (**59**) (i) Et_3N, F_3CCH_2OH, heat (**60**)

Ene Reactions

Ene-allenes (**61**) having a two-carbon bridge have been found to be good substrates under relatively mild conditions for ene reactions giving dienes (**62**), albeit with 2 + 2-cycloadducts (**63**) formed as minor byproducts in most cases.[74] Treatment of 2,5-bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone (**64**) with non-hindered propargylic alcohols has been shown to give, primarily or exclusively, bicyclic cyclopenta[*b*]furan-4-one derivatives (**65**), formally the products of 1,4-nucleophilic attack followed by ene reaction. As steric hindrance increases, Diels–Alder cycloaddition has been found to compete with this sequence, either directly or following 1,4-nucleophilic attack, giving products (**66**) and/or (**67**), respectively. Product (**65a**) has been shown, by X-ray crystallography, to have an (*E*)-*exo*-methylene bond, and a hydrogen bond between the second alcohol and the enone, as shown. This has led to the proposal that

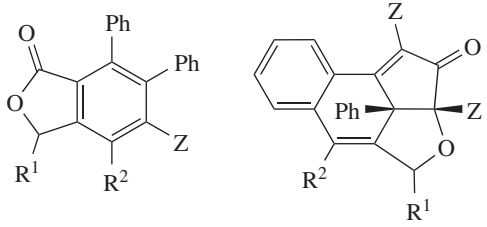


(**61**) (i) DMF, 120 °C, 24–108 h (**62**) (**63**)



(**64**) (**65**) (**65a**)

Z = CO_2Me throughout

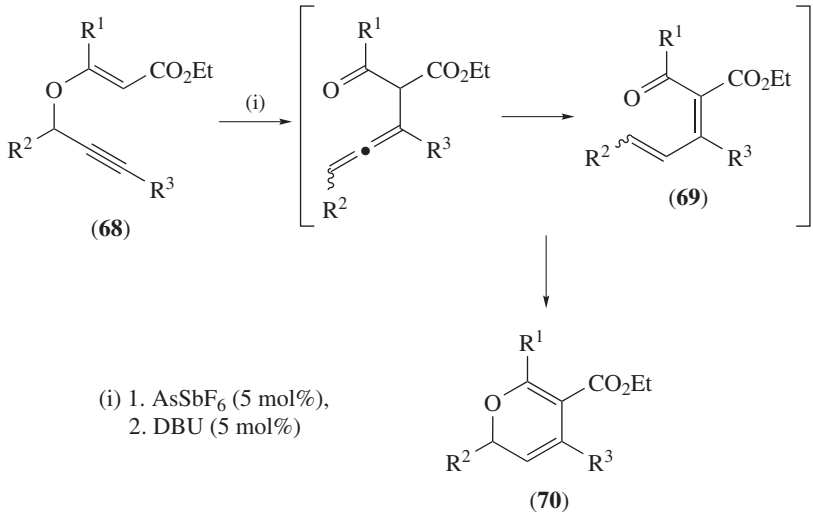


(**66**) (**67**)

the formal ene rearrangement, at least in the presence of a second –OH group, occurs in a stepwise fashion, promoted by intramolecular hydrogen bonding.[75]

Tandem Pericyclic Rearrangements

Formal 1,2-prenyl migration in suitably protected tryptamine and tryptophan derivatives bearing a prenyl substituent on the indole nitrogen has been studied experimentally and using DFT calculations. The rearrangement has been shown to proceed under Brønsted acid conditions, but better yields, and in the tryptophan derivative better *ee*s, have been obtained using a large excess of Lewis acid. DFT calculations have suggested that the migration involves charge separation to an allyl-like partial carbocation, which is stabilized by π-stacking over the indole ring. This has been found to favour sequential [3,3]-sigmatropic migration to C(3a) of the indole, [3,3]-sigmatropic migration to C(2) of the indole, and finally a [1,5]-hydrogen shift from C(2) to the indole nitrogen.[76] Suitably substituted propargyl vinyl ether derivatives (**68**) have been shown to transform into 2,4,6-trisubstituted 5-ethoxycarbonyl 2*H*-pyrans (**70**) on sequential treatment with $AgSbF_6$ and DBU. The reaction has been



SCHEME 11

proposed to occur by a silver-catalysed propargyl Claisen rearrangement, followed by base-catalysed allylic transposition, and finally six-electron electrocyclization, as shown in Scheme 11. This mechanism has been supported by the isolation in two cases of the conjugated dienone (**69**).[77]

Alkynyl propargyl sulfides have been shown to rearrange on heating by a [3,3]-sigmatropic rearrangement–four-electron electrocyclic ring closure sequence. When both alkynes bear terminal substituents, the product 4-methylenecyclobutenethiones have been found to be isolable in moderate to good yields, and it has been shown that an intermediate allenylthioketene can be trapped using diethylamine. Absence of a terminal substituent on the propargyl group has been found to destabilize the 4-methylenecyclobutenethione, but in one case has allowed isolation instead of the allenylthioketene.[78] It has been shown that 2-(4′-aryloxybut-2′-ynylthio)-1-acetylindoles rearrange to 9-acetyl-4-(4′-aryloxymethyl)-2,9-dihydrothiopyrano[2,3-*b*]indoles on refluxing in chlorobenzene. On stronger heating, or under Lewis acid catalysis, these products have been shown to rearrange to substituted 7-acetyl-11c-methyl-4b,5,7,11c-tetrahydro[1]benzofuro[2′3′:4,5]thiopyrano[2,3-*b*]indole derivatives. The first rearrangement has been accounted for by sequential [3,3]-sigmatropic thio-Claisen rearrangement in the (but-2-ynylthio)indole moiety, thioenol tautomerization, [1,5]-hydrogen shift, and six-electron electrocyclization, and the second by [3,3]-sigmatropic Claisen rearrangement of the (alk-2-ynyloxy)arene fragment followed by keto–enol tautomerization and 5-*exo-trig* cyclization.[79] It has further been shown that 2-(4′-aryloxybut-2′-ynylthio)-1-methylindoles, on mild oxidation followed by gentle heating, rearrange to 2-aryloxymethyl-3-hydroxymethyl-8-methylthieno[2,3-*b*]indole derivatives. This rearrangement has been attributed to the following reaction sequence: [2,3]-sigmatropic rearrangement of the corresponding sulfoxide; [3,3]-sigmatropic rearrangement of the resulting allenyl intermediate; thioenol tautomerization with

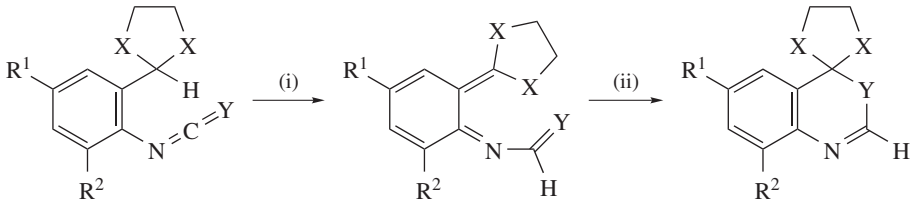
(i) PhSCl, Et_3N, THF
(ii) double [2,3]-sigmatropic rearrangement
(iii) 6-electron electrocyclization
(iv) 4+2 cycloaddition
(v) Raney-Ni, THF, reflux

SCHEME 12

5-*exo-trig* attack of sulfur on the carbonyl carbon thus formed; and finally S_N2' conversion of the resulting monothiohemiacetal into an allylic alcohol. Isolation, in two cases, of the last-mentioned intermediate in this sequence has supported this proposed mechanism.[80]

A tandem sequence of double [2,3]-sigmatropic rearrangement–six-electron electrocyclization–4 + 2-cycloaddition has been shown to convert acyclic ene-bis(propargyl alcohols) such as (**71**), via the corresponding bis-sulfenic ethers such as (**72**), into anthracene (with an intermolecular final cycloaddition) or phenanthrene or related (with an intramolecular cycloaddition) skeletons. The sequence is illustrated in Scheme 12 for synthesis of a steroid skeleton, estra-1,3,5(10)-trien-17-one (**73**).[81]

Heating (thio)acetal *N*-arylketenimines (**74a,b**) or acetal-bearing *N*-arylcarbodiimides (**74c**) has been found to produce spiro[1,3-dioxolane-2,4′(3′*H*)-quinolines] (**76a**), or the corresponding spirodithiolane (**76b**) or quinazoline (**76c**) derivatives, respectively. The proposed mechanistic sequence involves a [1,5]-hydrogen shift to the central carbon of the cumulene system giving (**75**), followed by six-electron electrocyclization to the new heterocycle, as shown in Scheme 13. This mechanism has been supported by DFT calculations, which have suggested that the [1,5]-hydrogen shift is rate limiting. The sequence has been found to proceed most readily for the acetal ketenimines, and least readily for the carbodiimides, so that thioacetal-bearing carbodiimides (**74**; X = S, Y = NAr) have been shown to be unreactive. The (thio)acetal group has been shown to be required for the reaction to proceed, and it has been suggested that hyperconjugative interactions between the O or S lone pairs and the C–H σ^* orbital weaken the C–H bond and allow the hydride shift to occur.[82]



(**74**) (**75**) (**76**)

a; X = O, Y = CPhR^3
b; X = S, Y = CPhR^3
c; X = O, Y = NAr

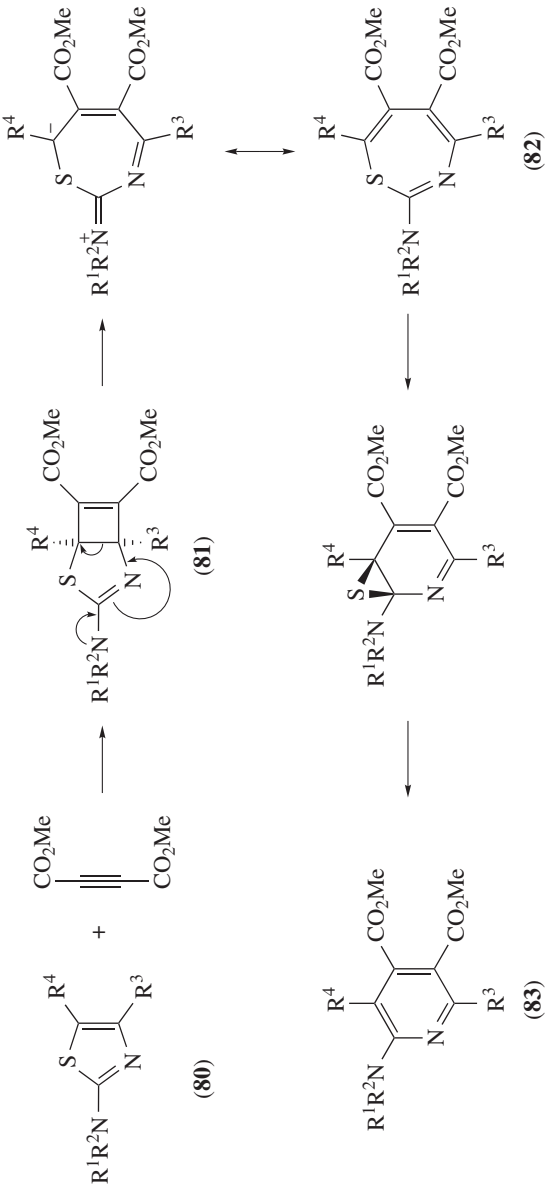
(i) [1,5]-hydrogen shift
(ii) 6-electron electrocyclization

SCHEME 13

Derivatives of 3-allyl-4-(dialkylallenyl)furan-2(5*H*)-one (**77**) have been shown to rearrange on heating to give fused bicyclic cyclooctatriene derivatives (**78**) in moderate to excellent yields. Although the products are formally those of an ene reaction between allyl and allene groups, two alternative mechanisms have been proposed: either direct [1,5]-hydrogen shift followed by eight-electron electrocyclization, or initial 2 + 2-cycloaddition followed by [1,5]-hydrogen shift and six-electron electrocyclic ring opening, as shown in Scheme 14. The last pathway has been supported not only by the known tendency of allenes to undergo 2 + 2-cycloaddition, but

(i) 2+2 cycloaddition
(ii) [1,5]-hydrogen shift
(iii) 6-electron electrocyclic rearrangement
(iv) 8-electron electrocyclization
(77)
(78)
(79)

SCHEME 14



SCHEME 15

also by the Diels–Alder trapping of intermediate (**79**) in the related conversion of 3-(dimethylallenyl)-2-(methallyl)cyclohex-2-enone into 4,4,6-trimethylbicyclo[6.4.0] dodeca-1(8),2,6-trien-9-one.[83]

Benzocyclobutenone and derivatives have been shown to react with diazomethylene anions to give 2,3-benzodiazepines under very mild conditions. A mechanism has been proposed which involves four-electron electrocyclic ring opening of the initial alkoxide, with important acceleration by the alkoxide anion. Torquoselectivity to set up an eight-electron electrocyclic ring closure to the benzodiazepine enolate has been attributed to the strong preference of the alkoxide anion for outward rotation. This mechanism has been supported by isolation of one of the β-diazo alcohols, and its conversion to a benzodiazepine on LDA treatment.[84]

Various 2-aminothiazoles (**80**) have been found to react with dimethyl acetylenedicarboxylate to produce dimethyl 2-amino-4,5-pyridinedicarboxylates (**83**). A mechanism has been proposed and supported experimentally and computationally, and is shown in Scheme 15. Polar stepwise 2 + 2-cycloaddition has been suggested to generate bicycle (**81**), which has been isolated in one case. Although symmetry-allowed (de) four-electron electrocyclic ring opening of (**81**) would be conrotatory and lead to a *trans*-alkene, it has been suggested that a symmetry-allowed disrotatory six-electron, five-atom, dipolar electrocyclic ring opening of the thiazole portion could lead to the all-*cis*-thiazepine (**82**). This proposal has experimental support from two sources. Electron-deficient substituents at C(4) have been observed to retard the overall reaction, perhaps by destabilizing the positive charge developing next to the N atom in the polar ring opening. Also, bicycle (**81**) has been shown to transform into the corresponding pyridine (**83**) on heating, but not in the presence of acid, suggesting the importance of a free exocyclic amine. Six-electron eletrocyclization of thiazepine (**82**), followed by sulfur extrusion, has been proposed for the generation of the observed pyridine products (**83**).[85]

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CHAPTER 14

Molecular Rearrangements: Part 2. Other Reactions

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Aromatic Rearrangements

Benzene Derivatives

The formation of α-phenyl-β-halovinyl cation, β-phenyl-α-halovinyl cation, and also the halogen-bridged and the spirocyclic phenyl-bridged cations, as intermediates of protonation of phenylethynyl halides, or of halogen addition to phenylethynes, has been evaluated by DFT at the B3LYP/6–31+G(d) level and, for comparison in representative cases, by B3LYP/6-311++G(d,p).[1] Structural and mechanistic studies of the lithium diisopropylamide (LDA)-mediated anionic Fries rearrangements of aryl carbamates have been described.[2] Substituents at the *meta* position of the arene (H, OMe, F) and the dialkylamino moiety of the carbamate (Me_2N, Et_2N, and i-Pr_2N) markedly influence the relative rates of ortholithiation and subsequent Fries rearrangement. The mechanism of the Fries rearrangement of aryl formates promoted by boron trichloride has been studied by means of ^1H, ^2H, and ^{11}B NMR spectroscopy and DFT calculations.[3]

After the formation of a 1:1 substrate – Lewis acid adduct, the rearrangement proceeds in two steps, beginning with the cleavage of the ester bond and the release of formyl chloride *in situ*, which, in turn, acts as a formylating agent, introducing

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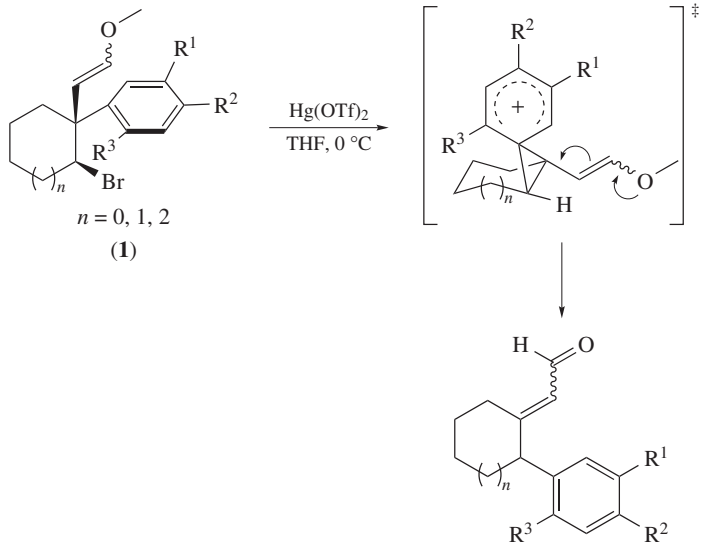
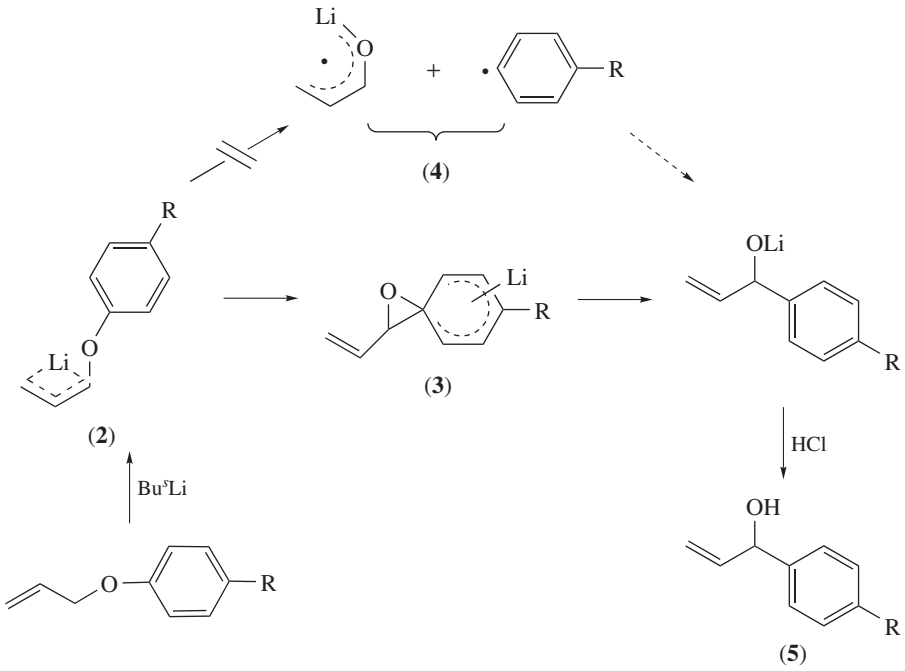


SCHEME 1

an aldehydic functionality into the aromatic ring. A synthetically useful Wagner–Meerwein rearrangement of α-quaternary β-bromovinyl methyl ethers (**1**) promoted by $Hg(OTf)_2$ has been developed (Scheme 1).[4]

It is noteworthy that the *E*- and *Z*-isomer ratios of the double bonds in substrates have little effect on the stereochemistry of the product double bonds. This rearrangement afforded not only an excellent method to place an aryl group at the γ-position of α,β-unsaturated aldehydes, but also a convenient synthetic approach to some natural skeletons with a tricyclic aromatic system. 1,3-Diphenylisobenzofuran Diels–Alder cycloadducts, with *n*-butyl- and phenyl-substituted acetylenic sulfones, underwent various types of rearrangements under pyrolytic, acid-catalysed, and photochemical conditions.[5] Dibenzoylketene has been reported to undergo degenerate 1,3-shifts of the phenyl group between acyl and ketene carbon atoms in the gas phase under vacuum thermolysis (FVT) conditions, but not in solution at 110–145 °C.[6] Imidoyl(benzoyl)ketene undergoes a degenerate 1,3-shift of the phenyl group on FVT. Calculations of the transition states for the transformations at the B3LYP/6–31G** level of theory are in agreement with the observed reaction preferences. A mechanistic study on the [1,2] Wittig rearrangement of α-lithiated allyl phenyl ethers (**2**) affording, after acidic hydrolysis, 1-phenylprop-2-en-1-ol (**5**) as the main product, has been reported (Scheme 2).[7]

Although the two competing intermediates, the hypothetical ketyl–aryl radical pair (**4**) and the oxaspirooctadienyllithium (**3**), are not the rate-determining transition states, they should lie at almost the same energetic level. The rearrangement is in accord with the intramolecular nucleophilic addition/elimination mechanism rather than with homolytic cleavage/recombination.



SCHEME 2

Ionic Rearrangements

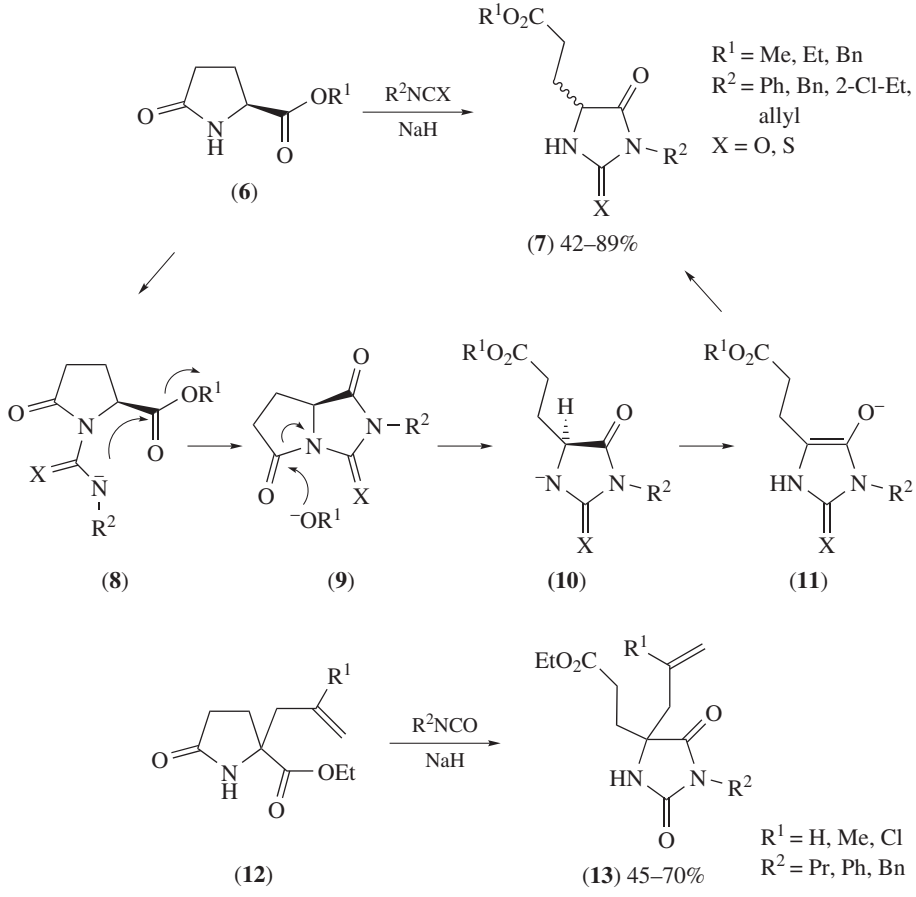
Anionic Rearrangements

A novel reaction of pyroglutamate (**6**) and an isocyanate promoted by NaH in THF leads to functionalized hydantoins (**7**) in good yields. The reaction involves the ring closure of intermediate (**8**) by a nucleophilic attack on the carbonyl of the ester function followed by expulsion of an alkoxide anion resulting in the formation of the bicyclic intermediate (**9**). The alkoxide anion in turn can open this bicyclic intermediate with formation of anions (**10**) and (**11**) leading to the final racemic hydantoins (**7**) (Scheme 3).[8]

Highly substituted hydantoins (**13**) can be obtained in similar yield and very mild conditions starting from pyroglutamates (**12**) (Scheme 3).

The base-catalysed acyl transfer (Baker–Venkataraman reaction) of enantiopure 2-acetyl-1-hydroxyanthraquinone esters of 2-methylbutanoic acid or of *O*-allyllactic acid produces the respective 1,3-diketones, precursors of anthra[1,2-*b*]pyran antibiotics, without any racemization.[9] (ee)

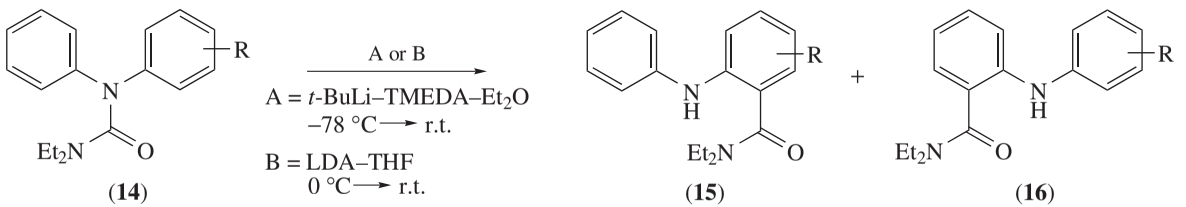
The acetylation of *p-t*-butyl[3.1.3.1]homooxacalixarene with acetyl chloride and CsF as a base takes place through an equilibrium with the occurrence of both intra- and inter-molecular acyl transfers. Control of the reaction conditions allows the various acetyl derivatives to be obtained.[10]



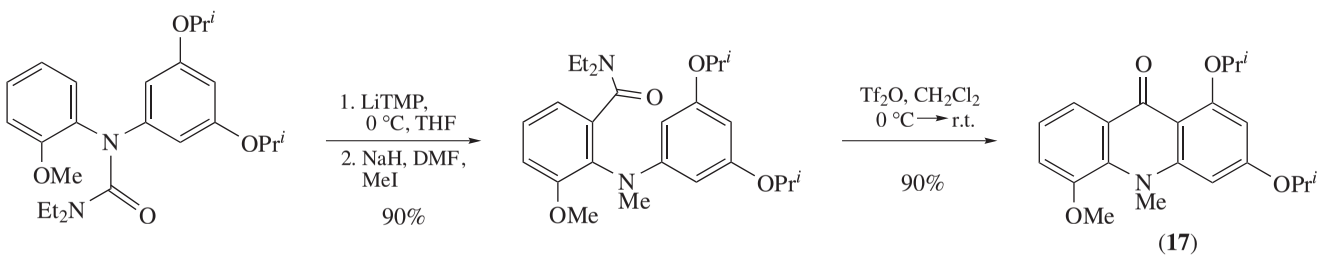
SCHEME 3

Base-catalysed benzil–benzilic acid rearrangement and the methyl analogue were investigated by DFT calculations. The reaction paths of the rearrangement were investigated in term of FMO theory, in particular the carbanion [1,2]-migration that was calculated to be the rate-determining step.[11] The double α-ketol rearrangement of (1*S*, 2*R*,4*R*)-2-acetyl-1-vinyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptane in the NaH–THF is reported.[12] Adducts of potassium enolate of (*E*/*Z*)-4-phenylbut-3-en-2-one (*ee*) with 6-aryl-3,4-disubstituted-2*H*-pyran-2-ones rearrange affording highly functionalized (*E*)-stilbenes and 4-aryl-6-styrylpyran-2-ylidineacetonitriles by two different reaction paths.[13]

N-Carbamoyldiarylamines (**14**) have been shown to undergo a new anionic *ortho N*-Fries rearrangement to anthranilamides with good to excellent regioselectivity and in synthetically useful yields (Scheme 4).[14] The *t*-butyllithium or LDA-mediated direct *ortho*-metallation strategy applied to substituted *N*-carbamoyldiarylamines (**14a**–**c**)



a: R = H	A: 81%		
	B: 90%		
b: R = 3-Cl	A: 92%		
	B: 94%		
c: R = 4-Cl	A: 87%		
	B: 97%		
d: R = 3-OMe	A: 59%		26%
	B: 6%		90%
e: R = 4-OMe	A: 54%		35%
	B: 4%		90%
f: R = 3,5-OMe	A: 75%		14%
	B: 7%		90%
g: R = 2-Ph	A: 73%		19%
	B: 47%		51%



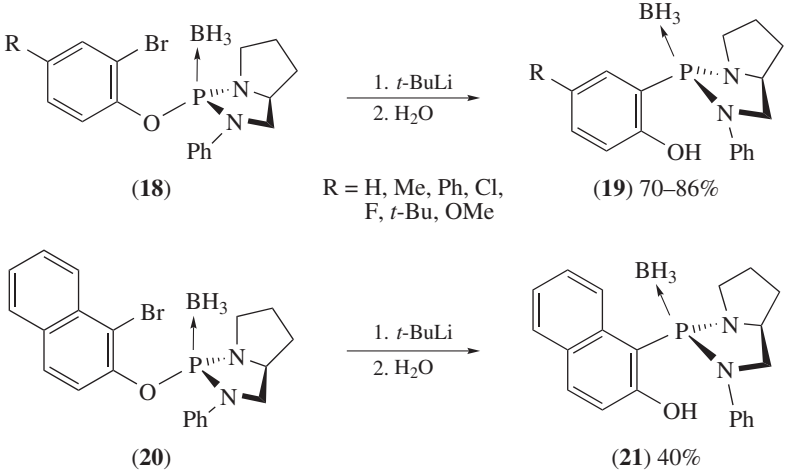
SCHEME 4

leads regioselectively to anthranilamides (**15a–c**), whereas (**14d–g**) give both (**15d–g**) and (**16d–g**) with varied regioselectivity accordingly to the base used. The strategy can be applied efficiently to the synthesis of acridone (**17**), an intermediate for the synthesis of acridone and pyranoacridone alkaloids.

Lithiation of aryltriazenes followed by treatment with an electrophile provides a new approach to benzylamines. The regioselectivity of the reaction can be controlled by means of the substituents on the aryl group. The reaction consists of an intramolecular carbon–carbon bond formation with the aryl ring of a lithiated alkyl group on a 3-nitrogen atom, a 1,2-proton shift, demonstrated by deuterium substitution, and the subsequent release of nitrogen gas.[15]

New *P*-stereogenic (*o*-hydroxyaryl)diazaphospholidines, in the form of their borane complexes (**19**), have been synthesized in a totally diastereoselective manner by a P–O to P–C migration rearrangement of (*o*-bromoaryloxy)diazaphospholidine–borane complexes (**18**) mediated by *t*-BuLi (Scheme 5).[16] The stereoselective rearrangement, confirmed by X-ray diffraction study of the structures of the product (**21**) and its precursor (**20**), occurs with clean retention of the phosphorus configuration.

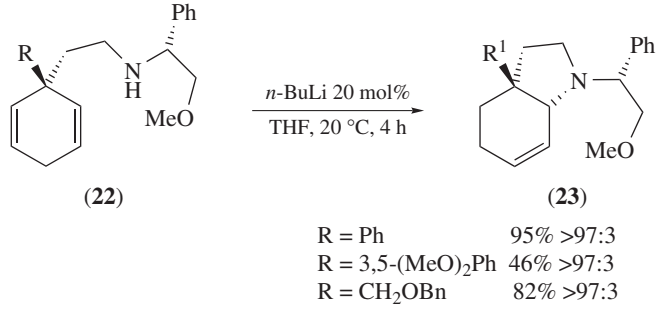
A review on anionotropic 1,2-rearrangements of borate complexes evidences the most important factors that are responsible for which group migrates, by showing a broad spectrum of reactions involving borate complexes.[17]



SCHEME 5

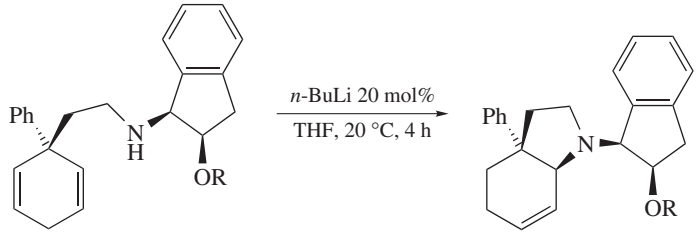
The rate constants, thermodynamic parameters of activation, equilibrium constant, and the isomerization enthalpy for conversion of cholest-5-en-3-one to cholest-4-en-3-one catalysed by EtONa in absolute ethanol were determined by classic and multivariate kinetic methodologies. The multivariate modelling kinetic treatment allowed the concentrations of the species involved to be calculated, revealed the 3,5-dienolate to be a highly reactive intermediate, and was able to discriminate among several applicable mechanisms, thereby supporting the one comprising two reversible steps.[18]

A desymmetrization of cyclohexa-2,5-dienes (**22**) and (**24**), obtained by Birch reductive alkylation, through a diastereoselective intramolecular hydroamination led with high selectivity to the corresponding bicyclic allylic amines (**23**) and (**25**) (Scheme 6).[19] (de)



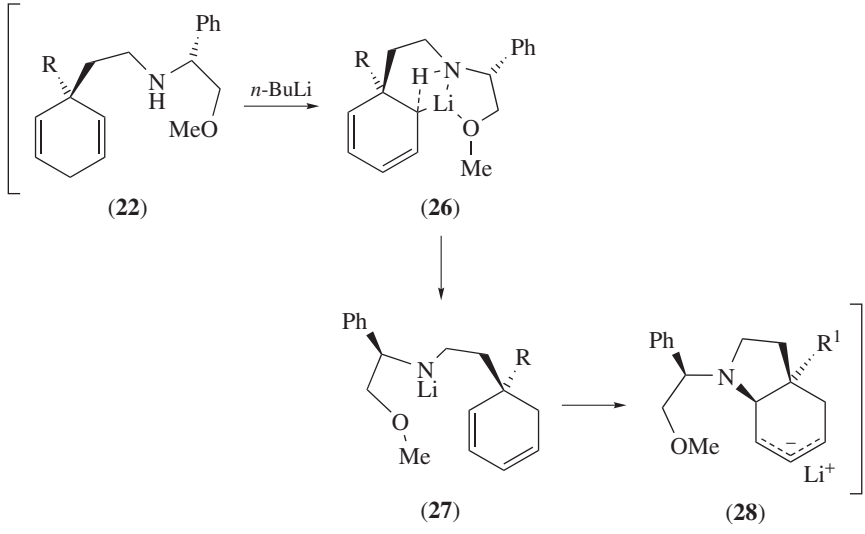
(**22**) (**23**)

R = Ph 95% >97:3
R = 3,5-$(MeO)_2$Ph 46% >97:3
R = CH_2OBn 82% >97:3



(**24**) (**25**)

R = Me 26% 90:10
R = MOM 73% 95:5



(**22**) (**26**) (**27**) (**28**)

SCHEME 6

The mechanism does not proceed through a direct hydroamination of one of the diastereotopic alkenes, but involves a series of very selective processes including a deprotonation of (**22**), diastereoselective protonation of (**26**), intramolecular addition of lithium amide (**27**) to the 1,3-diene moiety, and final regioselective protonation of the allyl anion (**28**), all mediated by a substoichiometric amount of *n*-BuLi.

The aza-Payne rearrangement of activated *N*-Ts-α,α-disubstituted-aziridinemethanols, induced by NaOH in the mixed solvent *t*-BuOH–H_2O–THF (4:5:1) or NaH in the mixed solvent THF–HMPA (10:1), and also some *N*-Boc-α,α-disubstituted-aziridinemethanols with the latter reagent–solvent combination, provides the corresponding epoxides in up to 99% yield.[20]

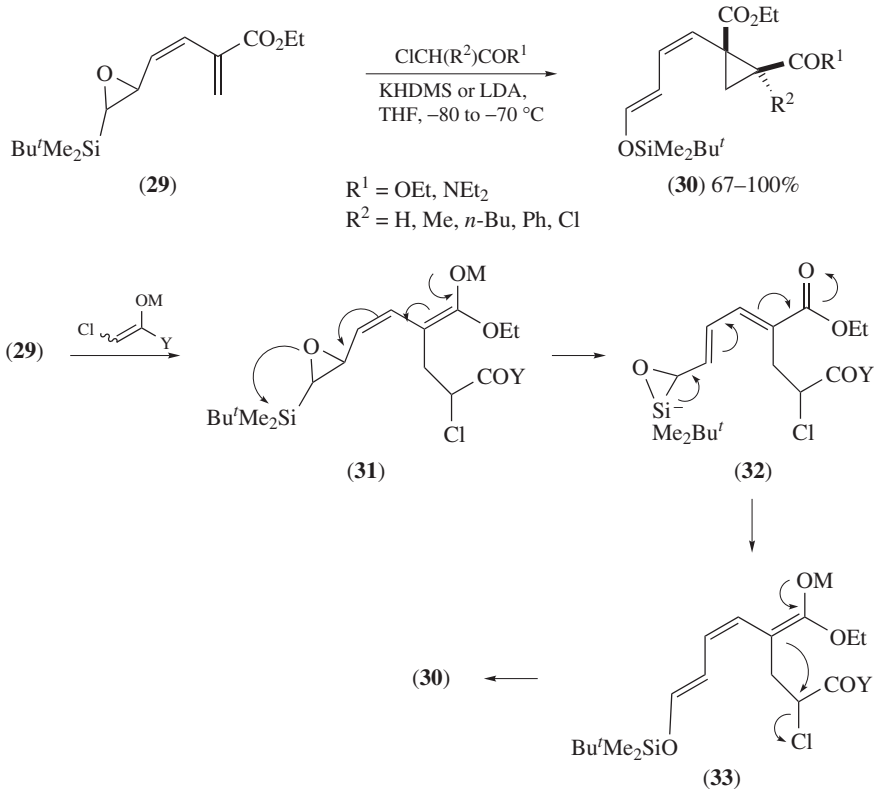
Treatment of 1,6:2,3-dianhydro- and 1,6:3,4-dianhydro-β-D-hexopyranoses with aqueous NaOH or NaI in acetone caused epoxide or pseudo-epoxide migration giving equilibrium mixtures. Experimental data were compared with DFT calculations and the role of chair–boat equilibration of 1,6-anhydro-3-deoxy-3-halo-β-D-glucopyranoses was analysed.[21]

The generation of a carbanion by a conjugate addition of the lithium enolates of 2-chloroacetates and 2-chloroacetamide to an enoate system, bearing an epoxysilane moiety at the vinylogous α-position (**29**), can induce epoxysilane rearrangement to afford highly functionalized cyclopropane derivatives (**30**) in good to excellent yields (Scheme 7).[22] With acetamides the reaction is diastereoselective. The domino process (de) involves Michael addition of the enolate followed by ring opening of the epoxide (**31**) to give intermediate (**32**). The exclusive formation of the internal (*Z*)-alkene in the reactions of both ester and amide enolates is warranted by the fast-reacting silicate intermediate (**33**) in an *s-cis*-diene conformation.

Metal alkoxides, such as sodium benzylate, in catalytic amounts promote the [2,3]-Wittig rearrangement of silyl enolates (**34**), to afford the corresponding rearrangement product (**35**) in good yields at room temperature (Scheme 8).[23]

It has been demonstrated that the oxygen anion of initially formed product (**36**) effectively catalysed the [2,3]-Wittig rearrangement as a Lewis base. Other Lewis-base catalysts such as lithio or sodio 2-pyrrolidone promote the same [2,3]-Wittig rearrangement of silyl enolates generated from α-allyloxy ketones, whereas rearrangements of enolates from α-allyloxy esters were efficiently catalysed by ammonium 4-methoxybenzoate.[24]

The [1,2]-Wittig rearrangement of several benzylic chloromethyl ethers by a 4,4′-di-*t*-butylbiphenyl (DTBB)-catalysed chlorine–lithium exchange has been carried out for the first time. Homobenzylic alcohols were obtained efficiently in good yields apart from a few cases.[25] A twofold [1,2]-Wittig rearrangement of bis-*O*-allyl-1,1′-binaphthalene-2,2′-diol (BINOL) occurs at $-75\,^{\circ}C$ with the LIC–KOR mixture (butyllithium + potassium *t*-butoxide) in 72% yield and with an unprecedented diastereoselectivity.[26] By X-ray crystallography, the axial chirality (*M*) was found to be associated (de) with the *S*-configuration of the oxygen-bearing side-chain and the *P*-helicity with the *R*-configuration. Benzyloxyallylsilane, treated with *s*-BuLi, undergoes an unusually rapid and efficient [1,4]-Wittig rearrangement. Results of a study of trapping



SCHEME 7

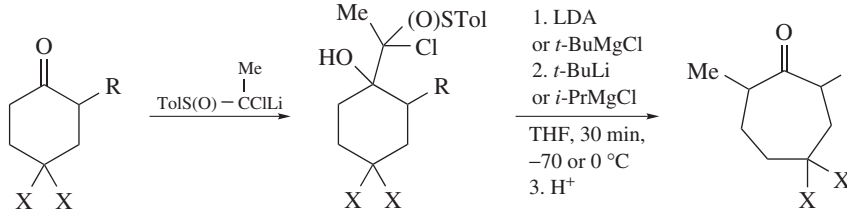
the intermediate α-carbanion with TMSCl prior to rearrangement indicate that α-deprotonation and bond reorganization are separate events.[27]

Adducts (**38**) of 2-substituted cyclohexanones (**37**) with lithium α-sulfinyl carbanion of 1-chloroethyl *p*-tolyl sulfoxide treated with LDA or *t*-BuMgCl give lithium or magnesium alkoxides, which on treatment with *t*-BuLi or *i*-PrMgCl afford one-carbon ring-expanded 2,7-disubstituted cycloheptanones (**39**) through β-oxido carbenoids (Scheme 9).[28] Interestingly, 2,3-disubstituted cycloheptanones were obtained in trace amounts or were not obtained at all. The enolate intermediates of this reaction are able to be trapped with electrophiles to give 2,2,7-trisubstituted cycloheptanones in moderate to good yields.

Treatment of 1-chloro-2-methylalkenyl *p*-tolyl sulfoxides with *N*-lithio-2-piperidone in THF at room temperature resulted in the formation of 1-chloro-2-(hydroxymethyl)alkenyl *p*-tolyl sulfides in good yields. The reaction is the first example of the Mislow–Braverman–Evans rearrangement retaining the sulfur atom on the original carbon.[29]

OSiMe3
O
R
(34)
1. M-OBn cat.
DMF, r.t., 1 h
2. H+
R = H, OMe, CN
OH
O
R
(35) 76–98%
(34)
DMF
(36)
OM
O
R
Na+
DMF
Si
O
O
O
O
R
OH
O
R
(35)
(34)

SCHEME 8



SCHEME 9

The reaction of 2-(diphenylmethylene)thietan-3-one with 1,2,4,5-tetrazines in KOH–MeOH–THF gives 4*H*-pyrazolo[5,1-*c*]thiazines. This novel condensation reaction proceeds via the intermediacy of an 8-(diphenylmethylene)-2*H*-1,4,5-thiadiazocin-7(8*H*)-one, which undergoes a multi-step rearrangement including a rare anti-Michael addition.[30]

Cationic Rearrangements

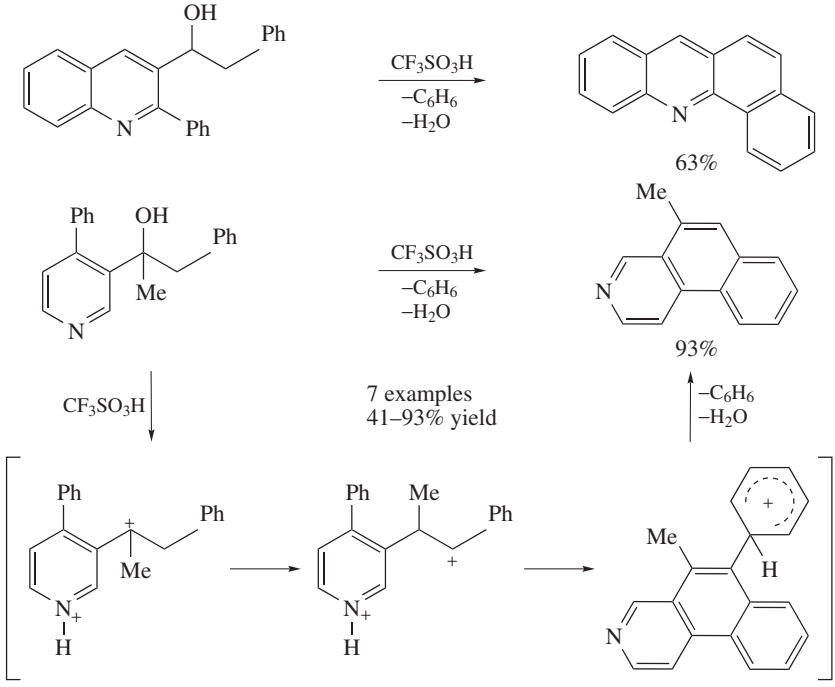
Superacid-promoted dicationic species containing heteroaromatic rings, where positive charge centres migrate through consecutive deprotonation–reprotonation steps, undergo cyclization reactions followed by aromatization and superacid-promoted elimination of benzene (Scheme 10).[31] The process leads to the synthesis of aza-polycyclic aromatic compounds in moderate to good yields. Seven examples include pirazole, oxazole, and thiazole heterocycles.

The unique electrocatalytic role of benzoic acid-protected silver nanoclusters in the Wolff rearrangement of α-diazo ketones has been disclosed. The presence of a Ag_n^0/Ag_n^+ redox couple facilitates a non-classical electron-transfer process, involving chemical reactions interposed between two electron-transfer steps occurring in opposite directions.[32]

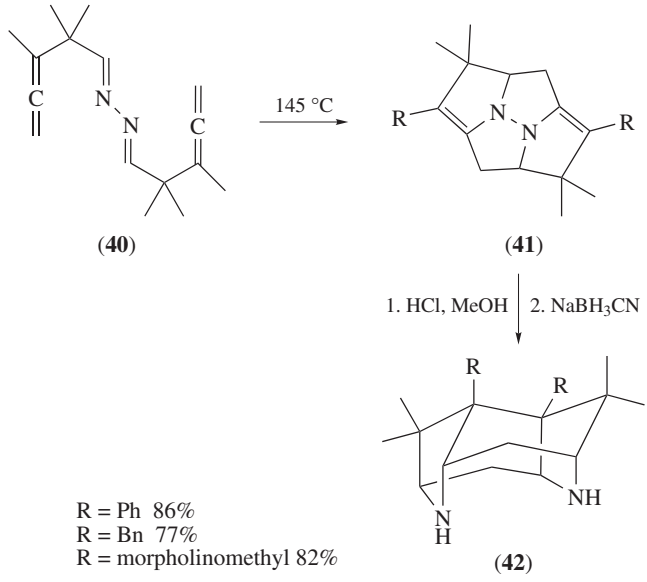
A new rearrangement of fused tetracyclic heterocycles, obtained by criss-cross intramolecular cycloadditions of homoallenylazines (**40**), mediated by HCl in MeOH, leads to high yields of cage compounds (**42**) after reduction with $NaBH_3CN$ (Scheme 11).[33]

The decarboxymethylation of substituted α-hydroxy-α-carbomethoxy hexacyclic substituted ketones (**43**), one of these used as an advanced intermediate in the synthesis of the alkaloid aspidophytine, can be effected by heating with MgI_2 in CH_3CN in good yields (75–84%) (Scheme 12).[34] The reaction was shown to proceed through a novel α-hydroxy β-dicarbonyl to α-ketol ester rearrangement mechanism, which is supported by the isolation of the carbonate (**45**) intermediate.

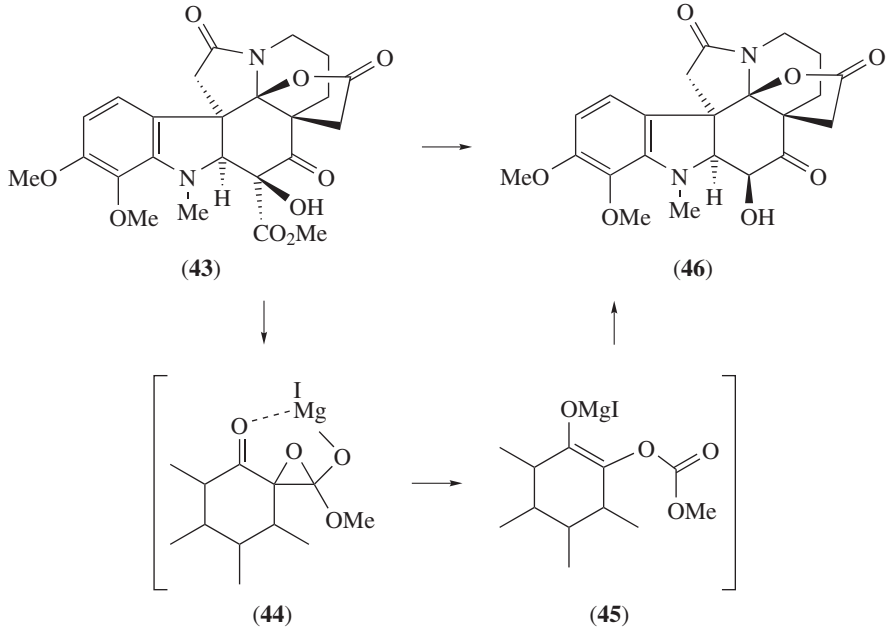
The BF_3-promoted rearrangement of several 4,5-epoxy-9-trimethylsilyldecalines having different relative stereochemistry and substitution at the oxirane ring is described. The presence of the silicon at C(9) favours two different main reaction pathways



SCHEME 10



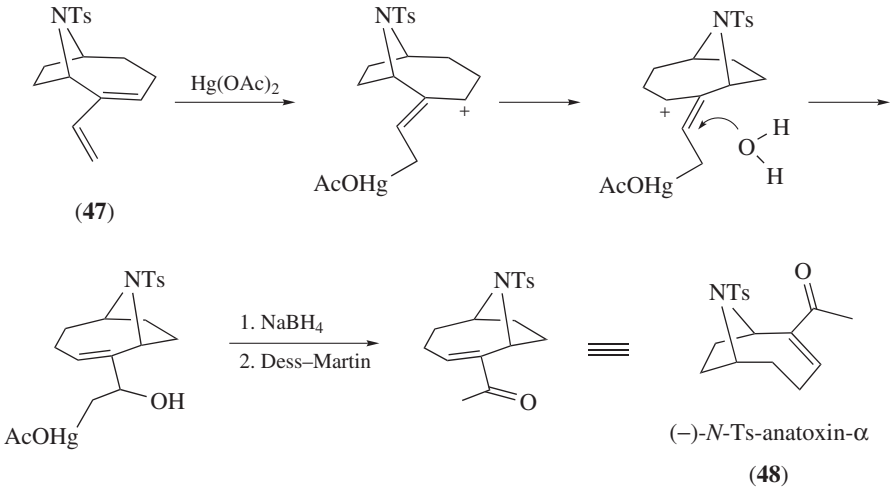
SCHEME 11



SCHEME 12

involving bridgehead-methyl or C(1)-methylene migration through the stabilization of a carbocation intermediate. The synthetic utility of these rearrangements is shown by the synthesis of natural (−)-aristolochene.[35] The acid-catalysed conversion of (de) isotwistanol skeleton to the tricyclo[5.2.1.$0^{4,8}$]decane skeleton has provided support for the proposed biosynthesis of allopupukeananes from pupukeananes.[36] The isomer- (de) ization of *trans*-3-deutero-*r*-1-methyl-*cis*-2-phenylcyclopropan-1-ol to three isomeric cyclopropanols was facilitated by reaction with a mixture of Ti(O-*i*-Pr)$_4$ and BF_3.OEt_2. The more Lewis acidic Cl_2Ti(O-*i*-Pr)$_2$ is able to catalyse the same reaction in the absence of BF_3.OEt_2. A reversible ring opening to a β-titanaketone is involved in this rearrangement. The mechanism proposed is able to explain both retention and inversion of configuration at the carbon bearing phenyl for these isomerization processes that involve ring opening and ring closure.[37] A microporous metal–organic frame- (de) work [Cu_3(btc)$_2$] (BTC = benzene-1,3,5-tricarboxylate) is a highly selective Lewis acid catalyst for the isomerization of terpene derivatives, such as the rearrangement of α-pinene oxide to campholenic aldehyde and the cyclization of citronellal to isopulegol. By using the ethylene ketal of 2-bromopropiophenone as a test substrate, it was demonstrated that the active sites in [Cu_3(btc)$_2$] are hard Lewis acids.[38] The protonation and acid-catalysed rearrangements of a tricyclo[4.2.2.$2^{2,5}$]dodeca-3,7,9,11-tetraene scaffold were studied.[39] The fragmentations of 3-nortricyclyl, *exo*-5-norbornen-2-yl, and *endo*-5-norbornen-2-yl oxychlorocarbenes, chlorocarbonates, and chlorosulfites in polar solvents proceed via similar ion pairs to mixtures of *exo*-2-chloro-5-norbornene and 3-nortricyclyl chloride. The stereochemical course of

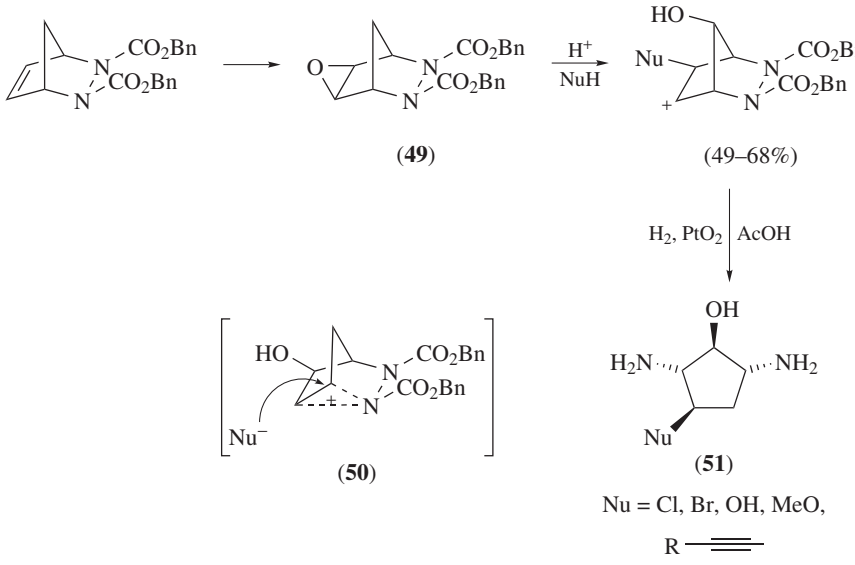
the conversions is mainly determined by least motion chloride return in ion-pair intermediates.[40] A theoretical investigation of the isomerization pathways from the norbornadiene to the cycloheptatriene radical cation has been carried out.[41] In the synthesis of (+)-anatoxin-*a* from *S*-(−)-pyroglutamic acid, an unexpected inversion of chirality, leading to (−)-*N*-Ts-anatoxin-*a* (**48**), was found to be the result of a skeletal rearrangement of 9-azabicyclo[4.2.1]nonene derivative (**47**) at the stage of the oxymercuration of diene (Scheme 13).[42] (ee)



SCHEME 13

Treatment of 1-indanols and 1-tetralols with hydrogen peroxide under acidic conditions caused substitution and hydroperoxide rearrangement to yield chroman-2-yl hydroperoxides or open-chain unsaturated geminal bis-hydroperoxides.[43] 2-(Arylmethylene)cyclopropylcarbinols in acetonitrile give the corresponding ring-enlarged *N*-(3-arylmethylidenecyclobutyl)acetamides in good yields under the catalysis of trifluoromethansulfonic acid.[44] Ionic liquid 1-methylpentylimidazolium bromide ([pmim]Br), catalyses, under sonication without solvent, the rearrangement of cyclopropylcarbinol derivatives to substituted all-*trans*-buta-1,3-dienes.[45] *N*-Acetylated 2,4,5-triphenylimidazolinium salts give an unprecedented acid-catalysed rearrangement leading to the *N*-benzoylated 2-methyl-4,5-diphenylimidazolinium salts.[46] (de)

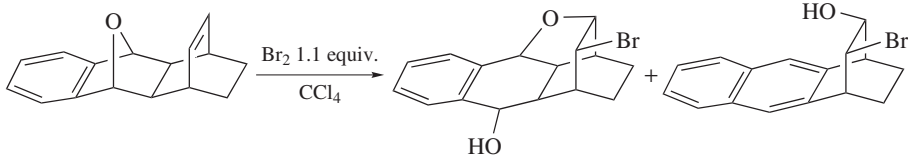
Several tetrasubstituted cyclopentanes (**51**) can be prepared in four steps from cyclopentadiene in good overall yield (30%) by the acid-catalysed rearrangement of epoxide (**49**) followed by a regio- and stereo-selective nucleophilic attack, with control of the relative configuration of four contigous stereogenic centres in a single operation (Scheme 14).[47] Participation of the nitrogen lone pair is likely to stabilize the cation intermediate (**50**). The Lewis acid-promoted rearrangement of 2,2,3,3-tetrasubstituted 2,3-epoxyalcohol derivatives, which have only a slight difference in stability of carbocation at the C(2) or C(3) positions, proceeds through the C(3) carbocation. With (de)



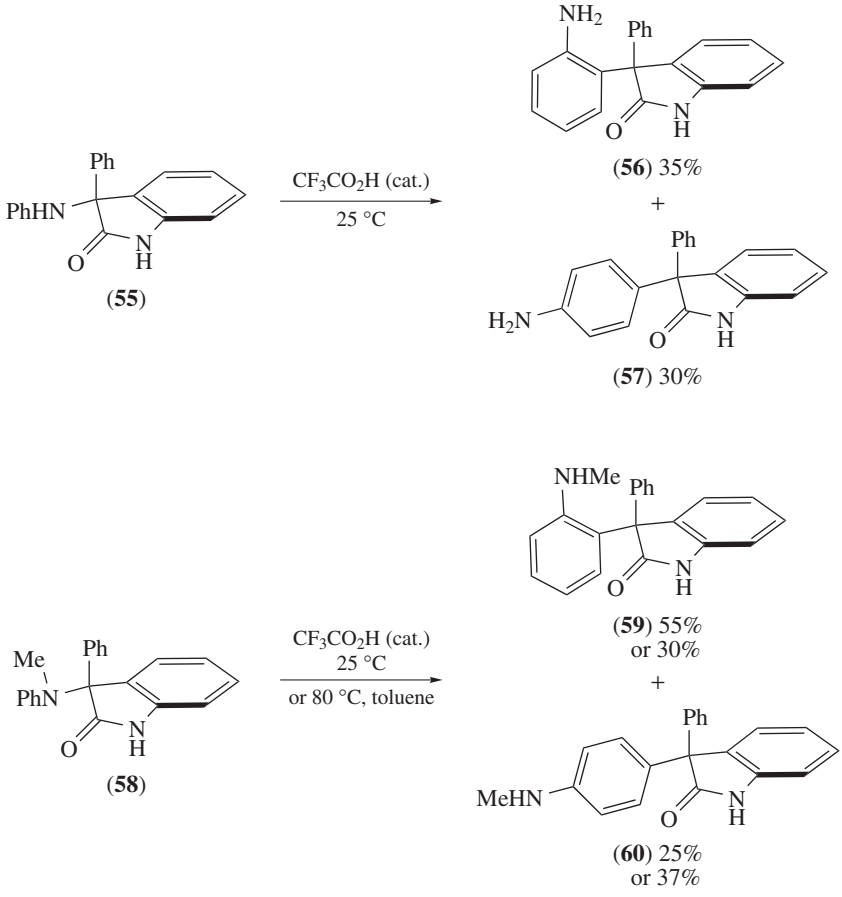
SCHEME 14

$SnCl_4$ as the LA, control of stereochemistry of the rearranged products is obtained only by changing the type of the protecting group.[48] The semi-pinacol rearrangement of alkenyl-substituted 2,3-epoxycyclopentanols gives stereoselectively α-alkenylated cyclopentanones.[49] Epoxides undergo an efficient and selective rearrangement to give carbonyl compounds (Meinwald rearrangement) in excellent yields by the catalysis of copper tetrafluoborate $[Cu(BF_4)_2.nH_2O]$.[50] An efficient one-pot domino procedure for allylation and propargylation of aryl epoxides has been developed by using $SnCl_2$ to promote the epoxide rearrangement and Pd(0) or Pd(II) to catalyse the allylation or propargylation, respectively, with allyl or propargyl bromides.[51] The adduct of cycloaddition of cyclohexadiene with 1,4-dihydronaphthalene-1,4-epoxide (**52**) by reaction with 1.1 equiv. of Br_2 afforded two main products, (**53**) and (**54**), in which a 1,5-oxygen migration has occurred (Scheme 15).[52]

With excess of Br_2, further bromination products of the central ring were obtained. 3-*N*-Aryl-2-oxindoles (**55**) undergo Hofmann–Martius rearrangement under acid-catalysed conditions, in contrast to their 3-*O* analogues (Scheme 16).[53] The thermal



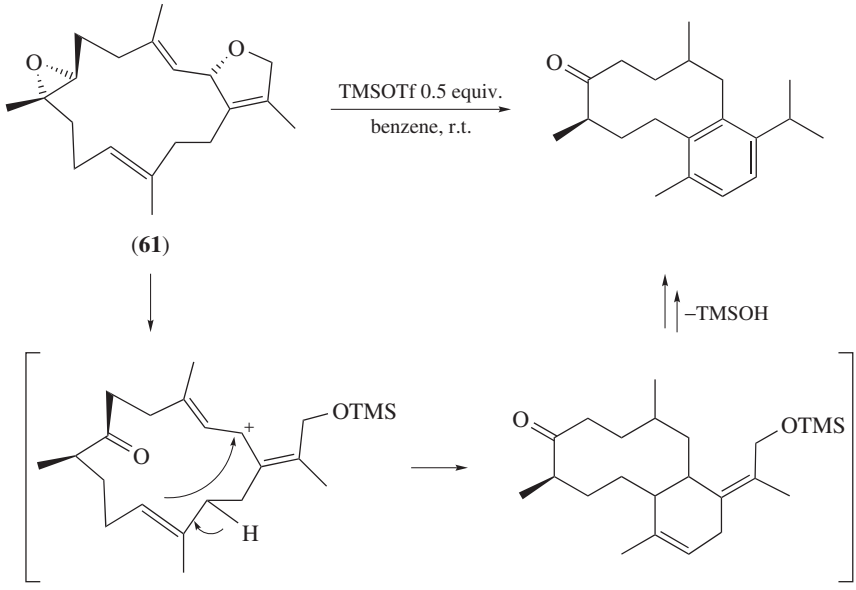
SCHEME 15



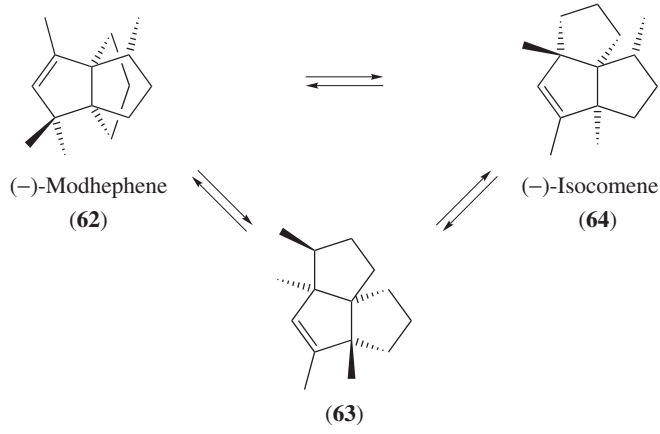
SCHEME 16

(and acid-catalysed) rearrangement is possible only with *N*-methyl-substituted compound (**58**). Higher regioselectivity is obtained with substituted *N*-aryls. The dissociative mechanism of the process, evident from the formation of *ortho*- (**56**) and *para*-substituted (**57**) rearrangement products, was also confirmed by crossover experiments.

An unusual transannular cyclization catalysed by TMSOTf occurs in a 14-membered marine cembranoid sarcophytoxide (**61**), together with an epoxide–ketone rearrangement (Scheme 17).[54] The concomitant opening of the epoxide ring in (**61**) creates flexibility, thereby permitting intermolecular ring closure. It should be noted that the pinacol-type epoxide ring rearrangement gives in this case the β-methyl that is anomalous according to the attack of the hydride of the leaving C–O bond from the back side.

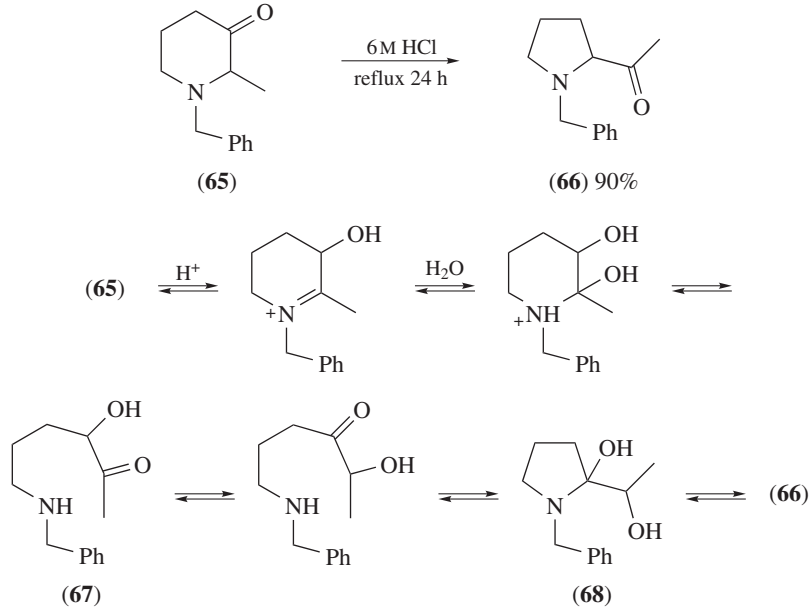


SCHEME 17



SCHEME 18

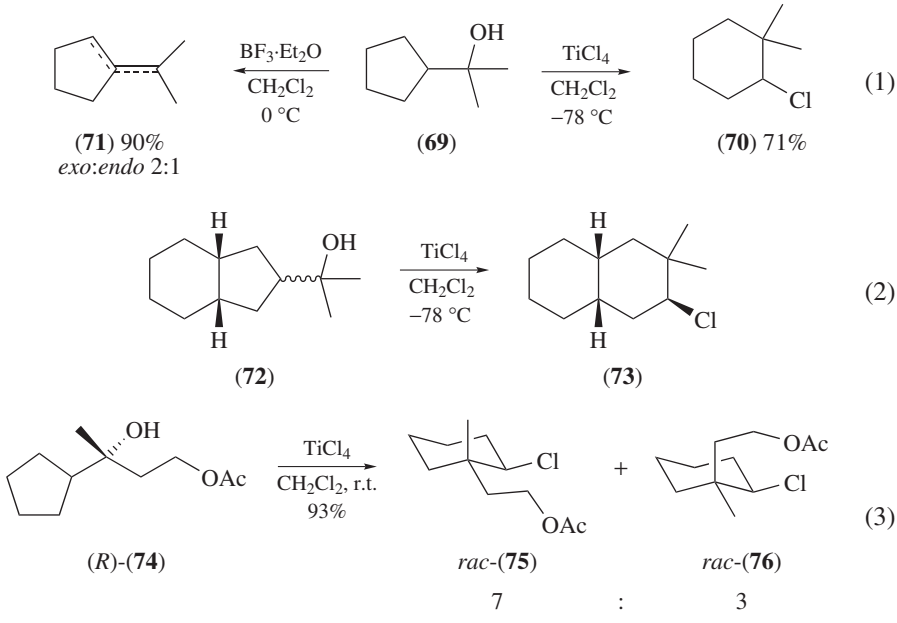
The rearrangement of (−)-modhephene (**62**) to a (−)-triquinane (**63**) through acid catalysis has been demonstrated (Scheme 18).[55] The rearrangement involved protonation, 1,2 s-bond and methyl shifts, and deprotonation. Monitoring by ^{1}H NMR suggested the (−)-isocomene (**64**) as an intermediate, further proved by transformation (*ee*) of natural (**64**) to (**63**).



SCHEME 19

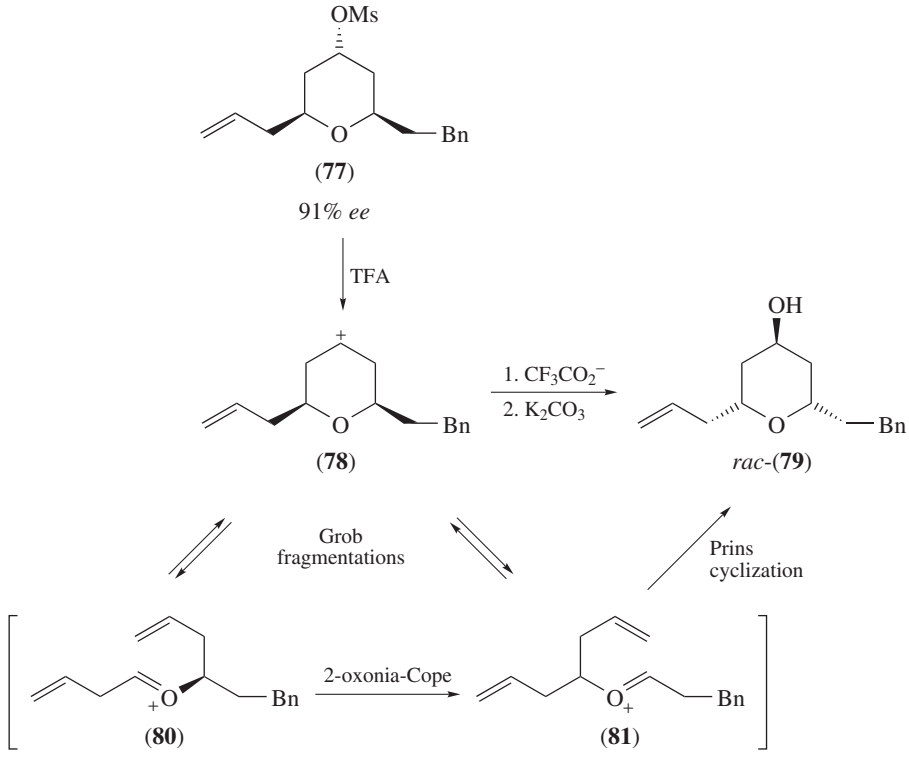
A selective high-yielding (90%) acid-catalysed ring contraction of 1-benzyl-2-methyl-3-piperidone (**65**) to 1-benzyl-2-acetylpyrrolidine (**66**) occurs by refluxing in 6 M HCl for 24 h (Scheme 19).[56] 2-Dimethyl-substituted or 2-unsubstituted-3-piperidone do not give the rearrangement under the same conditions. The process appears to be thermodynamically controlled. Kinetic studies and the synthesis of a competent intermediate suggest that the process evolves through a reverse Amadori rearrangement giving an open-chain intermediate (**67**) that closes to the five-membered pyrrolidine (**68**) at high temperature and to the piperidone (**65**) at room temperature. The mixture of products obtained by the reaction of 1-substituted 3-alkyl/aryl-3-amino-1*H*,3*H*-quinoline-2,4-diones with nitrourea rearranges in boiling acetic acid to give a mixture of ring-contracted indol-2-ones.[57]

The ring expansion of a tertiary cation into an unstable secondary cation, the so-called anti-Markovnikov rearrangement, has been studied as a mean to understand the nature, concerted or stepwise, of the correlated natural process of sterol biosynthesis.[58] $TiCl_4$ (2 equiv.) at $-78\,^{\circ}C$ is able to promote the rearrangement of cyclopentyldimethylmethanol (**69**) to the chlorocyclohexane (**70**) (eq. 1, Scheme 20), whereas $BF_3.Et_2O$ gives only deprotonation products of the isomerized carbocation. Both diastereoisomers of bicyclic alcohol (**72**), expressly designed to study the stereochemical outcome of the rearrangement, give the same ring-enlarged product (**73**) under the same conditions (eq. 2, Scheme 20). Optically pure compound (**74**) gives, at room temperature, ring-enlarged diastereomeric products (**75**) and (**76**) in racemic form (eq. 3, Scheme 20).



SCHEME 20

These results demonstrate that the products of the rearrangement do not reflect the stereochemistry of the starting materials, as would be expected in a concerted anti-Markovnikov rearrangement. Therefore, the processes studied occur via a totally cationic stepwise mechanism, suggesting the same mechanism for sterol biosynthesis. Energy profiles of cyclization energies for the cationic cyclization of oxidosqualene to lupeol, lanosterol, and hopen-3b-ol were calculated by DFT methods. The profiles indicated that rings A and B form more exergonically than rings C and D owing to a better arrangement of cation-stabilizing methyls in the early annulations.[59] The authors warn that molecular modelling results revealed systematic errors in energy calculations from B3LYP and other quantum mechanical methods. This type of B3LYP error appears to affect many transformations involving the conversion of C=C or C=O bonds to two single bonds. This problem is manifest in the molecular modelling literature but has seldom been recognized. A quantum chemical study of solvent and substituent effects on the 1,5-hydride shift in 2,6-dimethyl-2-heptyl cations has been also carried out.[60] A novel solvolysis reaction of a tetrahydropyranyl mesylate has been demonstrated.[61] α-Phenylated 1,8-bis(dimethylamino)-2-naphthylmethyl carbocations have been shown to rearrange into 1,1,3-trimethyl-2,3-dihydropirimidinium cations through an intramolecular hydride shift from the 1-NMe_2 group.[62] The racemization of solvated product (**79**), obtained as a single diastereomer, suggests that the intermediate tetrahydropyranyl cation (**78**) is a common intermediate for consecutive Grob fragmentations and 2-oxonia-Cope and Prins cyclizations (Scheme 21).



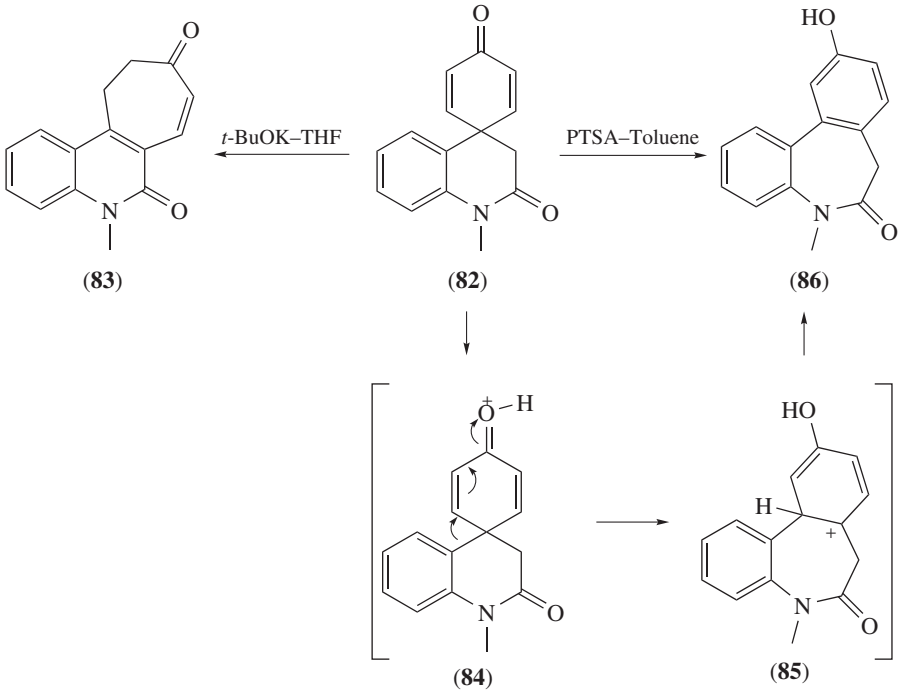
SCHEME 21

The data collected are consistent with an asynchronous mechanism of the Grob fragmentation. The ring expansion of the spirocyclohexadienone system of quinolinone (**82**) can occur under both acidic and anionic conditions, leading to different tricyclic fused compounds (Scheme 22).[63] Under acidic conditions, the more nucleophilic C-aromatic carbon of (**84**) migrates to form the benzoazepinone (**85**). Under basic conditions, the more acidic quinolinone protons drive the rearrangement to (**83**). Reaction of quinidine and epiquinidine and its acetates with $HF–SbF_5$ affords *gem*-difluoro compounds also with quinuclidine ring rearrangement.[64]

de

Rearrangements Involving Electron-deficient Heteroatoms

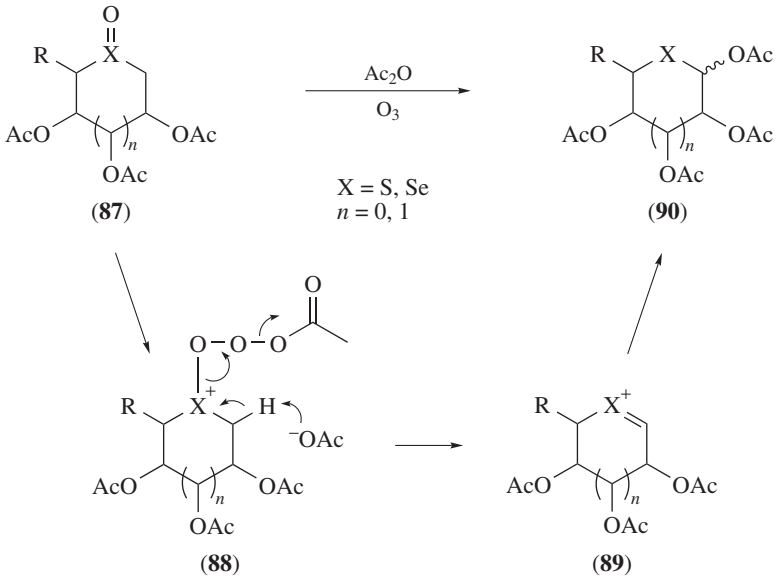
The Pummerer reaction can be oriented towards two different chemical pathways through the careful selection of the β-carbon substituent moieties. Highly stabilizing carbocation substituents, i.e. leading to carbocations of pK_{R^+} values higher than 14.5, promote Pummerer fragmentation reactions ($C_\alpha–C_\beta$ bond rupture), whereas the others giving $pK_{R^+} < 14.5$ lead to the usual Pummerer rearrangement.[65] A Pummerer-like rearrangement of heterocycles (**87**) containing selenium and sulfur leads to thio- or



SCHEME 22

seleno-sugars (**90**) involving linear ozonide acetates (**88**) as putative intermediates (Scheme 23).[66] Trapping experiments with rubrene and electron paramagnetic resonance studies with the radical trap DMPO have been performed to probe whether the rearrangement proceeded heterolytically via extrusion of singlet oxygen or homolytically via the generation of radical species.

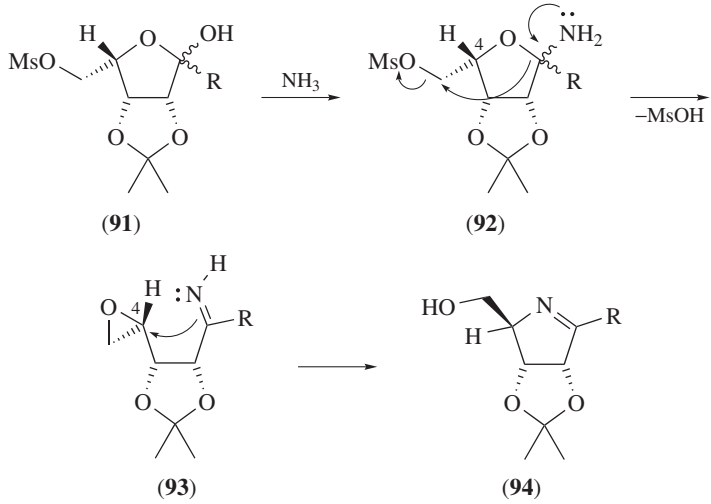
A new transition state of the addition step in the Baeyer–Villiger rearrangement has been found.[67] The role of proton acceptor is played by the carbonyl oxygen atom and the free energy barrier is 12.7 kcal mol^{-1} lower than that previously reported. Prins–pinacol reactions of cyclohexyl- and cyclopentyl-triisopropylsilyloxy ethers having (2*Z*)-(6,6-dimethoxyhexylidene) or (2*Z*)-(5,5-dimethoxypentylidene) side-chains, promoted by $SnCl_4$, has been employed to provide bicyclic products in which five-, six-, or seven-membered rings are joined by a C–C single bond.[68] A very efficient process for the Curtius rearrangement that allows the direct conversion of aromatic carboxylic acids into carbamates and ureas has been developed.[69] This process is based on the use of various commercially available chloroformates and sodium azide, which presumably generate the corresponding azidoformate. The formate serves to activate the carboxylic acids and as a source of nucleophilic alkoxide. A cavity-containing metal–ligand assembly has been used as a catalytic host for the 3-aza Cope rearrangement of allyl enammonium cations.[70] Upon binding, the rates of rearrangements are



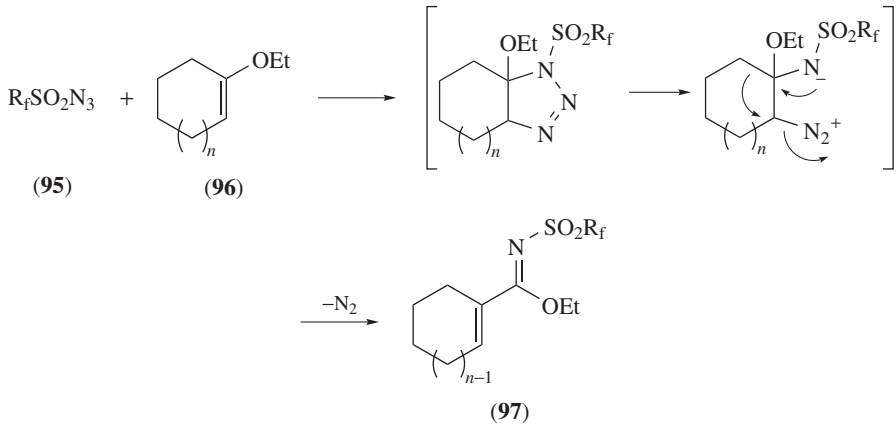
SCHEME 23

accelerated for all substrates studied up to 850-fold. Activation parameters were measured for three enammonium cations in order to understand the origins of acceleration. Those parameters reveal that the supramolecular structure is able to reduce both the entropic and enthalpic barriers for rearrangement and is highly sensitive to small structural changes of the substrate. The space-restrictive cavity preferentially binds closely packed, preorganized substrate conformations, which resemble the conformations of the transition states. Attached rings in which both rings are chiral can be prepared in this fashion with high stereoselectivity and moderate enantiospecificity. A facile synthesis of five membered antiviral azasugars (**94**), which involves an *exo*-imino to *endo*-iminocyclitol rearrangement, has been reported (Scheme 24).[71] The mechanism of conversion of (**91**) to (**94**) shows that the key step is the intramolecular 5-*exo-tet* ring opening of the epoxide with inversion of configuration at C(4). The *exo*-imino to *endo*-iminocyclitol process works equally efficiently in the D- and L-hexose series, with the interesting consequence that a double inversion occurs at two carbon atoms, C(4) and C(5). *de*

The reaction of fluoroalkanesulfonyl azides (**95**) with cycloalkenyl ether and ynamine have been studied (Scheme 25).[72] Ring-contracted *N*-fluoroalkanesulfonyl amidine analogues (**97**) were obtained when (**95**) was reacted with cycloalkenyl vinyl ethers at 0 °C. Two novel ring-contracting rearrangements of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones (**98**) yielding 1-(arylamino)-3-oxo-1,3-dihydroisobenzofuran-1-carboxamides (**99**) and 2-aryl-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxamides (**100**) have been described (Scheme 26).[73]

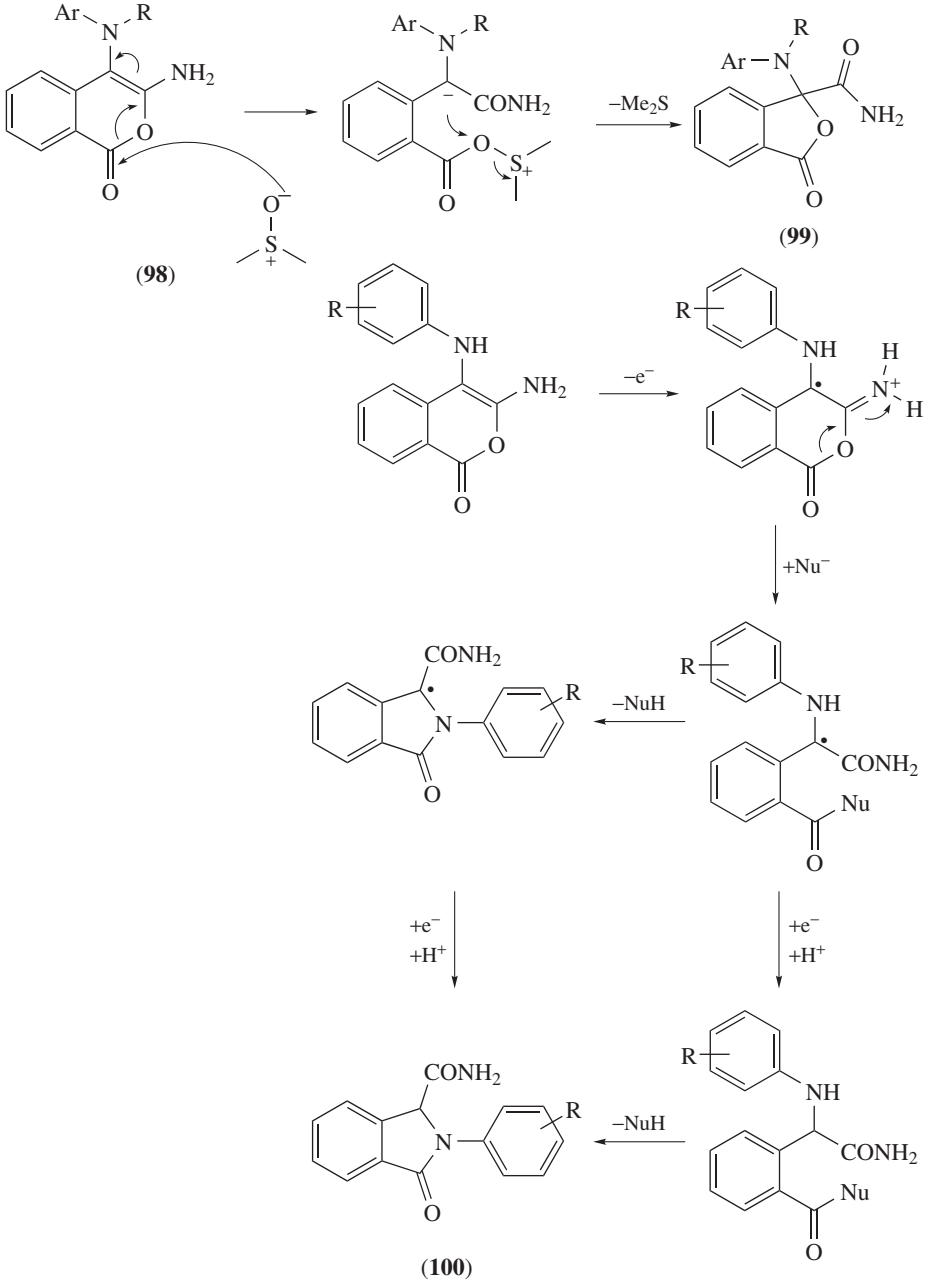


SCHEME 24



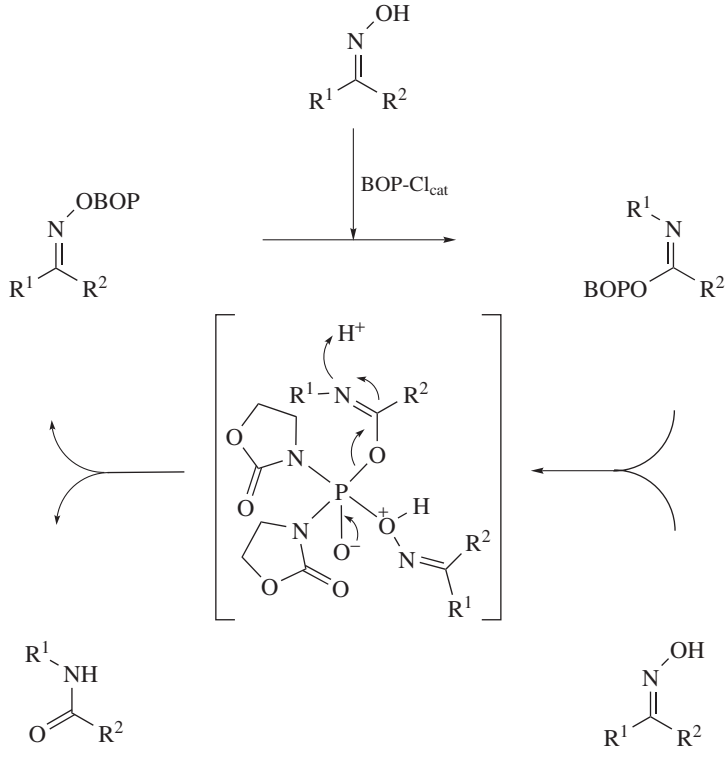
SCHEME 25

Two factors effect the second transformation in an appreciable yield, the I_2–Et_3N system and Cu^{2+} ($CuBr_2$ and $CuCl_2$) salts. Apparently, an oxidative step is required to effect the opening of the electron-rich diaminopyran-2-one ring. The driving force for both reactions is the formation of a primary amide from a cyclic *O*-acyl imidate. An efficient synthesis of 2-aryl-1-benzazocines via Beckmann rearrangement of 5*H*-benzocyclohepten-5-one oxime mesylates has been described using aryl Grignard reagents to induce the rearrangement directly without any additional protic agent.[74] Iodotrimethylsilane has also been employed to promote Beckmann rearrangement of



Scheme 26

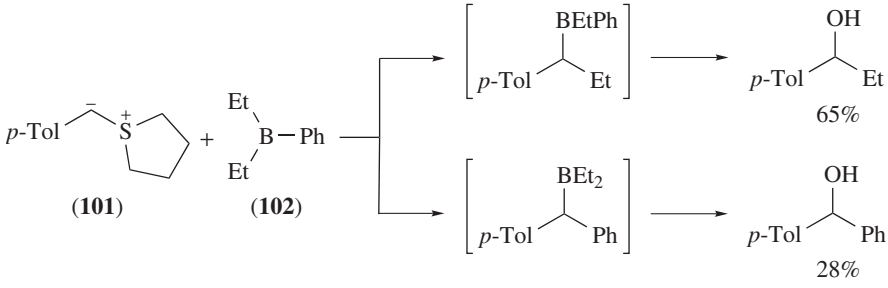
the mesylates, followed by the treatment of the intermediate imidoyl iodide with phenylmagnesium bromide to complete the synthesis of benzazocines. The first generation of organophosphinic chloride systems, commercially available BOP–Cl or BOP-Cl–$ZnCl_2$, has been developed for highly effective catalysis of the Beckmann rearrangement of ketoximes to corresponding amides (Scheme 27).[75]



SCHEME 27

The Lewis acid $ZnCl_2$ has been used as co-catalyst in order to use a lower catalyst loading. The rearrangement of α-chlorocyclobutanone oximes, derivatives of steroids, has been described as characterized by a Beckmann fragmentation–substitution.[76] The results are interpreted in terms of structural and stereoelectronic effects and are supported by AM1 calculations. The stability of the transient carbocations appears to play the major role in reactions leading to the abnormal Beckmann rearrangement products. [2,3]-Sigmatropic rearrangements of allylic ammonium ylides derived from (de) glycinoylcamphorsultams have been described as highly selective in terms of relative and absolute stereocontrol only when acyclic alkenes are present.[77] When chiral esters of ylids derived from *N*-methyltetrahydropyridine undergo rearrangement, the reactions show exclusive *cis* stereoselectivity but the products are obtained with virtually

no absolute stereocontrol. A review has summarized recent developments in the field of Schmidt reactions.[78] Fused carbocyclic compounds possessing seven- and eight-membered rings can be constructed from allylic ethers in a stereoselective manner by tandem carbenoid generation, ylide formation, and [2,3] rearrangement.[79] The relative configurations of the stereogenic centres in the substrates have an important influence on the course of the rearrangement reaction: reactions of substrates possessing favourable relative stereochemistries deliver exceptionally high yields of the required [2,3] rearrangement products. A useful method for the stereoselective synthesis of trifluoromethyl 1,4-oxathiolane through ring expansion of 1,3-oxathiolane ylide using trifluoromethyl diazoacetate in the presence of $Rh_2(OAc)_4$ has been presented.[80] The mechanistic possibilities of the triazolinedione–alkene ene reaction have been tested by the use of the vinylcyclopropyl moiety as an efficient probe.[81] In non-hydroxylic solvents, this reaction afforded only the ene adducts via a closed three-membered aziridinium imide intermediate, whereas in hydroxylic solvents a dipolar intermediate is favoured and trapped by the cyclopropyl moiety to form the corresponding cyclopropyl-rearranged solvent-trapped adducts. An explanation of the unexpected low phenyl migratory aptitude observed in reactions of mixed alkyl–arylboranes with benzylic sulfur ylides has been reported (Scheme 28).[82]



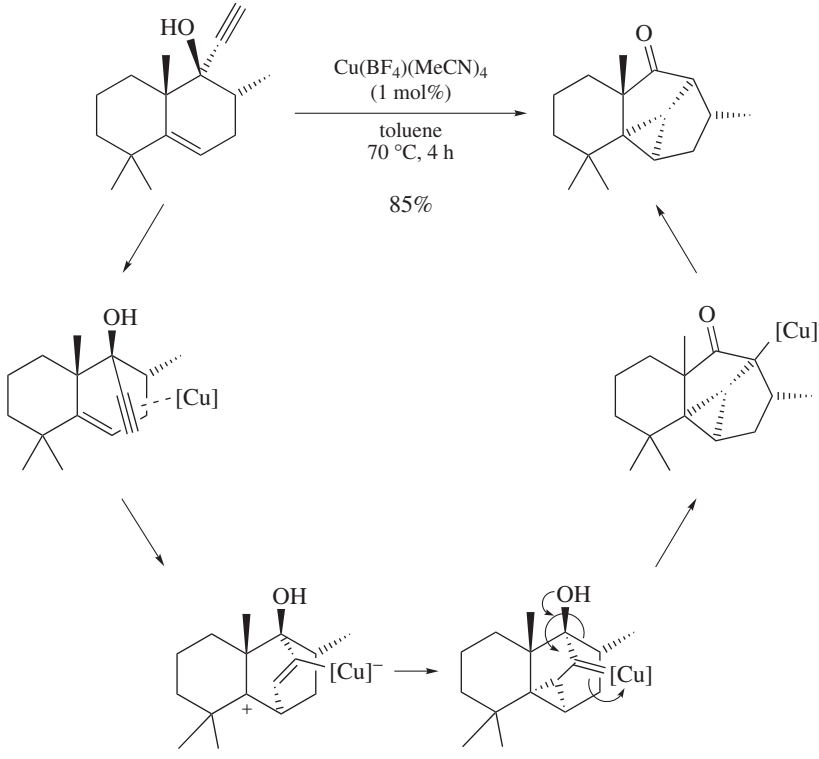
SCHEME 28

Reaction of ylide (**101**) with borane (**102**) gave predominantly the product resulting from alkyl migration: a 2.3:1 ratio in favour of ethyl migration over phenyl migration was observed. The authors have shown that the following factors impact on which group migrates in mixed aryl–dialkylborates: (i) conformation of the ate complex (there is a preference for the phenyl group to be *syn* to the sulfonium group because of stabilizing electrostatic interactions and this favours alkyl group migration); (ii) the presence of a phenyl group on boron inherently impedes the migration of the other (alkyl) groups; (iii) the phenyl group is usually a better migrating group than methyl because it can stabilize the transition state by donation of an electron pair from its π system into the σ^*_{C1-S} orbital (neighbouring effect), but this effect is highly attenuated when the migrating terminus C(1) is less electrophilic (e.g. when R = Ph); and (iv) steric effects also play a role. Larger groups will suffer increased barrier to migration when the migrating terminus is hindered. Boron trifluoride and indium(III)

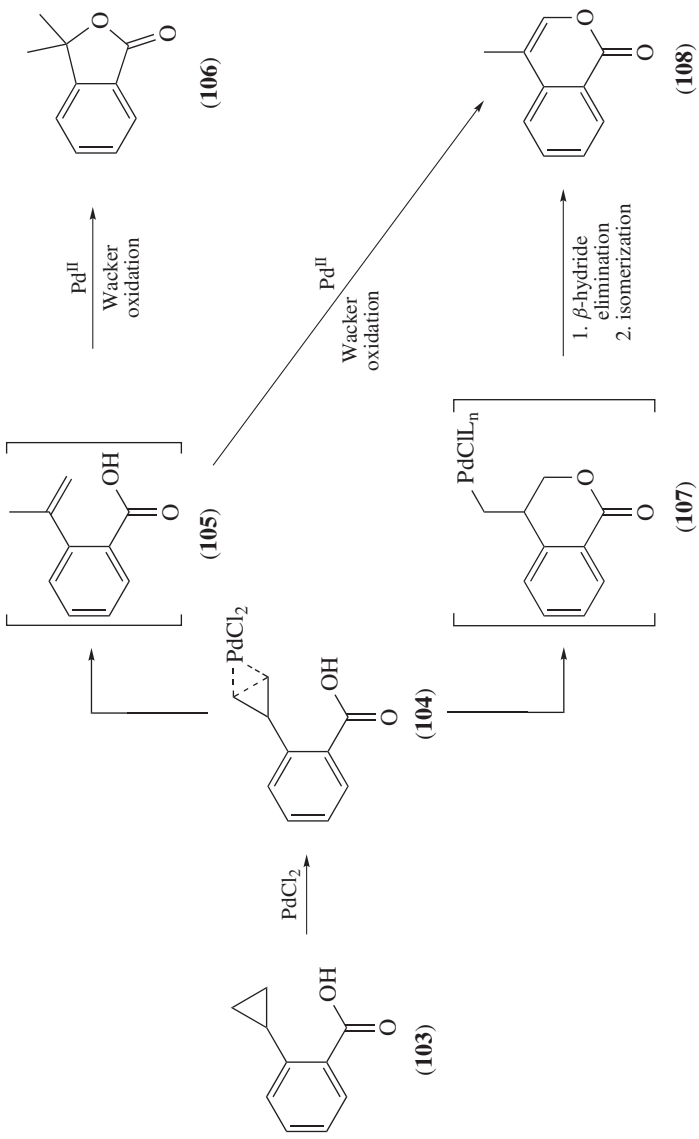
trifluoromethanesulfonate have been used to catalyse efficiently the isomerization of thionolactones to thiolactones in good yields.[83] This reaction, when applied to an optically active γ-thionolactone, proceeds with a complete inversion of configuration by using $BF_3.Et_2O$. It has been reported[84] that ionic liquid-promoted Michaelis–Arbuzov rearrangement can be performed at room temperature in a short period and without any protective atmosphere of an inert gas. A review of the catalytic use of Lewis acid for the functionalization of C(sp^3)–H bonds through formation of iminium and oxonium ions has appeared.[85]

Rearrangement Involving Organometallic Compounds

Mild Ni(0)-catalysed rearrangements of 1-acyl-2-vinylcyclopropanes to substituted dihydrofurans have been developed.[86] The room temperature isomerizations afford dihydrofuran products in high yield. A highly substituted, stereochemically defined cyclopropane has been employed in the rearrangement to evaluate the reaction mechanism. The Cu(II)-catalysed cycloisomerization of tertiary 5-en-1-yn-3-ols with a 1,2-alkyl shift affords stereoselectively tri- and tetra-cyclic compounds of high molecular complexity (Scheme 29).[87] A proposed mechanism has been outlined in which



SCHEME 29

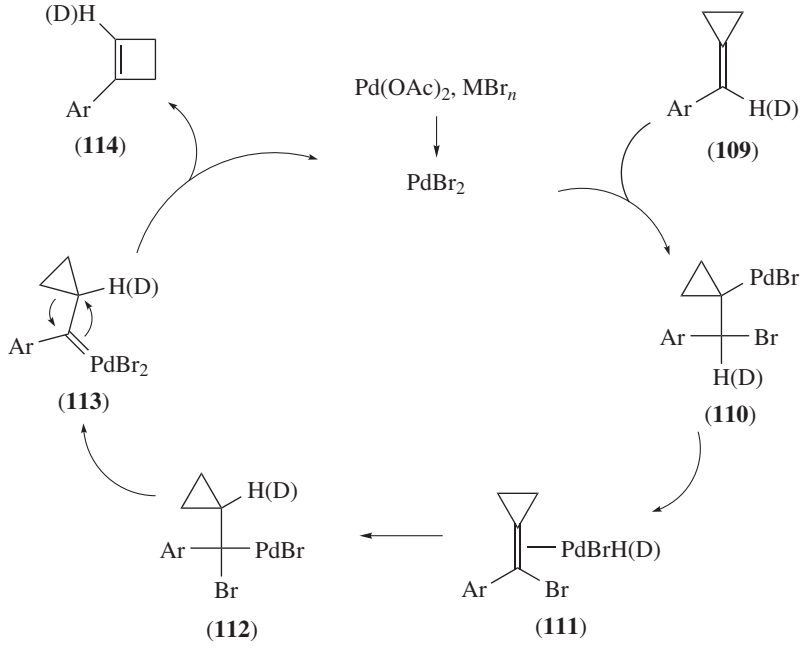

OH
O
(103)
PdCl2
PdCl2
OH
O
(104)
PdII
Wacker
oxidation
OH
O
(105)
O
O
(106)
PdII
Wacker
oxidation
PdClLn
O
O
(107)
1. β-hydride
elimination
2. isomerization
O
O
(108)

SCHEME 30

the cyclopropanation precedes the skeletal rearrangement and the perfect stereocontrol of the cyclopropanation with respect to the orientation of the acetylene unit has been supported.

A novel method for the synthesis of five- to seven-membered α-alkylidene lactams by the palladium-catalysed intramolecular cyanoamidation of alkynyl and alkenyl cyanoformamides has been developed.[88] The reaction proceeded exclusively in a 5-*exo* mode, giving the corresponding (*Z*)-alkenes as major products. Electroneutral cyclopropane rings can be catalytically activated using $PdCl_2$ to give lactams and lactones.[89] Six-membered derivatives are always the major products. Interesting mechanistic trends have been uncovered, pointing toward dependence of the cyclopropane activation pathway on nearby substituents, as shown in Scheme 30 for one model reaction. The α-methylstyrene derivative (**105**) was detected by ^{1}H NMR during the cyclization of (**103**), suggesting that a possible pathway in the case of carboxylic acid-containing substrates is Pd(II)-catalysed isomerization of the cyclopropane ring to the branched alkene followed by a Wacker oxidation. However, the formation of (**108**) can also be explained by direct carboxypalladation followed by β-hydride elimination and subsequent alkene isomerization. The carboxypalladation is expected to occur upon initial coordination of Pd(II) to the more electron rich distal C–C bond of the arylcyclopropane.

A versatile palladium-catalysed ring enlargement reaction where arylidenecyclopropanes are converted into the corresponding cyclobutene compounds has been reported (Scheme 31).[90] A plausible mechanism for the unusual ring enlargement



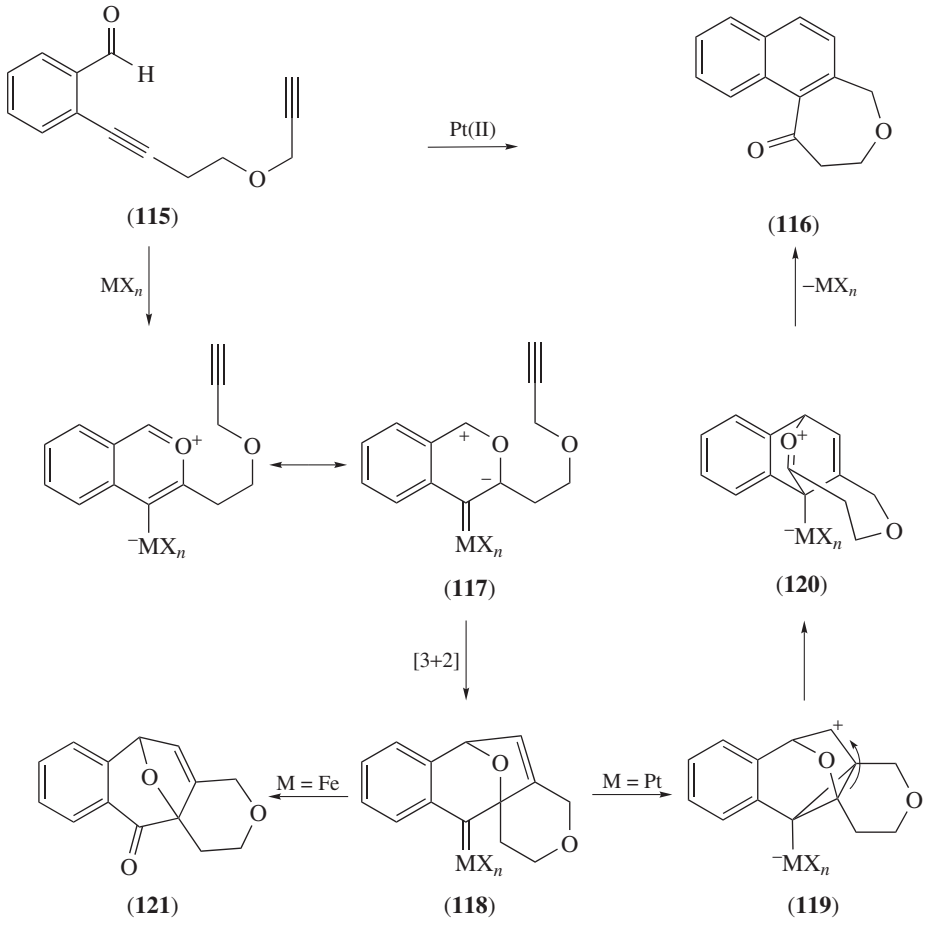
SCHEME 31

of (**109**) to (**114**) shows the regioselective bromopalladation of arylidenecyclopropane (**109**) with $PdBr_2$, which might be produced *in situ* from $Pd(OAc)_2$ and MBr_n (M = Cu, Zn, Mg, Li), to afford intermediate (**110**). Intermediate (**110**) undergoes β-hydrogen elimination to form intermediate (**111**), which subsequently generates palladium carbenoid (**112**) via hydropalladation with a reversed regioselectivity. Via an α-bromo migration, (**112**) is transformed to a palladium carbene (**113**), which yields the product (**114**) and regenerates the palladium bromide catalyst. To test the plausibility of this proposed mechanism, a deuterium labelling experiment has been performed.

The mechanism of cycloisomerization of hepta-1,6-dienes catalysed by [(t-BuCN)$_2$ $PdCl_2$] has been investigated by isotopic labelling and by study of the reactions of dimethyl 1-arylhept-1,6-dienyl-4,4-dicarboxylates and dimethyl hept-1,5-dienyl-4,4-dicarboxylate.[91] The mechanism proposed involves the generation of a monochloro-bearing palladium hydride which undergoes a simple hydropalladation, carbopalladation, Pd/H dyotropy, β-H elimination sequence. A key point that emerges is that chelation of the 1,6-diene at various stages in the mechanism plays an important role in determining the regioselectivity of the reaction. Cyclization reactions on 6-[(2-hydroxyphenyl)ethynyl]purines, 6-[(2-hydroxymethylphenyl)ethynyl]purines, and 6-[(2-hydroxyphenyl)propyn-1-yl]purines have been studied.[92] 6-(2-Benzofuryl)purines are readily available via a one-pot Sonogashira coupling–cyclization between 6-iodopurine and 2-ethynylphenol. When the same reaction was performed with *o*-(hydroxymethyl)ethynylbenzene, 6-[isobenzofuran-1(3*H*)-ylidenemethyl]purine was formed, mainly as the *E*-isomer. Acid-catalysed isomerization of the *E*-compound afforded the *Z*-isomer. The latter compound was also formed from a two-step reaction: Sonogashira coupling with *O*-silylated alkyne followed by deprotection and subsequent 5-*exo* cyclization. Sonogashira coupling between 6-halopurines and 2-propynylphenol gave only the alkyne coupling product and no cyclization took place. The activation of alkylidenecyclopropanes with catalytic amounts of $PtCl_2$ or, preferentially, $PtCl_2$–CO (1 atm), undergoes ring expansion to substituted cyclobutenes.[93]

The platinum-catalysed intramolecular domino annulation reaction of *o*-alkynylbenzaldehydes has been described as a versatile approach to naphthalenes with annulated carbocycles or heterocycles of various sizes (Scheme 32).[94] A plausible mechanism for the platinum(II)-catalysed annulation reaction shows that the double annulation process most probably proceeds through the benzopyrylium cation (**117**), which results from the nucleophilic attack of the carbonyl oxygen at the alkyne, activated by the Lewis-acidic platinum salt. A subsequent intramolecular Huisgen-type 3 + 2-cycloaddition of the second alkyne is assumed to generate intermediate (**118**). Rearrangement to (**119**) and the formal 4 + 2-cycloaddition product (**118**) leads to the aromatized final (**116**), liberating the active catalyst. In the case of $FeCl_3$ as the Lewis acid, we assume that intermediate (**118**) is oxidatively transformed to (**121**).

An efficient method for pentannulation using acyloxy-functionalized pyrans that evolve from readily available propargylic esters has been developed. Utilizing a range of epoxides, pentannulation is achieved using $PtCl_2$ to obtain bicycles containing a



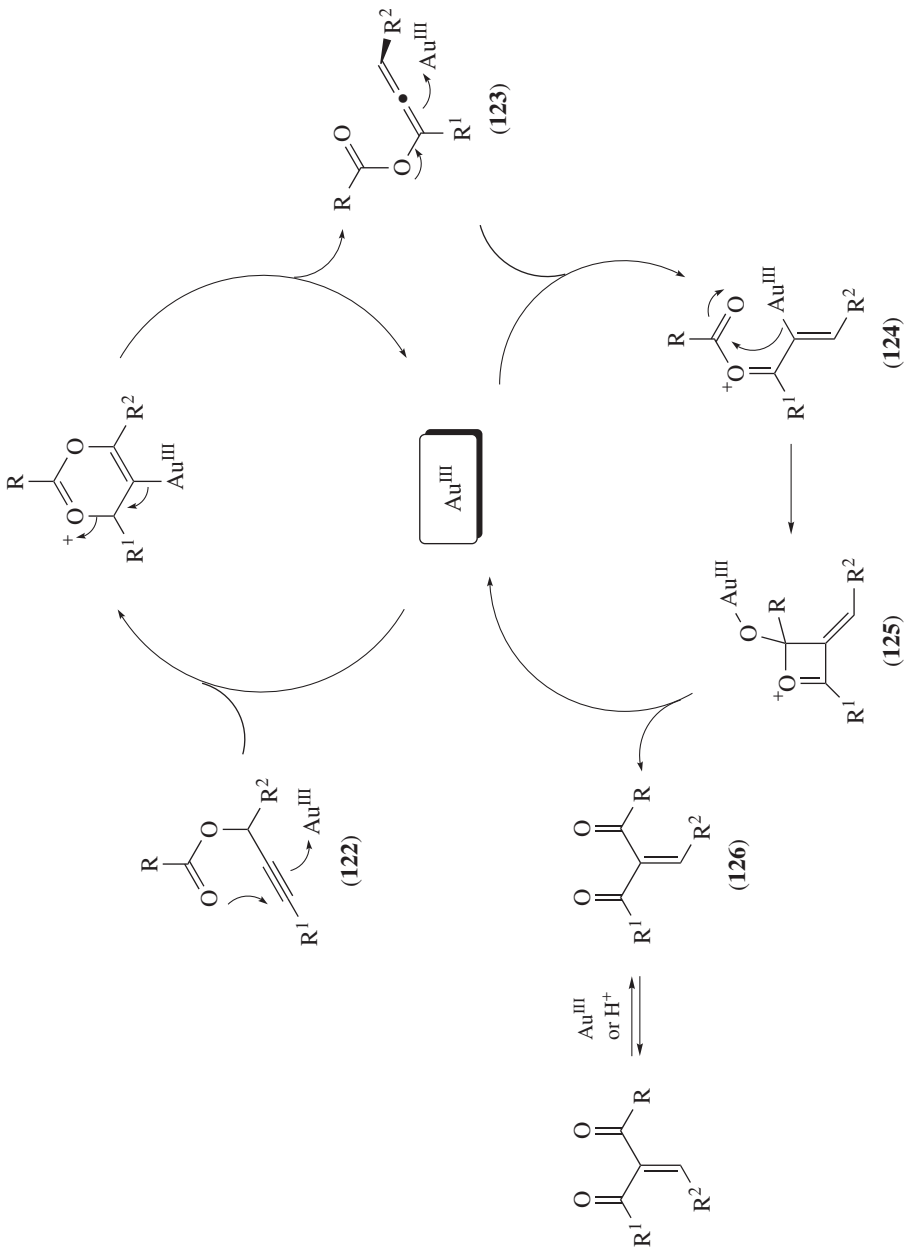
SCHEME 32

tertiary stereocentre.[95] A facile annulation reaction catalysed by Au^{I} or Au^{III} species of alkyne-tethered indoles forming six-, seven-, and eight-membered annulated indoles has been reported.[96] A cationic Au^{I} complex has been described as the best catalysts for the formation of six- and seven-membered rings through 6-*endo-dig*, 6-*exo-dig*, and 7-*exo-dig* cyclizations. Indoloazocines have been obtained with $AuCl_3$ as catalyst through a rare 8-*endo-dig* process. An exhaustive study of the cyclization of 1,6-enynes with different gold(I) complexes in the presence of alcohols results in cyclized products alkoxy- or hydroxy-functionalized or in their skeletal rearrangement products.[97] Gold(I) complexes are selective alkynophilic catalysts, promoting reactions through the exclusive coordination of the metal complex to the alkyne of

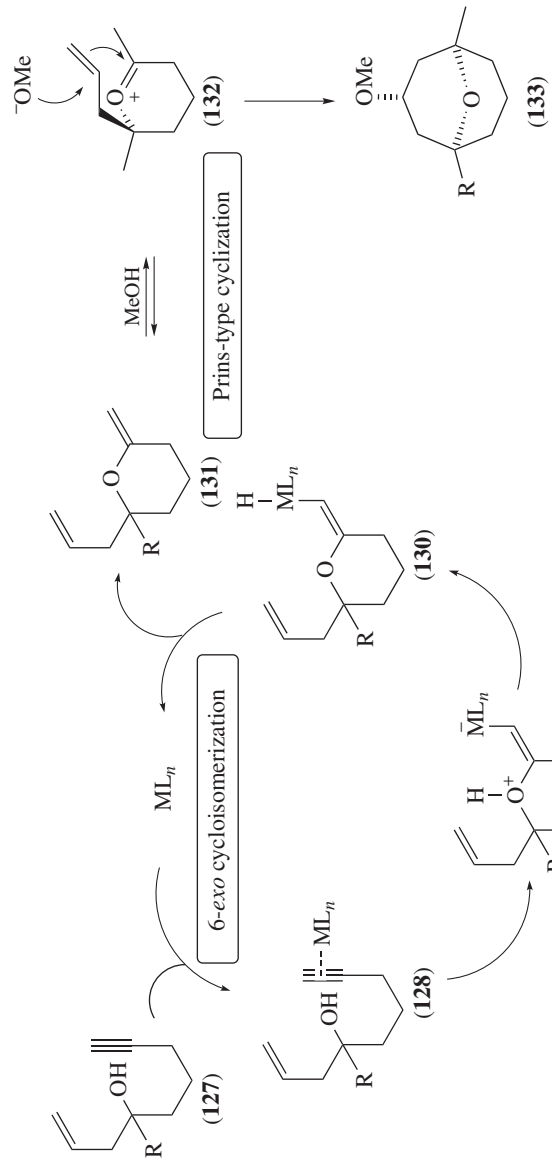
the enyne. With these catalysts, the first examples of skeletal rearrangement of enynes by the endocyclic cyclization pathway have been documented. This endocyclic cyclization proceeds by a mechanism different from those followed in the presence of Pd^{II}, Hg^{II}, or Rh^{I} catalysts. The mechanistic puzzle of transition metal-catalysed skeletal rearrangements of enynes has been outlined.[98] Three pathways actually compete in metal-catalysed cyclizations of enynes in which the metal selectively activates the alkyne: an endocyclic process and two exocyclic cyclizations, one proceeding by *anti* attack of the alkene and a second one resulting in a *syn* addition. Although cyclobutenes may be formed in transition metal-catalysed cyclization of some enynes, particularly, 1,7-enynes, these compounds are not necessarily the intermediates in the skeletal rearrangement. Cyclobutenes are formed by ring expansion of *syn*-cyclopropyl metal–carbenes formed in the *syn* pathway. The mechanism of the stereospecific gold(I)-catalysed Rautenstrauch rearrangement of (*E*)-1-ethynyl-2-methylbut-2-enyl acetate to 3,4-dimethylcyclopent-2-enone has been computationally addressed using DFT (B3LYP/6–31G*, SDD for Au).[99] The results indicate that the bond formation (de) event follows the Au(I)-induced acetyl transfer to the vicinal alkyne and that it is the helicity of the pentadienyl cation intermediate which keeps memory of the chiral information. The fidelity of the centre-to-helix-to-centre chirality transfer requires that the rates of helix interconversion and pivaloyl rotation are slower than the cyclization, as calculations predict.

A highly efficient synthesis of α-alkylidene or benzylidene β-diketones from readily available propargylic esters has been developed.[100] The proposed key transformation is a novel intramolecular acyl migration to nucleophilic Au^{III}–C(sp^2) bonds (Scheme 33). The propargylic ester (**122**) undergoes an initial Au-catalysed 3,3-rearrangement to form carboxyallene (**123**), which can be further activated by the same Au^{III} catalyst *in situ*. The resulting intermediate (**124**) has been shown to react efficiently with nucleophiles at the oxocarbenium moiety; however, in the absence of suitable nucleophiles, an acyl group migration ensues as the nucleophilic Au^{III}–C(sp^2) attacks the acyl carbonyl group intramolecularly, generating a tetrahedral intermediate (**125**). The collapse of (**125**) results in α-ylidene β-diketone (**126**) with concomitant regeneration of the Au catalyst. The formation of the double bond isomer of (**126**) is most likely due to isomerization catalysed by either Au^{III} or H^+. The same authors have developed a unique Au-catalysed 1,5-enyne cycloisomerization involving carboxy group migration and Au-mediated C–C single bond formation.[101]

A highly efficient and general method for the diastereoselective synthesis of eight-membered carbocycles (**133**) based on a new tandem platinum- or gold-catalysed cycloisomerization–Prins-type cyclization reaction of alkynol (**127**) has been developed (Scheme 34).[102] The reaction is initiated by coordination of the platinum or (de) gold complex to the triple bond of the starting alkynol (**127**) to form intermediate (**128**) according to the Dewar–Chatt–Duncanson model. Intramolecular addition of the hydroxy group to the internal carbon atom of the triple bond generates (**129**). Migration of the hydrogen atom from the oxygen to the metal atom then leads to the formation of hydride complex (**130**), which, after reductive elimination, produces the exocyclic enol ether (**131**) and regenerates the catalytic species. At this point, the



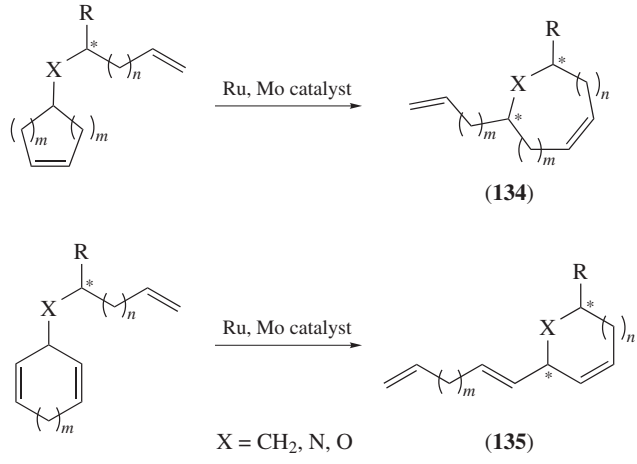
SCHEME 33


OH
R
(127)
ML$_n$
6-*exo* cycloisomerization
ML$_n$
OH
R
(128)
H
ML$_n$
O
R
(130)
MeOH
O
R
(131)
Prins-type cyclization
$^-$OMe
O$^+$
(132)
OMe
O
R
(133)
H
$\bar{M}L_n$
O$^+$
R
(129)

SCHEME 34

second part of the tandem sequence–the Prins-type cyclization–is initiated. In the alcohol solvent an equilibrium between intermediate (**131**) and oxocarbenium ion (**132**) is likely to occur. This oxocarbenium ion may exist as an ion pair with the counterion, which also serves as the nucleophile. The cyclization step is believed to proceed through a chair-like transition state, thereby favouring nucleophilic trapping from an equatorial trajectory. This is consistent with the configuration of the stereogenic centres observed in the final products (**133**). The first examples of gold-catalysed cycloisomerizations of 1,6-ene-ynamides that lead to substituted cyclobutanones or azabicyclic compounds, depending on the substitution pattern, and proceed with high level of diastereoselectivity has been reported.[103] The gold-catalysed cycloisomerization of (*de*) various α-aminoallenes affords the corresponding 3-pyrrolines in good to high chemical yields and – if the amino group is unprotected – with complete axis-to-centre chirality transfer.[104] In cases involving *N*-protected substrates, an interesting dependence (*de*) of the chirality transfer on the protecting group was observed. Gold(I) precatalysts such as AuCl and AuI are extremely reactive and dramatically shorten the reaction times for the intramolecular hydroamination of unprotected α-aminoallenes. Mechanistic studies with stoichiometric amounts of $AuBr_3$ suggest that a gold(I) compound (formed by oxidation of the aminoallene) is the catalytically active species even if the reaction is started with a gold(III) precatalyst. A cationic phosphinegold(I)-catalysed tandem cyclopropanation–hydroarylation reaction, which produces formal $4 + 3$-annulation products from vinyl arenes and propargyl esters, has been developed.[105] The cyclopropanation represents the first intermolecular reaction of diynyl esters and proceeds with excellent regio- and diastereo-control. 7-Azanorbornenes undergo ring opening/ring closing metathesis upon treatment with the second-generation Grubbs catalyst to give hexahydroindoline derivatives.[106] (*de*)

A new concept of diastereoselective ring-rearrangement metathesis has been developed for the synthesis of various carbo- and hetero-cycles (**134**) and (**135**) (Scheme 35).[107] A strong influence of the substitution pattern of the directing stereocentre on (*de*)



SCHEME 35

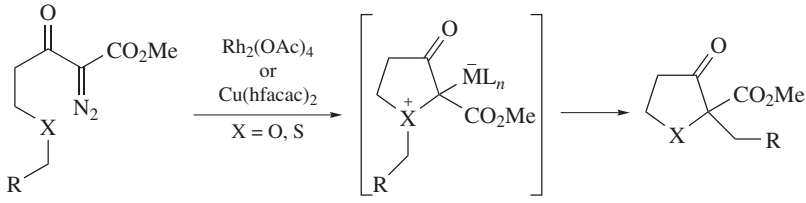
the configuration of the new stereocentre has been observed. The diastereoselectivity depended on the precatalyst applied.

An efficient and regioselective synthesis of isomeric fluorinated lactam derivatives through a ring-closing metathesis reaction or a tandem ring-closing metathesis–isomerization protocol has been reported.[108] The presence of the *gem*-difluoro moiety in the starting materials exerts a pivotal effect by directing the isomerization step. A formal total synthesis of eleutherobin using the ring-closing metathesis reaction of a densely functionalized diene as the key step has been reported.[109] The unusual (de) kinetically controlled ring-closing metathesis stereochemical outcome has been investigated using computational methods. Semiempirical PM3 calculations have shown that the *E*-isomers of the 10-membered carbocycles resulting from the RCM reaction are less thermodynamically stable than the *Z*-isomers. Alkene metathesis catalysts containing chiral, monodentate *N*-heterocyclic carbenes (NHC) have been synthesized and their application to asymmetric ring-closing metathesis has been studied.[110] (de) Two proposed models for the formation of the observed products have been discussed: if the incoming alkene binds *cis* to the NHC, the stereodefining interaction is the face of the ruthenium to which the olefin binds; if the incoming alkene binds *trans* to the NHC, the stereodefining interaction is the position of the alkylidene under the *N*-bound aryl ring. In both cases, the position of the pendent alkene in the forming ring also plays an important role in the transition state.

The direct rearrangement of the allenylidene–ruthenium complex into an indenylidene–ruthenium derivative has been studied.[111] It has been established that this acid-promoted reaction involves electrophilic alkenylcarbyne–ruthenium intermediate formation. The *in situ*-prepared indenylidene–ruthenium complexes are efficient catalyst precursors for ring-opening metathesis polymerization of cyclooctene and cyclopentene. The late transition metals have been demonstrated to be able to induce unprecedented reactivity in methyl aromatic ethers that have their *ortho*-positions blocked by methyl substituents.[112] DFT calculation have shown that the 1,2-shift of the stannyl group on formation of ruthenium–β-stannylvinylidene complexes is more facile than the corresponding 1,2-hydrogen shift of the coordinating terminal alkynes.[113] The (de) ruthenium-catalysed cyclization of a propargylic alcohol with an oxabenzonorbornene in methanol leads to an unexpected isochromene framework.[114] The catalytic cycle that leads to this product is believed to implicate an oxidative cyclization of the two unsaturated partners with the ruthenium catalyst, followed by a β-hydride elimination, tautomerization and hydroruthenation. The ruthenacyclobutane obtained further undergoes 2 + 2-cycloreversion to form an Ru–carbene intermediate that uncommonly rearranges through a [1,3]-alkoxide shift and finally reductively eliminates to produce the desired compound.

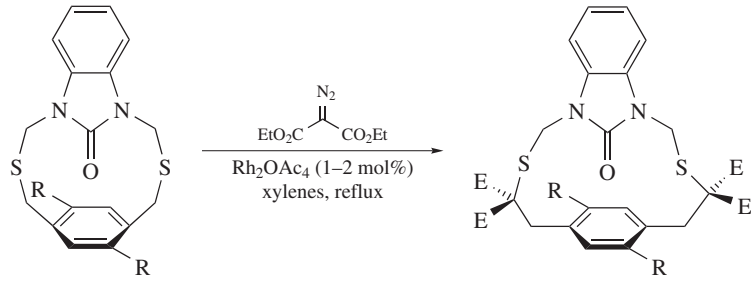
Iodonium ylides (**136**), generated *in situ* with bisacetoxyiodobenzene, are converted to allyl- or benzyl-substituted oxonium or sulfonium ylides (**137**) via rhodium- or copper-catalysed carbene transfer.[115] Such ylides undergo [1,2]- or [2,3]-rearrangement to the corresponding 2-substituted heterocycles (**138**). An example of the rhodium-catalysed reaction is reported in Scheme 36.

It has been demonstrated that, in addition to electronic factors, steric factors play an even more important role in affecting the 1,2-migratory aptitude in rhodium



(**136**) (**137**) (**138**)

SCHEME 36

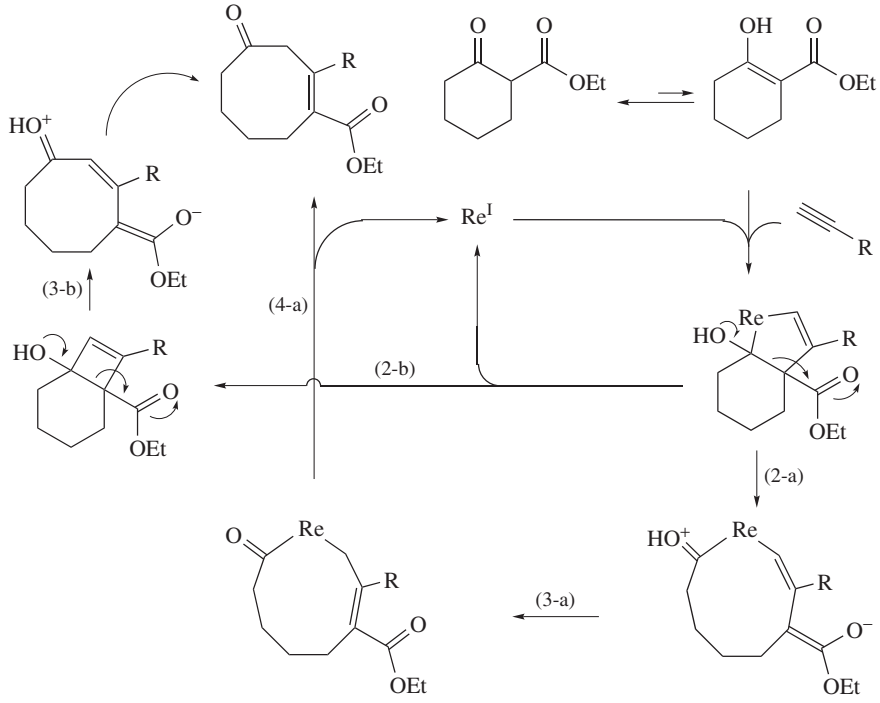


(**139**) (**140**)

SCHEME 37

(II)–carbene reactions.[116] New benzimidazolidinone cyclophanes (**140**) have been synthesized from (**139**) through a rhodium(II)–carbene-mediated double Stevens rearrangement employed as a ring expansion technique (Scheme 37).[117] The insertion is highly regioselective and provides access to larger carbocyclic cyclophanes after sulfur atom extrusion. An efficient rearrangement of 1,3-diynes possessing propargylic heteroatom substituents to functionalized 1,5-dien-3-ynes in the presence of electrophilic transition metal catalysts has been demonstrated.[118] The mechanism of bond reorganization process is most consistent with the involvement of the formation of putative platinum and gold carbene species followed by its metallotropic [1,3]-shift.

The same authors have demonstrated that 1,3-diynes behave in predictable yet distinctive manners compared to simple enynes under electrophilic transition metal-mediated reaction conditions. This characteristic behaviour of 1,3-diynes is presumably caused by the slightly electron-withdrawing nature of the alkynyl substituent, which not only renders preferentially the formation of 5-*exo*-type alkylidenes but also allows for the subsequent [1,3]-metallotropic shift. Several salient features of reactions with this functionality include the following: (a) an acetate is more reactive than the tethered alkene as an initiator, generating [1,2]-acetate migrated alkylidene intermediate, whereas an alkene is a better terminator than an acetate/bromide to generate the cyclopropane moiety; (b) allene products are not formed at all under current reaction conditions; (c) 5-*exo*/6-*endo*-type alkylidene formation depends on the heteroatom substituent in the tether; (d) facile metallotropic [1,3]-shift of the intermediate alkylidenes occurred whenever possible.



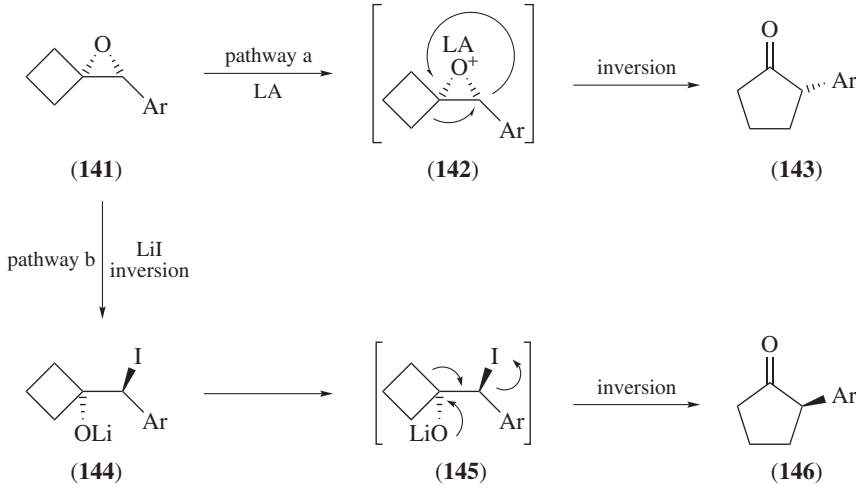
SCHEME 38

A rhenium catalyst promoted insertion of terminal alkynes into a carbon–carbon single bond next to a carbonyl group of non-strained cyclic compounds under mild conditions (Scheme 38).[119] The proposed reaction mechanism is as follows: (1) the formation of a rhenacyclopentene intermediate by the reaction of a rhenium catalyst, β-keto ester, and terminal alkyne. After the formation of the rhenacyclopentene intermediate, there are two possible pathways; the difference is the timing of reductive elimination. Path A: (2-a) ring opening by a retro-aldol reaction; (3-a) isomerization; (4-a) reductive elimination. Path B: (2-b) reductive elimination; (3-b) ring opening by a retro-aldol reaction; (4-b) isomerization. 1-Phenoxyocta-2,7-diene in the presence of rhenium- or tungsten-based catalysts affords *ortho*-substituted phenols with a Claisen-type mechanism, whereas the metathesis of the internal double bond exclusively occurs with Grubbs catalysts.[120] The reductive olefination of aldehydes via chromium Brook rearrangement has been reported.[121] The [1,5]-Brook rearrangement to give silyl ethers has been reported to proceed efficiently with sodium and potassium bases.[122]

Rearrangements Involving Ring Opening

1-Acyloxybenzocyclobutenes, having an α,β-unsaturated carbonyl group at the C(1) position, undergo the periselective thermal ring expansion to give 2-benzoxocin

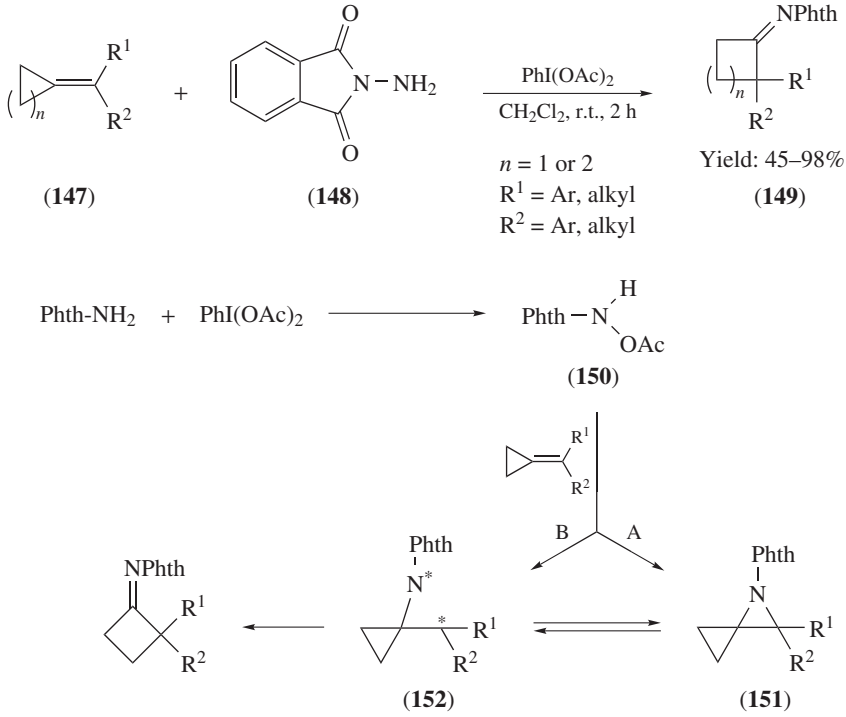
derivatives in high yields.[123] The asymmetric epoxidation of benzylidenecyclobutane and subsequent epoxide rearrangement to 2-arylcyclopentanones (**143**) and (**146**) with either inversion or retention of configuration using Et_2AlCl or LiI has been reported (Scheme 39).[124]



SCHEME 39

The rearrangement with Et_2AlCl is likely to go through a concerted process with inversion of the configuration (pathway a). Slightly more enantioselectivity is lost for epoxides with electron-donating groups, such as the 4-MeOPh moiety, during the rearrangement. This lowered enantioselectivity could be because of the competition from a stepwise S_N1-type process via a carbocation which is stabilized by electron-donating groups. The rearrangement with LiI is likely to go via intermediate (**144**) with double inversion (pathway b). A simple one-pot procedure for ring enlargement of α-chloromethyl *N*-containing heterocycles has been developed.[125] By reaction of chloromethyltetrahydroisoquinoline and its thieno analogue with benzyl or allyl bromide under basic conditions, ring expansion and *N*-substitution were achieved simultaneously. The key to the transformation was proposed to involve the formation of aziridinium salt and subsequent bond breaking between the nitrogen and tertiary carbon atoms. The ring expansion of isopropenyldihydrofuran derivatives has been described for the synthesis of oxepinolactones.[126] The metal-free ring expansions of alkylidenecyclopropanes and an alkylidenecyclobutane (**147**) mediated by a phtalimidonitrene, generated from *N*-aminophthalimide (**148**) and bisacetoxyiodobenzene, has been described for the synthesis of aryl-substituted cyclobutylidene and cyclopentylidene hydrazine derivatives (**149**) obtained in good to excellent yields (Scheme 40).[127]

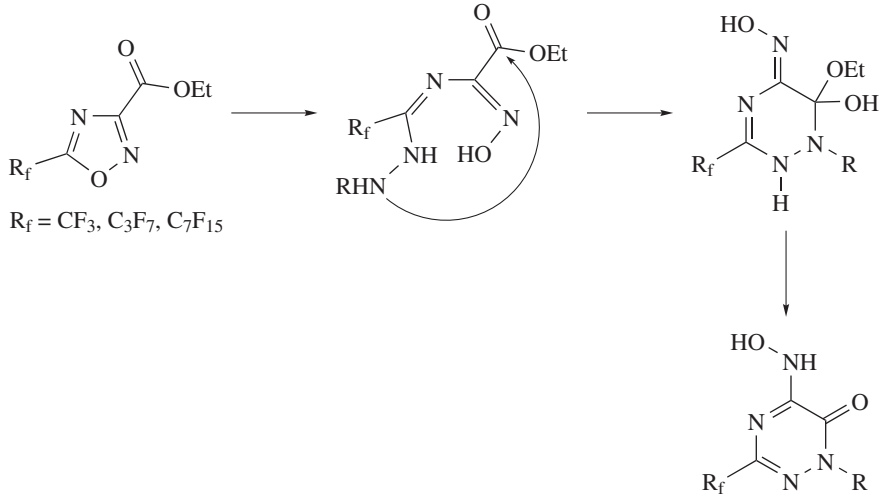
Two plausible mechanisms for these ring-expansion reactions have been proposed. First, *N*-aminophthalimide reacts with diacetoxyiodobenzene to generate the active nitrene equivalent (**150**). Intermediate (**150**) then assumed to react with alkylidenecyclopropane in two paths. In path A, the reaction of alkylidenecyclopropane with (**150**)



SCHEME 40

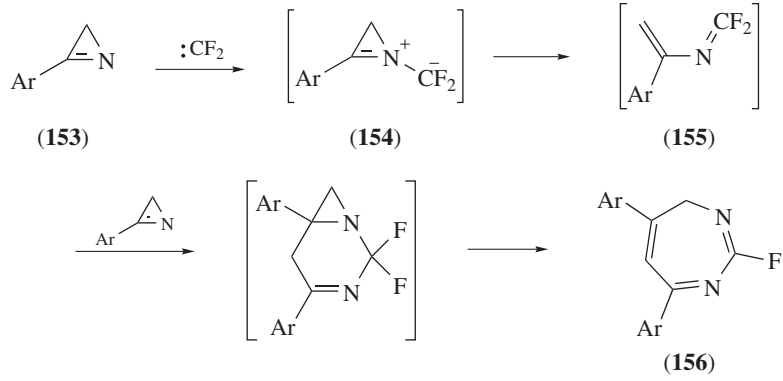
generates the corresponding aziridine (**151**), which undergoes a facile rearrangement to form the final 2,2-disubstituted cyclobutylidene hydrazine product via an ionic or diradical intermediate (**152**). Alternatively, in path B, reaction of alkylidenecyclopropane with (**150**) directly generates intermediate (**152**), which then undergoes a cation- or radical-induced ring-expansion rearrangement to furnish the final product. Intermediates (**152**) have not yet been distinguished as ionic or diradical species. The hydrazinolysis reaction of 5-perfluoroalkyl-1,2,4-oxadiazoles with hydrazine or methylhydrazine as bidentate nucleophiles has been studied (Scheme 41).[128] The reaction occurred through the addition of the bidentate nucleophile to the C(5)–N(4) double bond of the 1,2,4-oxadiazole followed by ring opening and ring closure involving the second nucleophilic site of the reagent to give fluorinated 1,2,3- and 1,2,4-triazoles, (*Z*)-oximes of 1,2,4-triazin-5-ones and 5-hydroxylamino-1,2,4-triazin-6-ones.

The observed regioselectivity shows the preferential attack of the NH_2 end of the methylhydrazine on the C(5). A new tandem cleavage–cyclization reaction of tetrahydroisoquinoline derivatives has been reported for the synthesis of benzoazocines.[129] A novel and readily available method for the synthesis of pyrroles possessing substituents with various groups via thermal rearrangement of iminocyclopropenes has been developed.[130] The regioselectivity in this iminocyclopropene rearrangement has also been disclosed. New perspectives on Boekelheide–Fedoruk ring expansions have



SCHEME 41

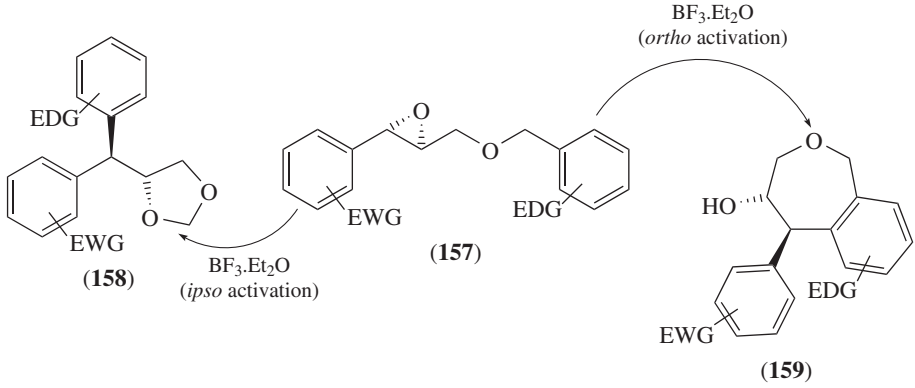
been outlined for the reactions of 1-substituted-imidazolium-3-dicyanomethanilides with maleic anhydride.[131] 5,7-Diaryl-2-fluoro-4*H*-1,3-diazepines (**156**) have been synthesized from 3-aryl-substituted 2*H*-azirines (**153**) and difluorocarbene.[132] The reaction involves isomerization of azirinium ylide (**154**) into a 2-aza-1,3-diene (**155**) which undergoes 4 + 2-cycloaddition with the starting azirine (**153**) followed by ring expansion and dehydrofluorination (Scheme 42).



SCHEME 42

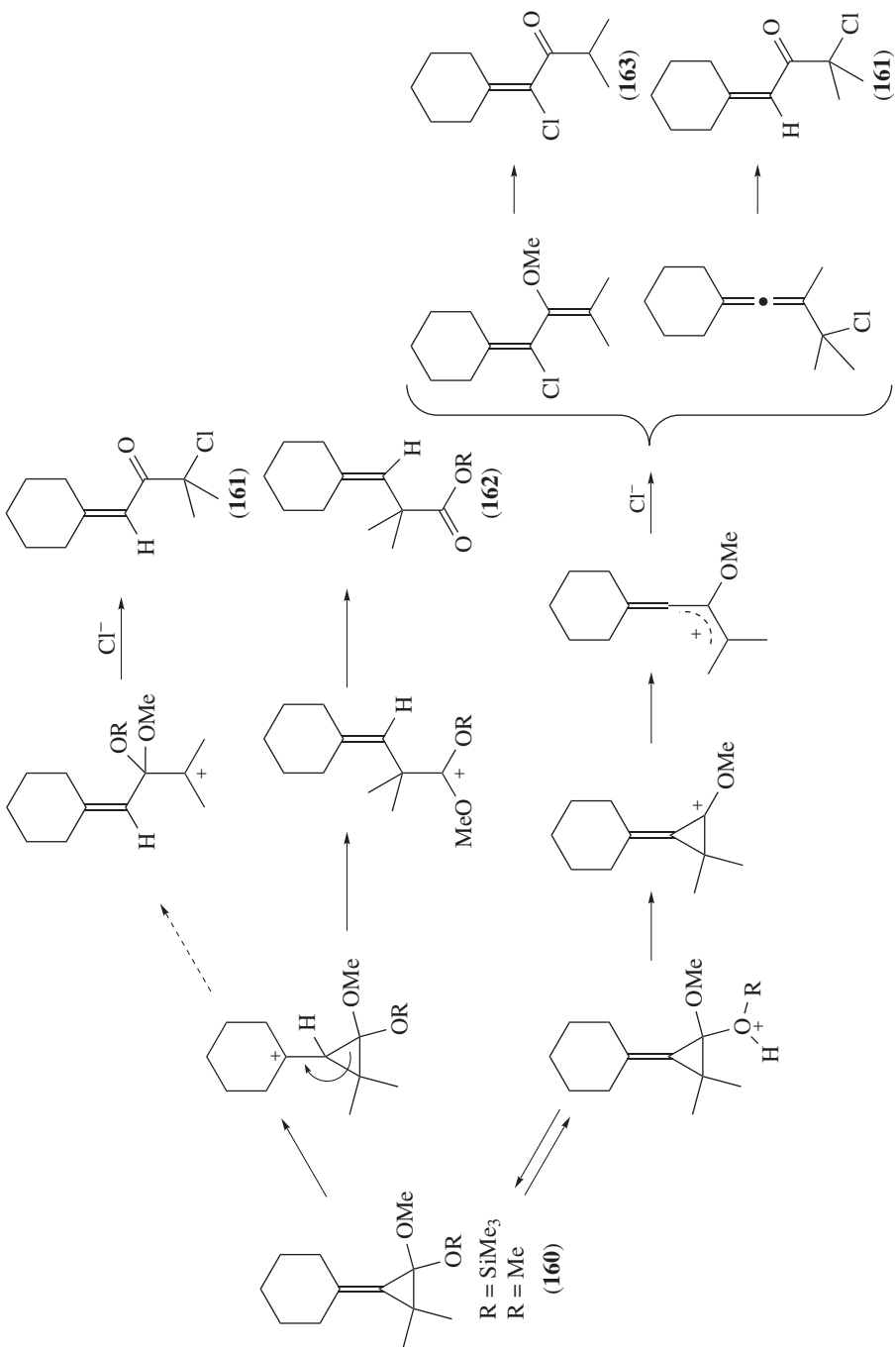
A new ring transformation of 1,2,3-thiadiazoles into furan-2-carbothioamides has been described.[133] An unprecedented rearrangement of 5,5-diazidobarbituric acids to parabanic, tetrazoles and benzyl allophanate has been reported.[134] Computational data for the energetics of internal nucleophilic reactions, both in ring-opening reactions

where strain energy is released and in model, strain-free systems has been reported.[135] The authors show that in internal nucleophilic ring-opening reactions the exothermicity of the internal reaction is much reduced compared with the same ring opening induced by an external nucleophile. Upon treatment with $BF_3.Et_2O$ at low temperature, enantiopure benzyl-type ethers of arylglycidols (**157**), with electron-withdrawing substituents at the skeletal aryl group and electron-donating substituents at the benzyl group, undergo stereospecific rearrangements of Friedel–Crafts type, leading to enantiopure 4-diarylmethyl-1,3-dioxolanes (**158**) or to enantiopure *trans*-4,5-disubstituted tetrahydrobenzo[*c*]oxepin-4-ols (**159**) (Scheme 43).[136] The course of the reactions is controlled by the substitution pattern at the benzyl ether. Whereas benzylic systems activated toward *ipso* substitution afford diarylmethanes through a Friedel–Crafts reaction followed by fragmentation, benzylic systems activated toward *ortho* attack lead to enantiopure oxepinols (**159**) through a *7-endo-tet* ring closure of Friedel–Crafts type. The epoxy-Ramberg–Bäcklund reaction has been outlined, in which α,β-epoxy sulfones are converted into a range of mono-, di-, and tri-substituted allylic alcohols, on treatment with a base.[137] Modification of this method allowed the preparation of enantio-enriched allylic alcohols following the diastereoselective epoxidation of enantio-enriched vinyl sulfones that were accessed efficiently from the chiral pool.

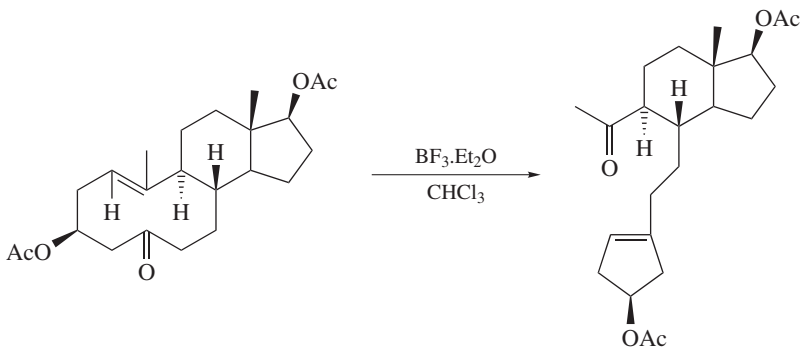


SCHEME 43

The oxidation of 2-alkoxy-3,4-dihydro-2*H*-pyrans with dimethyldioxirane followed by Jones oxidation, which leads to rearrangement and stereocontrolled formation of 4,5-*cis*-disubstituted tetrahydrofuranones, has been reported.[138] Ring-opening reactions of 2-cyclohexylidene-3,3-dimethylcyclopropanone acetal (**160**) has been reported to be readily induced by treatment of hydrogen chloride in various solvents, and leads to a mixture of isomeric ketones (**161**) and (**163**) and ester (**162**) in different ratios and yields depending on the solvent used (Scheme 44).[139] Bond cleavage takes place at the C(1)–C(2) or C(2)–C(3) bond, and the ratio of C(1)–C(2) to C(2)–C(3) cleavages changes from >99:1 to <1:99 depending on the solvent. The two modes of bond cleavage must be initiated by protonations at the carbon–carbon double bond and


OMe
OR
R = SiMe3
R = Me
(160)
H
OMe
OR
OR
OMe
H
Cl−
(161)
H
OR
O
MeO
+
OR
(162)
OMe
O
R
H
+
OMe
+
OMe
Cl−
OMe
Cl
Cl
(163)
Cl
H
O
(161)
Cl

SCHEME 44



(**164**) (**165**)

SCHEME 45

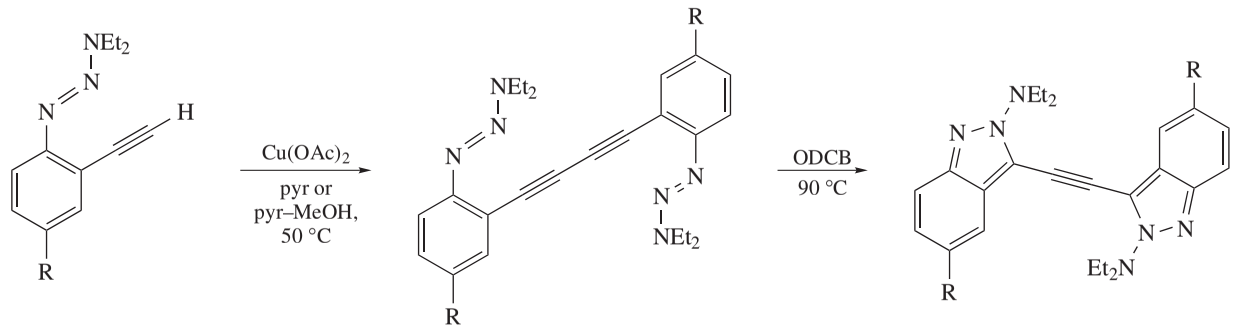
the acetal oxygen. The regioselectivity can be rationalized by the rate-determining protonation at carbon and the equilibrium protonation at oxygen.

Treatment of 3β,17β-diacetoxy-5,10-secoandrost-1(10)-en-5-one (**164**) with BF_3.Et_2O has been shown to proceed with cleavage of the macrocycle and formation of a new compound (**165**) containing a cyclopentene ring.[140] Based on DFT calculations, (*de*) a possible mechanism has been proposed involving an intramolecular Lewis acid promoted 2 + 2-cycloaddition, followed by a cycloreversion of the intermediate oxetane (Scheme 45).

A skeletal rearrangement of dihalospiropentanes in the presence of alkyllithium reagents has been systematically studied using a number of *gem*-dibromospiropentanes.[141] The synthesis of stable azomethine ylides by the rearrangement of 1,3-dipolar cycloadducts of 3,4-dihydroisoquinoline-2-oxides with DMAD has been described.[142] The effect of the substituents on the rate of the rearrangement of such compounds suggested a new mechanism involving consecutive C–C bond heterolysis and 1,3-sigmatropic shift. The effects of phenyl substitution on the lifetime and product distribution of cyclobutylidene rearrangements have been reported.[143] The phenyl substitution influences the preference for rearrangement via 1,2-carbon shift or 1,2-hydrogen shift.

Isomerizations

Several alkyne-linked bis-2*H*-indazoles have been synthesized by the double cyclization of butadiyne-linked (**167**) phenyltriazenes or phenyldiazenes, in turn obtained by $Cu(OAc)_2$-mediated homocoupling of ethynylphenyltriazenes (Scheme 46).[144] The reactions proceed rapidly under neutral conditions with mild heating, affording the heterocycles in excellent yields. By using Pd as catalyst under oxidative conditions, bis-2*H*-indazoles (**170**) were obtained directly from ethyne-linked phenyltriazenes (**169**). DFT calculations revealed for these reactions low barriers to cyclization that



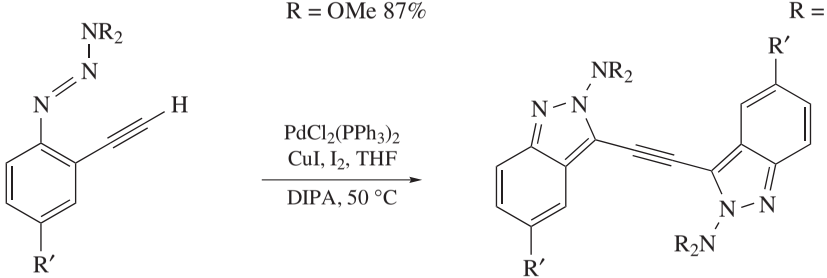
(**166**)

(**167**)

R = H 98%
R = *t*-Bu 99%
R = Cl 96%
R = NO_2 96%
R = CN 98%
R = OMe 87%

(**168**)

R = H 98%
R = *t*-Bu 99%
R = Cl 97%
R = NO_2 97%
R = CN 98%
R = OMe 87%



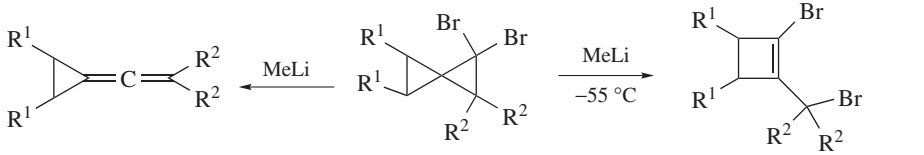
(**169**)
R = Et; R′ = OMe
R–R = $-(CH_2)_5-$; R′ = *t*-Bu

(**170**)
99%
97%

SCHEME 46

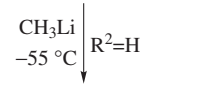
proceed through stepwise or non-synchronous yet concerted reaction mechanisms, thus not permitting the viable trapping of carbene intermediates. These bis-cyclizations remarkably illustrate the concept of coarctate reactions.

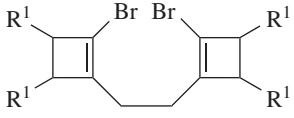
gem-Dihalogenospiropentanes (**171**) in the presence of alkyllithium reagents at −55 °C, in contrast to the common reactivity leading to allenes (**174**), undergo a skeletal rearrangement leading to cyclobutenes (**172**), and their homocoupling dimers (**173**) in the case of $R^2 = H$ (Scheme 47).[145] The mechanism of the process, occurring through the intermediacy of an Li-carbenoid species, is discussed.



(**174**) (**171**) R^1–R^1 = $(CH_2)_6$; R^2–R^2 = $(CH_2)_2$

(**172**) 70%



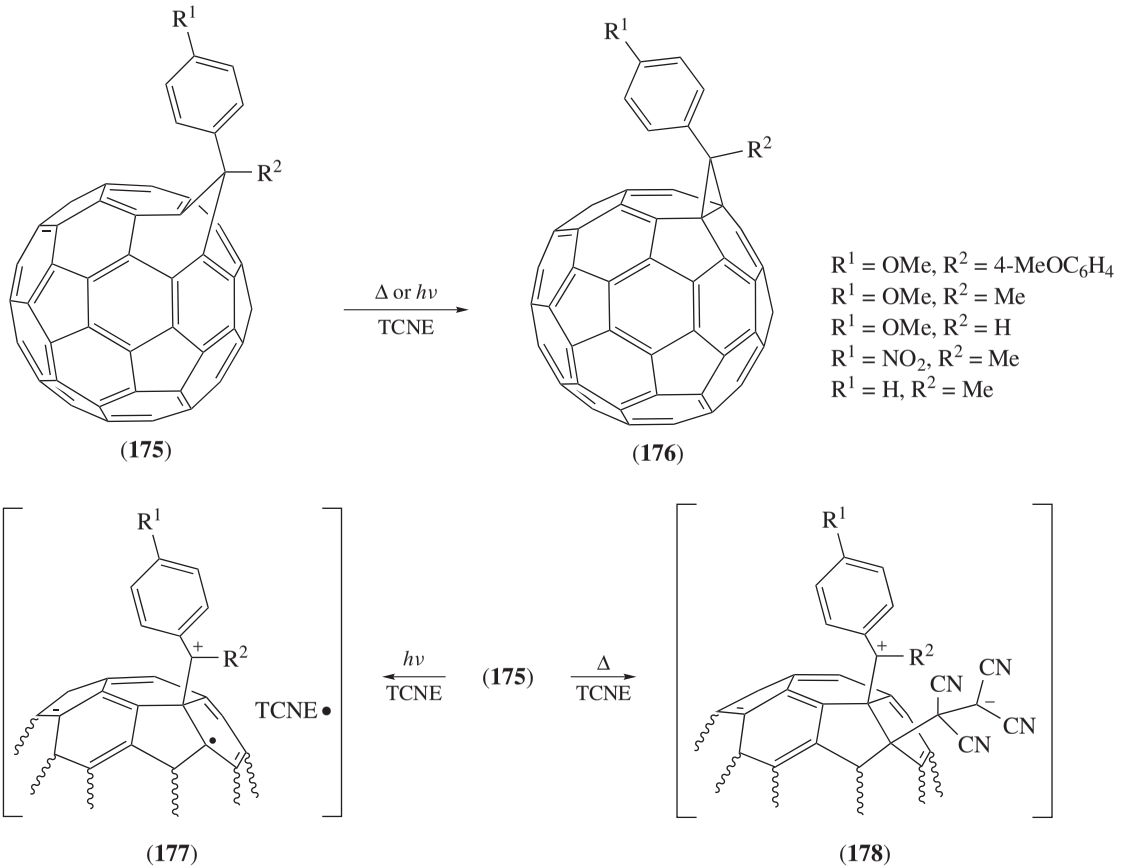


(**173**)

R^1–R^1 = $(CH_2)_4$	44%
R^1–R^1 = $(CH_2)_6$	45%
R^1 = R^1 = spiro-butyl	76%
R^1 = H; R^1 = spiro-butyl	50% (three isomers)
R^1 = H; R^1 = spiro-cyclohexyl	75%

SCHEME 47

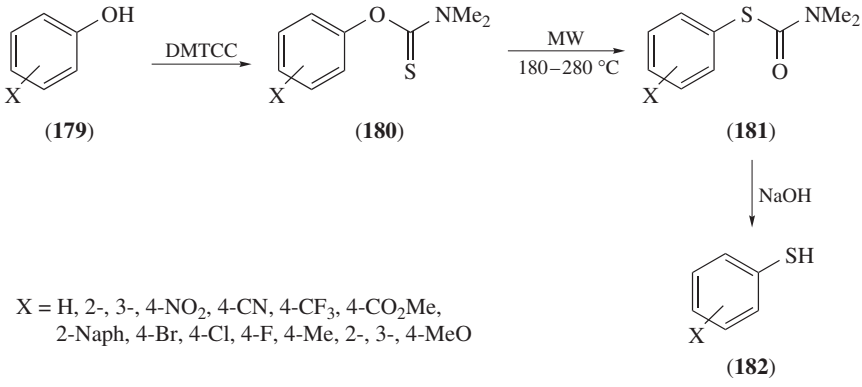
Computational calculations (CASPT2 and (4/4)CASSCF) have been performed to explain why addition of a second pair of geminal fluorines to methylenecyclopropane lowers the barrier to rearrangement by 6.7 kcal mol^{-1} more than addition of the first pair. The results confirm those of previous calculations showing that the non-additive lowering of activation energy for the rearrangement of 2,2,3,3-tetrafluoromethylenecyclopropane to 1-(difluoromethylene)-2,2-difluorocyclopropane is due to destabilization of the first by the presence of the vicinal CF_2 groups in this fluorocarbon.[146] The Arrhenius parameters for the structural isomerization of 1,1,2,2-tetramethylcyclopropane to 2,4-dimethylpent-2-ene,[147] and of 1,1,2-trimethylcyclopropane to three isomeric methylpentenes and two dimethylbutenes,[148] have been measured over a wide temperature range (670–1120 °C); E_a and log$A$ values were higher than previously reported from experimental work. Albeit substitution of methyl groups for hydrogen atoms on the cyclopropane ring is expected to weaken the C−C


R1
R2
Δ or hν
TCNE
(175)
(176)
R1 = OMe, R2 = 4-MeOC6H4
R1 = OMe, R2 = Me
R1 = OMe, R2 = H
R1 = NO2, R2 = Me
R1 = H, R2 = Me
TCNE•
hν
TCNE
(175)
Δ
TCNE
CN
(177)
(178)

SCHEME 48

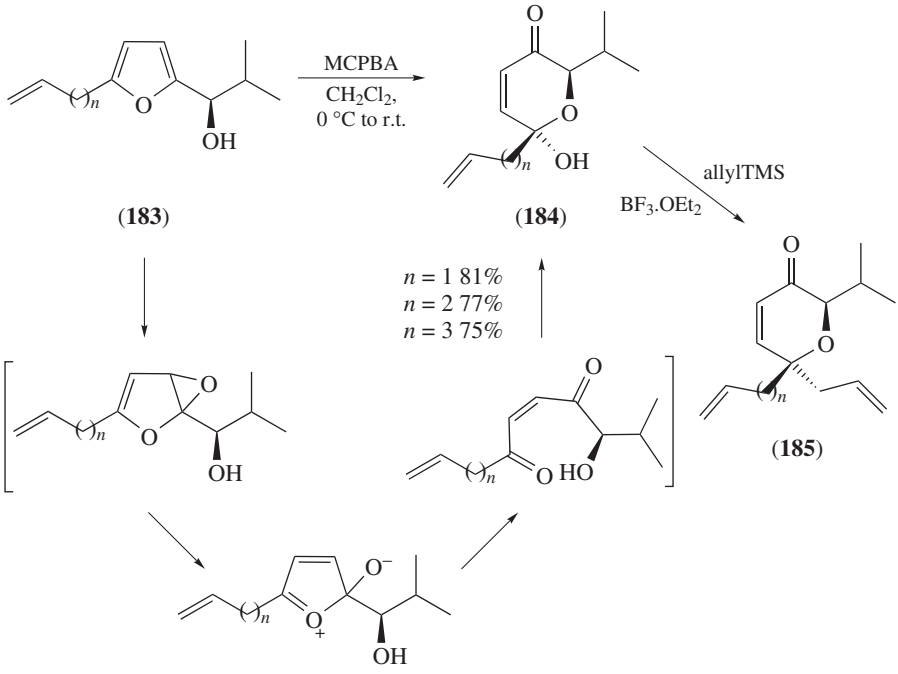
ring bonds, with activation energies for structural isomerizations reducing as the substitution is increased, the present study shows that the trend does not continue beyond dimethylcyclopropane isomerization. Steric interactions and conformational restrictions, in addition to reductions in C–C bond energy, may become increasingly important in determining the energy surface near the transition state in isomerizations of the more highly substituted methylcyclopropanes.

The thermal and photochemical rearrangements of a series of aryl-substituted [6,5] open fulleroids (**175**) to [6,6] closed methanofullerenes (**176**) are accelerated in the presence of an electron acceptor such as TCNE (Scheme 48).[149] Kinetic studies and study of oxidation potentials of these [6,5] open fulleroids suggest that the rearrangement facilitated by the electron acceptor occurs thermally by a zwitteronic-type intermediate (**178**), whereas the photochemical reactions proceed via (**177**), the intermediate of an excited-state electron-transfer process. The stereomutations and 1,3-carbon shifts involved in the degenerate thermal isomerizations of deuterium-labelled (*Z*)-ethylidene-2-methylcyclobutanes have been reconsidered; several mechanistic models have been analysed in the light of current theory.[150] The Newman–Kwart rearrangement (NKR), a synthetic technique for converting phenols (**179**) to thiophenols (**182**) via their *O*- (**180**) and *S*-thiocarbamates (**181**), has been re-evaluated and microwave heating was found to be ideal to run the reaction (Scheme 49).[151] Conversions higher then 95% were achieved in 20 min reactions at 180 °C for EWG substituents up to 280 °C for ED substituents.



SCHEME 49

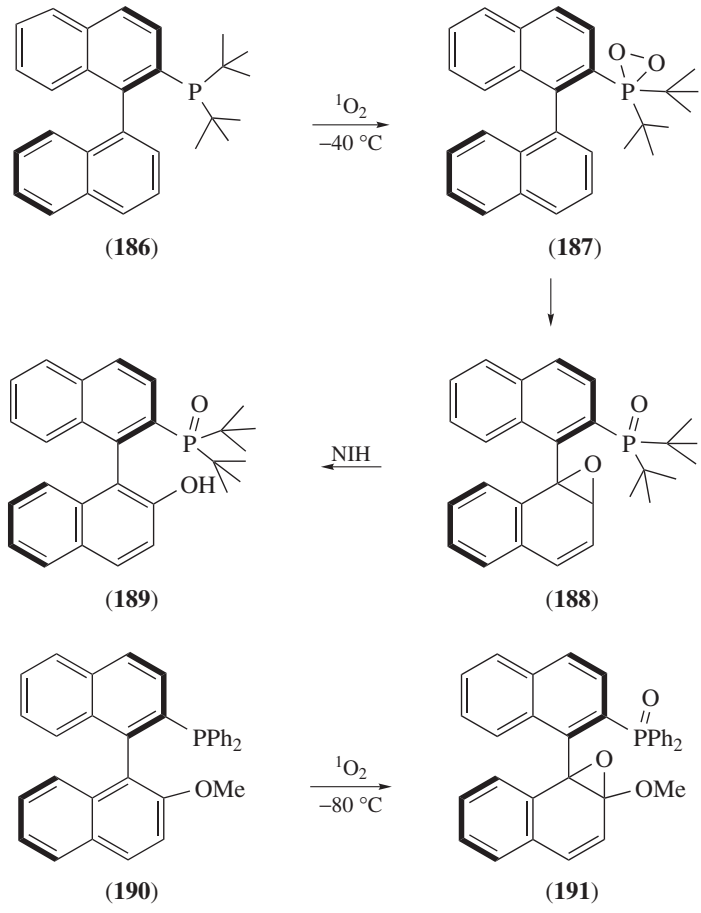
The results of a computational study of NKR for a variety of thionocarbamates using density functional (B3LYP) and *ab initio* (MP2) methodologies support the generally accepted mechanism that the NKR proceeds through a four-membered cyclic transition state.[152] Achmatowicz rearrangement of furyl carbinols (**183**) affords, with high diastereoselectivity (α:β = 8:1) and good yields, alkenylated pyrans (**184**), which could be efficiently allylated at the anomeric carbon, giving (**185**), as a route to spirocyclic pyrans (Scheme 50).[153] No side-chain epoxidation of (**183**) was detected, based on NMR analysis, and consequently the hydroxy-directed oxidation was efficient in giving a completely selective rearrangement.



SCHEME 50

Singlet oxygen reacts with binaphthyl phosphine derivatives such as 1,1′-binaphthyldi-*t*-butylphosphine (**186**) to form the corresponding binaphthyl-2-oxide phosphine oxides (**188**). This new intramolecular arene epoxidation reaction proceeds with complete retention of stereochemistry. The binaphthyl-2-oxide di-*t*-butylphosphine oxide undergoes a slow 'NIH rearrangement' to form the corresponding hydroxylated product (**189**). A transient phosphadioxirane intermediate (**187**) has been directly observed by low-temperature NMR. Kinetic analyses show that all of the phosphadioxirane intermediate is converted to product (Scheme 51).[154] With electron-donating groups on the binaphthyl moiety, such as (**190**), the intramolecular arene epoxidation to (**191**) is so rapid even at $-80\,^{\circ}C$, and more rapid than the oxidation of unreacted starting material, that the intermediate phosphadioxirane cannot be detected. Kinetic data on the acid-, base-, or un-catalysed rearrangement of a series of 3- or 4-substituted (*Z*)-phenylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole into (2-aryl-5-phenyl-2*H*-1,2,3-triazol-4-yl)ureas (an example of the Boulton–Katritzky reaction) were collected with the aim of gaining information about the effect of the substituent on the course of the reaction.[155]

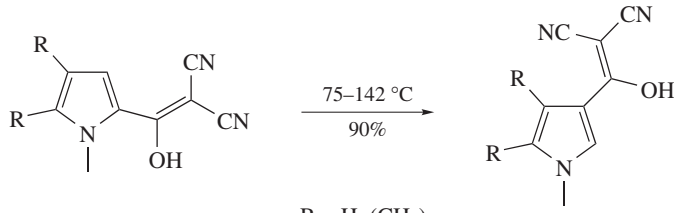
A thermally induced rearrangement of arylhydrazones of furoxan-3-carbonyl compounds into 2-aryl-5-[(hydroximino)arylmethyl]-2*H*-1,2,3-triazole 1-oxides has been observed for the first time.[156] 2-(2,2-Dicyano-1-hydroxyethenyl)-1-methylpyrroles (**192**) are readily rearranged to their 3-isomers (**193**) in nearly quantitative yield when heated to 75–142 °C. The inter- or intra-molecular auto-protonation of a pyrrole ring



SCHEME 51

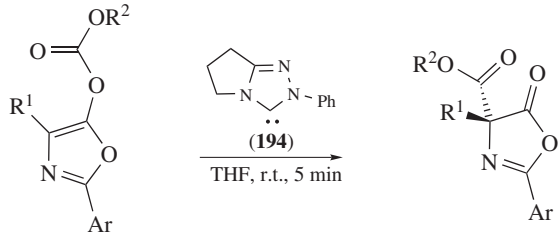
by the acidic enol hydroxyl to form a mesomeric pyrrolium cation or zwitterion is suggested to be a key step in the rearrangement (Scheme 52).[157]

Carbonate groups of hydroxyamino acids can migrate to produce carbamate derivatives with high efficiency and purity, without by-product formation, under pure aqueous mild basic conditions (buffer pH 7.4).[158] An *N*-heterocyclic carbene (**194**), generated *in situ* by treatment of a triazolium salt with KHMDS, promotes the fast rearrangement of α-amino acid derived *O*-acyl carbonates (**195**) to their corresponding *C*-acylated isomers (**196**), generating a C–C bond and a quaternary stereocentre with high efficiency, under mild reaction conditions and with low catalyst loadings (1 mol%) (Scheme 53).[159] Attack of carbene on the carbonate carbonyl gives the reactive acyl transfer product (**197**) which acylates the enolate (**198**), thereby regenerating the carbene catalyst.

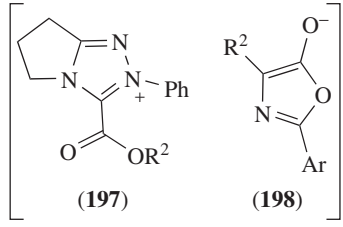


(**192**) R = H, $(CH_2)_4$ (**193**)

SCHEME 52



(**195**) Ar = 4-$MeOC_6H_4$, R^1 = Me, Bn, *i*-Pr, *i*-Bu, R^2 = Me, Bn, Ph (**196**) 67–84%



(**197**) (**198**)

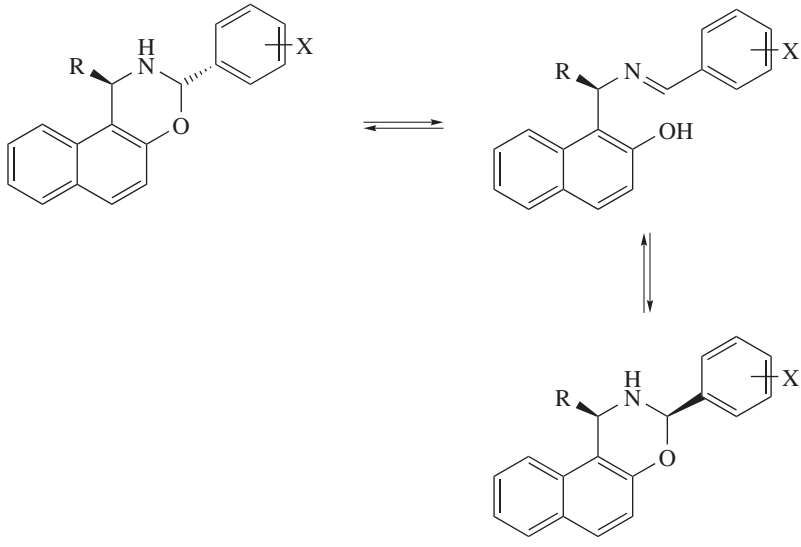
SCHEME 53

A study of the mechanism of DABCO-catalysed isomerization of γ-hydroxy-α,β-acetylenic esters to γ-oxo-α,β-*trans*-alkenyl esters through deuterium incorporation experiments, shows that an intermediate cumulene is protonated by the conjugate acid of the amine to give an allenol finally protonated with water.[160] The effects of different substituents on type I-dyotropic rearrangements of open-chain and cyclic 1,2-dibromo hydrocarbons have been studied by means of DFT calculations. The activation energy (E_a) of this transformation decreases with the π-donor ability of the substituent attached to the reacting ethylenic system.[161] The thermal rearrangement reactions of $H_3SiCH_2NH_2$ were studied by *ab initio* calculations.[162] The results show that two dyotropic thermal rearrangements (rearrangements involving simultaneous or consecutive migration of two σ-bonds) can occur. The one involving the migration

of the silyl group from the carbon to the nitrogen atom, coupled to a migration of a hydrogen atom from nitrogen to carbon, that forms (methylamino)silane ($MeNHSiH_3$) is favoured by activation energy over the other involving migration of the amino group to silicon. This result is consistent with experimental results for rearrangements under strong basic conditions. A computational study [B3LYP/6–311+G(d,p)] of the stabilization energies, singlet–triplet energy gaps, and lowest transition states for a set of cyclic alkenylidenes was performed in order to find the strongest interactions between the C–C double bond and the carbene centre. The stability of carbenes is optimized when the carbene centre is included in a norbornenylidene structure and when the double bond is electron rich and incorporated within another five-membered ring to enforce pyramidalization. A further stabilization can be obtained if the norbornenylidene structure is substituted with electronegative atoms such as fluorine. Strongly stabilized carbenes such as those with a norbornenylidene structure ('foiled' carbenes) show a reduced reactivity towards intermolecular reactions but have the propensity to undergo a retro-Skattebøl rearrangement.[163]

Tautomerism

Studies on substituent effects[164] and substituent-influenced anomeric effects in the ring–chain tautomerism of 1-alkyl-3-arylnaphth[1,2-*e*][1,3]oxazines have been reported (Scheme 54).[165] Multiple linear regression analysis of the calculated overlapping energies for the lone pairs of electrons on the nitrogen and oxygen atoms showed that the relative stability differences between the *trans* and *cis* ring forms is the result of an alkyl substituent-induced quantitative conformational change in the naphthoxazine ring system.



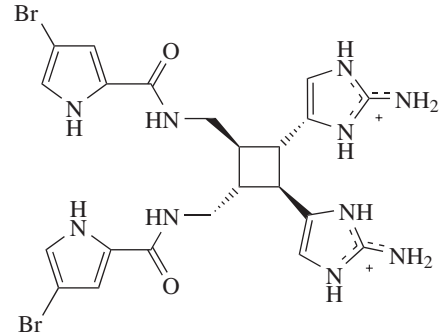
SCHEME 54

Radical Rearrangements

The antiviral natural compounds nagelamide E (**201**) and ageliferin (**202**) were obtained in very different yields, 40% and 2%, by heating an aqueous solution of natural compound sceptrin (**199**) at 200 °C under microwave irradiadion. The process suggested the involvement of a vinylcyclobutane–cyclohexene rearrangement with the closure of the diradical intermediate (**200**) followed by tautomerization. The fact that ageliferin and nagelamide E are synthesized by thermal rearrangement in approximately the same ratio as they are isolated from Nature suggests the possible involvement of a similar process in the biosynthesis of these compounds. Computational studies of model systems indicate that the rearrangement of sceptrin (**199**) most likely proceeds through a stepwise diradical process that starts from sceptrin (**199**) in dicationic form, definitely necessary for rearrangement, and that hydrogen-bonding interactions present in the 6-*endo-trig* closing transition state favour the formation of the product of suprafacial transition state with retention, i.e. ageliferin (**202**) (Scheme 55).[166] The formation of epimeric nagelamide E (**201**) involves inversion of the imidazole-bearing stereocentre, but, due to the low yield, it could be the side product of the rearrangement, but also an artifact produced from (**200**) during isolation, therefore not even produced in Nature.

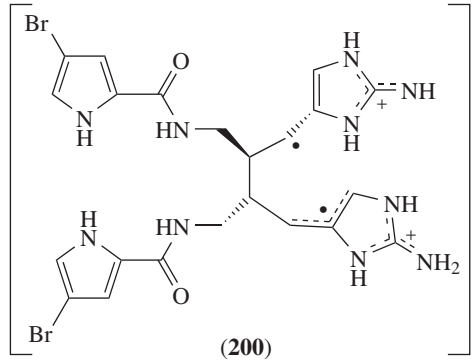
The isomerization of 5-vinyl-2-norbornene to 5-ethylidene-2-norbornene has been performed using a catalytic system consisting of an alkali metal hydride and an amine. The activity of the alkali metal hydride increased with increasing size of the alkali metal: KH > NaH > LiH. Among the various amines tested, only aliphatic 1,2-diamines exhibited the activity for the isomerization. Electron paramagnetic resonance (EPR) and UV–visible spectroscopic experiments on the active species suggest that the isomerization of 5-vinyl-2-norbornene proceeds through a radical mechanism.[167]

3-Vinylmethylenecyclobutane (**205**) rearrangement has an experimental activation energy of 35.7 kcal mol^{-1}, which is comparable to the energy expected for the homolysis of one of the endocyclic allylic C–C bonds, and is therefore expected to give rise to diradical pathways and non-concerted reaction products. In contrast, the highly substituted 3-vinylmethylenecyclobutane (**203**) was found to rearrange stereoselectively to give the [3,3]-sigmatropic shift product (**204**) in greater than 90% yield (Scheme 56). To determine the nature of the mechanism, the effects of substituents, and the cause of the observed stereoselectivity, a theoretical study using density functional theory (B3LYP) and complete active space *ab initio* methods (CASSCF and CASPT2) has been carried out for the parent 3-vinylmethylenecyclobutane (**205**) rearrangement and also for substituted models for the stereoselective rearrangement of (**203**) to (**204**).[168] Calculations indicate that for the parent compound (**205**), transition structures and diradical intermediates are very comparable in energy, and that diradical intermediates (**206**) and (**207**) (Scheme 56) have substantial conformational freedom and very low barriers for forming stereo- and regio-isomeric forms of the ring-enlarged product (**208**). In the substituted system, stereoelectronic effects of the trialkylsiloxy group and the ester and methyl substituents on the methylene group all conspire to cause a reaction that occurs by distinct bond-cleavage and bond-formation events, nevertheless exhibiting the high stereo- and regio-selectivity that is the usual feature

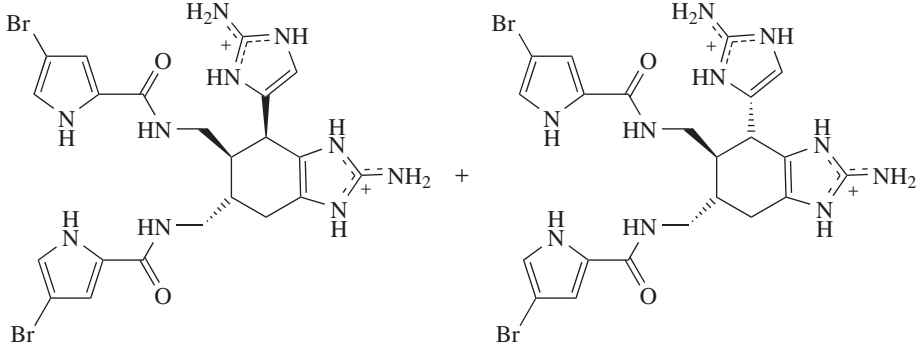


sceptrin (**199**)

MW, H_2O,
200 °C, 5 min



(**200**)

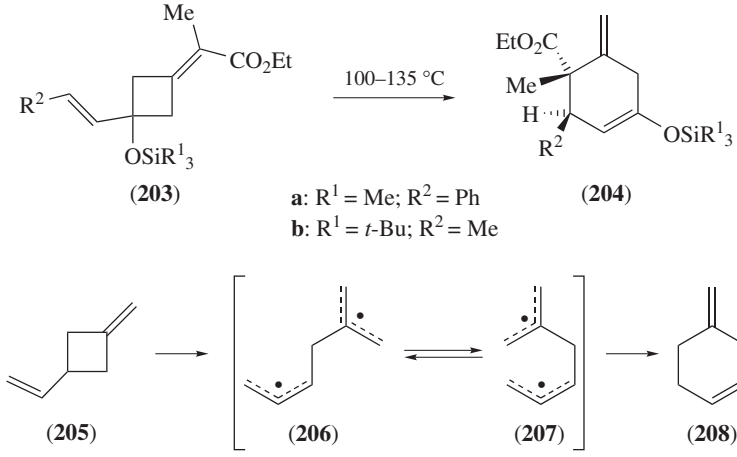


nagelamide E (**201**)
2%

+

ageliferin (**202**)
40%

SCHEME 55



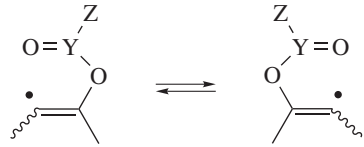
SCHEME 56

of concerted processes. Dynamics simulations of the four-fold degenerate rearrangement of bicyclo[3.1.0]hex-2-ene, which yields a non-statistical product distribution, were carried out. The simulated product ratio agrees with experiment and is found to be entirely dynamically determined. A geometric model is produced to estimate qualitatively the dynamically determined product ratio independently of trajectory calculations. The characteristics of this rearrangement are expected also to apply to others involving modestly stabilized diradical intermediates.[169]

Addition of *O*-centred radicals $XO^{\bullet}$ to cyclodecyn-5-one (**209**) leads to the isomeric vinyl radicals (**210**) and (**214**) that undergo transannular cyclization on to the carbonyl group. The resulting allyloxyl radicals (**211**) and (**215**) subsequently attack the C=C bond in a 3-*exo* fashion to give the X-oxy radical intermediates that decompose into the isomeric α,β-epoxy ketones (**213**) and (**217**) by release of a radical $X^{\bullet}$ (Scheme 57). When this reaction was performed with $NO_3^{\bullet}$, (**213**) and (**217**) were exclusively formed. With other radicals, such as the hydroxyl ($HO^{\bullet}$) or the sulfate radical anion ($SO_4^{\bullet-}$), or organic *O*-centred radicals, such as acyloxyl [$RC(O)O^{\bullet}$] or alkoxyacyloxyl radicals [$ROC(O)O^{\bullet}$], a third product, identified as the spirodiketone (**220**), formed through β-cleavage in (**215**) followed by cyclization and homolytic fragmentation. The finding that the yield of (**220**) was regularly significantly higher than 50% suggested that, as the initial radical attack should occur with equal probability, the initial radical addition should be reversible and the vinyl radical (**210**) should directly rearrange to (**214**). Therefore, the 1,2-nitroxyl and 1,2-acetoxyl rearrangements of β-(nitroxy)vinyl and β-(acetoxy)vinyl radicals (**221**) and (**222**), respectively, have been studied for the gas phase by various *ab initio* and density functional methods (Scheme 58).[170] The calculations lead to the conclusion that, in the case of the $NO_3^{\bullet-}$-induced radical oxygenation of cycloalkyne (**209**), all processes following the initial $NO_3^{\bullet}$ addition are fast and irreversible, because the terminating homolytic scission of the O–N bond requires practically no activation energy. Therefore, a 1,2-rearrangement of the nitrate moiety in a vinyl radical has no time to occur. In contrast,

SCHEME 57

in radical oxygenations involving acetoxyl (and other *O*-centred) radicals, the final homolytic cleavage of the O–C bond is the rate-determining step. In these systems, all cyclization steps are reversible, especially the 1,2-rearrangement of the acetoxy group in the vinyl radicals (**221**) and (**222**). The final product ratio (**213**):(**217**):(**220**) reflects, therefore, the relative rates between the various competing processes. The calculations showed a significant method-dependent outcome that should be taken into account in similar studies.

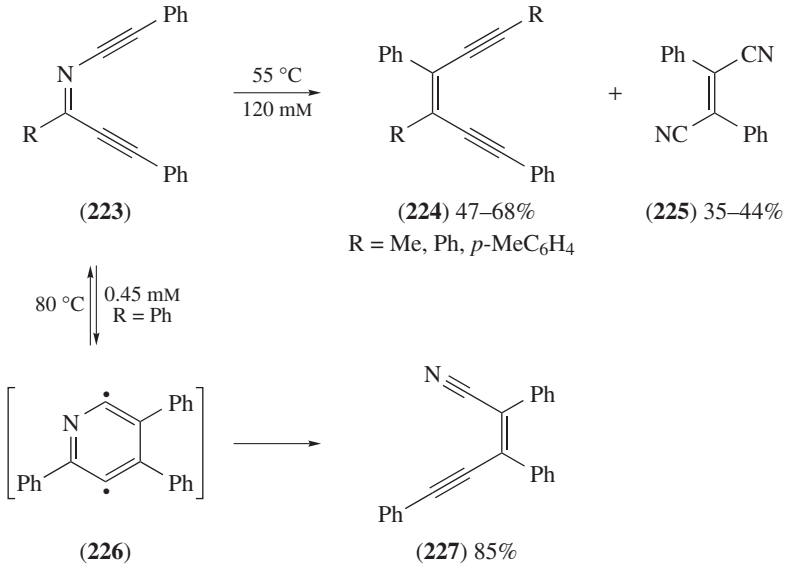


(**221**) (**222**)

SCHEME 58

The radical reaction of a series of *N*-(2-bromoallyl)-*N*-methylarylcarboxamides promoted by Bu_3SnH–AIBN led to the production of 4-aryl-1-methylpyrrolidin-2-ones and directly reduced materials in comparable yields (30–40%). A cascade process, involving sequential 5-*exo*-*trig* spirocyclization on the aryl ring, β-scission, and 5-*endo*-*trig* cyclization of the resulting acyl radical, is proposed to explain the pyrrolidinone products.[171] The lithium enolate formed from methyl *S*-trityl mercaptoacetate can be *C*-alkylated in high yield at or below $-40\,^{\circ}C$, but at higher temperatures the [1,2]-thio-Wittig rearrangement of the enolate is the predominant process leading to *S*-alkylated tritylacetate. ESR experiments indicate that this rearrangement occurs by a radical mechanism involving the homolytic cleavage of the *S*-trityl bond followed by C–C bond formation and *S*-alkylation.[172] The cathodic reduction or a base treatment of a 1-cyanomethyltetrahydrothiophenonium salt gave the stabilized ylide, which reacted with benzaldehyde to give 3-hydroxy-3-phenylpropionitrile. In the absence of benzaldehyde, the ring-expanded product 2-cyanotetrahydrothiopyran was obtained through a [1,2]-Stevens rearrangement in excellent yield (92%) by both methods. The reaction mechanism was investigated by using B3LYP density functional calculations and is proposed to be radical.[173] Aza-enediynes (*C*,*N*-dialkynylimines) (**223**) undergo thermal aza-Bergman rearrangement to β-alkynyl acrylonitriles through 2,5-didehydropyridine intermediates (**226**). Certain aza-enediynes, particularly in more concentrated solutions, undergo a parallel conversion to fumaronitrile (**225**) and (*Z*)-enediynes (**224**). Kinetic and labelling studies indicate that the conversion to enediyne is second order in aza-enediyne and proceeds by a series of 'head-to-tail' coupling and fragmentations (Scheme 59).[174]

1,2-Dialkynylimidazoles, another type of aza-enediynes, by thermolysis (80–100 °C) in chlorobenzene or CH_2Cl_2, or in DMF containing 1 equiv. of HCl, afford 5-chloroimidazo[1,2-*a*]-pyridine products deriving from the HCl trapping of the aza-Bergman cyclization product.[175] In search of new cyclizations, a computational study of the thermal rearrangements of 3-heteroatom-pent-1-en-4-yn-1-ones, enyne-ketenes



SCHEME 59

containing a variable heteroatom or carbon group at the 3-position, was carried out at the BLYP/6–311+G*//BLYP/6–31G* level of theory. While cyclizations to oxo-hetero-cyclopentadiendiyl (2,6-cyclization) are most favourable and predicted to be experimentally feasible for X = CH^-, NH, O, and S, protonation of these substituents raises the corresponding 2,6-cyclization barriers. Cyclizations to homoaromatic oxa-cyclohexadienediyl (1,6-cyclization) are highly improbable due to competition with other low-lying alternative pathways.[176] Treatment of various *o*-methoxy-substituted aryltriazenes with methyl iodide in a sealed tube at 120–130 °C gave aryl iodides together with 1,5-hydrogen atom transfer (originating from an *o*-triazene alkyl chain) products in excellent yields and roughly 1:1 ratio. The replacement of an *ortho*-hydrogen by a methoxy group has a crucial effect on the decomposition of triazene and particularly on the formation of 1,5-hydrogen atom transfer products. More than likely, 1,5-H shift reactions can be attributed to a radical mechanism mediated by iodine anion.[177] A reinvestigation of 2,6-difluorophenylnitrene, both experimentally and computationally, showed that it can be selectively and completely transformed into its two isomers, the bicyclic azirine and the cyclic ketenimine, by light of suitable wavelengths. All three isomers are ionized in Ar matrices, but only the phenylnitrene and the cyclic ketenimine yield stable radical cations, whereas the bicyclic azirine decays to both of these compounds on ionization. The cyclic ketenimine yields a novel aromatic azatropylium-type radical cation.[178]

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