STEREOSELECTIVE SYNTHESIS NOTES

Definitions

Chemoselectivity –
We can envisage two modes:
a) Substrate selectivity. Preferential reaction of one of several functional groups in the molecule with the reagent. In general the less reactive the reagent the more selective the reaction of chemically similar functional groups that can be achieved.
b) Product selectivity. In the case where reaction of a functional group can lead to several chemically distinct products, this occurs when a non-statistical ratio of products is observed.

Regioselectivity –
Preferential formation of one structural isomer over any others.

Stereoselectivity –
Preferential formation of one stereoisomer over any others. Obviously a diastereoselective reaction leads to the preferential formation of one diastereoisomer and an enantioselective reaction leads to the preferential formation of one enantiomer.

The term stereospecific is used in two instances:
(i) For a reaction where a single stereoisomer is converted completely to a single product stereoisomer. Textbook definitions define a process as being stereospecific only when starting materials differing only in their configuration are converted to stereoisomerically different products.
(ii) Can also be applied to a process that is completely stereoselective.

Topicity
Groups or faces of a molecule may display topicity. Strict definitions refer to whether such groups / faces are interchangeable by particular types of symmetry operations, but it is more useful to consider the concept in relation to the outcome of possible "future" reactions.
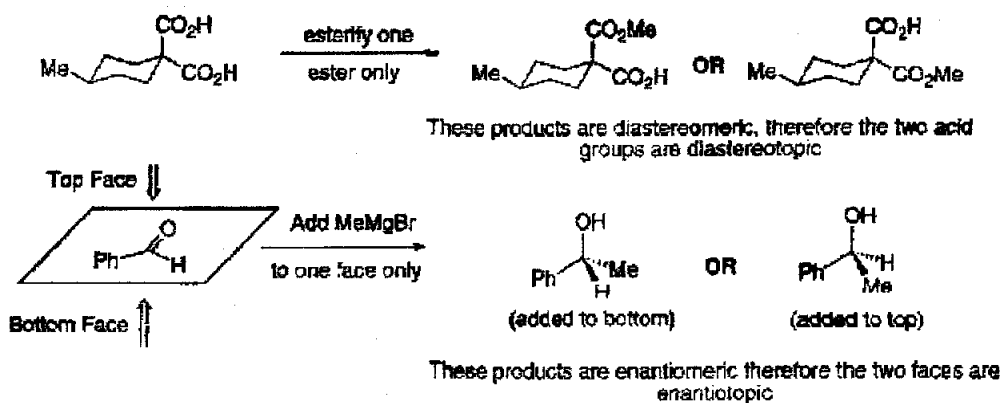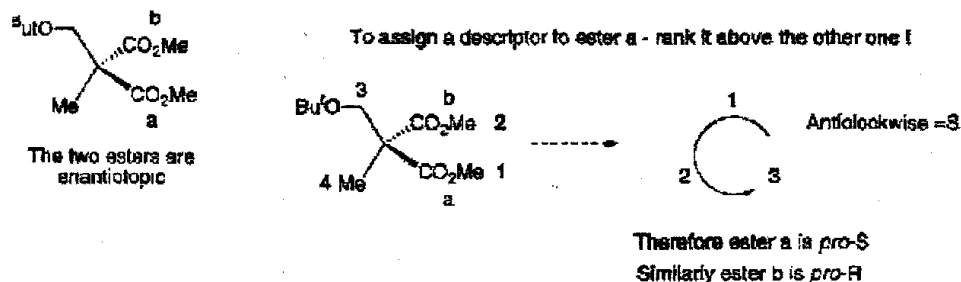

Prochirality
When replacement of one of a pair of groups or reaction on one of two molecular faces leads to the formation of a chiral material then these groups / faces are termed prochiral. Prochirality descriptions to both groups and faces can be assigned by the use of the standard Cahn-Ingold-Prelog rules. These are very useful, particularly when considering addition reactions.
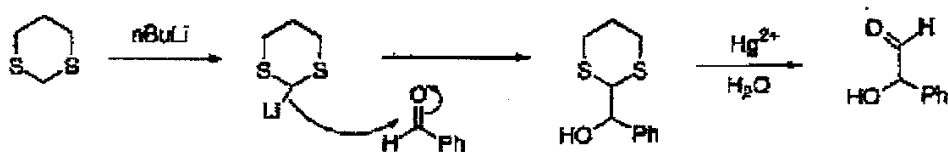
Faces:
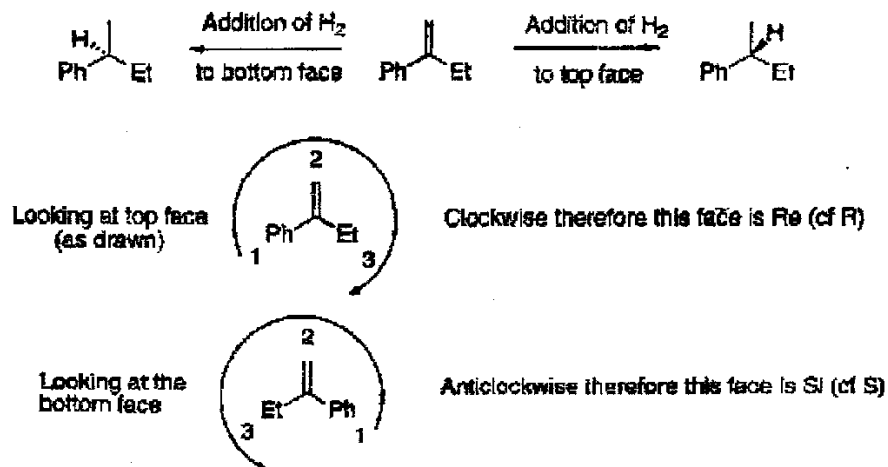
Groups:

Give the group under consideration priority over the other enantiotopic group, and then rank as normal with the CIP rules:

The two esters are enantiotopic

To assign a descriptor to ester a - rank it above the other one !

Therefore ester a is *pro-S*
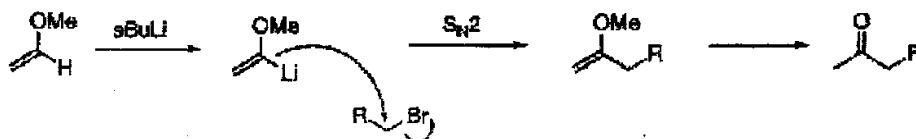Similarly ester b is *pro-R*

Umpolung Chemistry
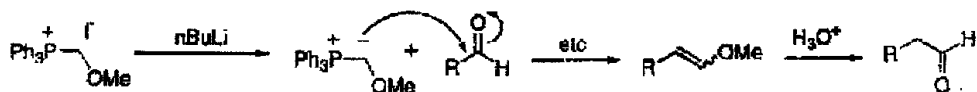
Polarity reversal. Some common examples follow:
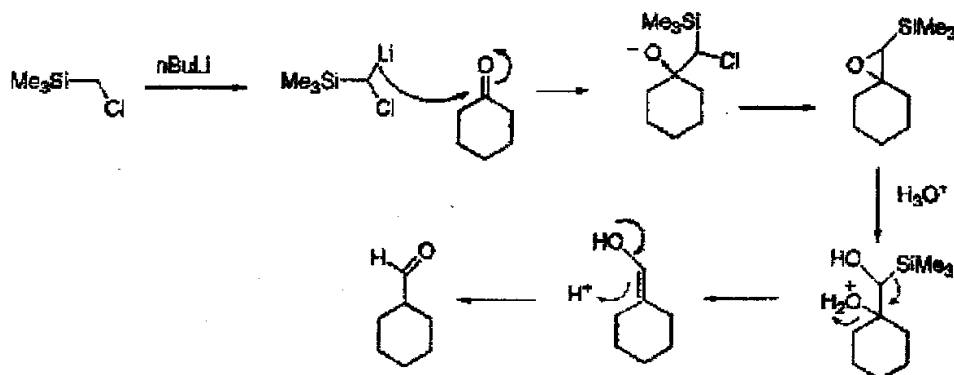
Dithianes:
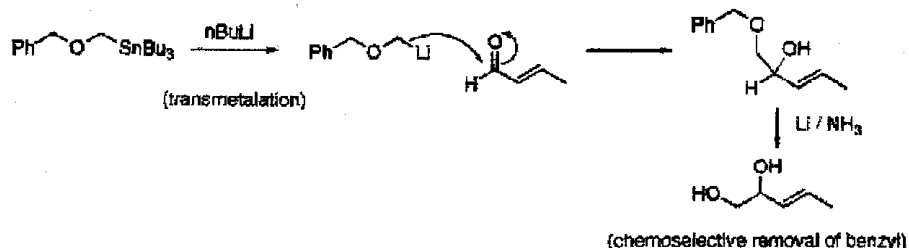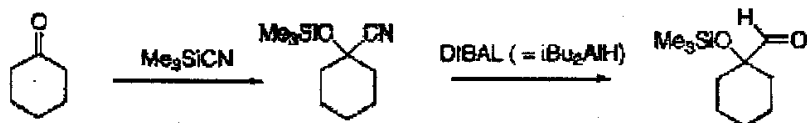

Enol Ethers:

Wittig Reagents:

Silicon Reagents:

Alcohol Carbanion Equivalents:

Cyanide:

Selectivity of Enolate Formation
(More on this can be found further on)

Kinetic Control – enolate composition is governed by the relative rates of proton abstraction.
Thermodynamic Control – enolate composition is governed by the relative stabilities of the enolates.

Kinetic Enolates
Usually the less substituted enolate.
Favoured by rapid irreversible deprotonation at low temperatures. Use of bulky bases favours kinetic deprotonation at the least hindered site, e.g. LDA, Bu^tLi. Li is usually used as the counterion since the higher covalent character prevents equilibration.

Thermodynamic Enolates
Usually the more substituted enolate.
Former at higher temperature under conditions of reversible deprotonation, e.g. in the presence of a weak acid. Judged as the more stable enolate by consideration as an olefin: increased substitution increases the stability.

## Diastereoselectivity in Additions to Acyclic RCHO and R_2CO

1,2 Asymmetric Induction
The influence of a chiral centre α to the carbonyl group.

Cram's Rule and Modifications

A purely empirical rule. The three substituents on the α carbon are ranked L (large), M (medium), and S (small) in terms of steric bulk. The carbonyl compound is presumed to react in a

conformation where the largest (L) of the substituents on the α carbon is eclipsed with the carbonyl substituent R (hydrogen in the case of aldehydes). The direction of nucleophilic attack is then predicted to be the same side of the carbonyl as the small substituent, S, rather than attack form the side of the medium substituent M.
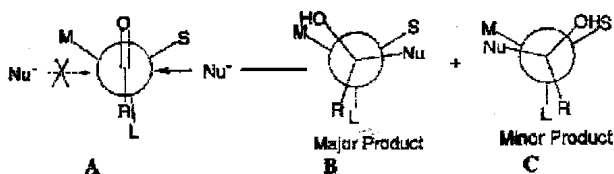

Although this rule has great utility there are significant exceptions to it. The following points are notable:

(a) No distinction is made between ground state and reactive conformations. The postulate that conformation A makes a significant contribution to the ground state conformation is unlikely.

(b) In view of the low rotational barriers around C-C bonds then more than one reactive conformation may be involved (by the Curtin-Hammett Principle). The likelihood that amongst thermally available conformations that conformation A makes a significant contribution is small since conformation A leads to fully eclipsed conformations B and C.

(c) The substituents on the α carbon are classified merely with respect to their steric bulk; any dipolar effects are ignored.

Modifications:

(i) Cornforth's dipolar model suggests that any electronegative substituent on the α carbon will preferentially occupy the L position – due to favourable dipolar interactions. Nucleophilic addition then occurs from the less hindered face.
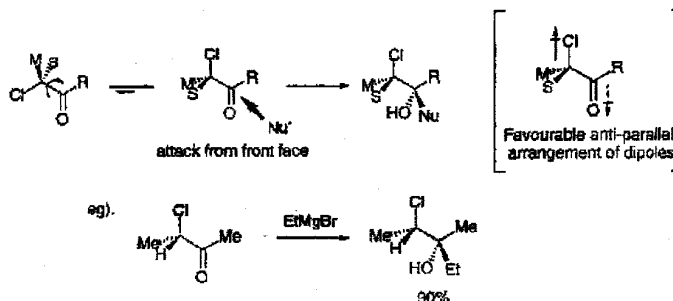

(ii) **Chelation** Model is used in the case of an α substituent that is capable of binding to the metal (itself complexed with the carbonyl group), e.g. α alkoxy, hydroxy and amino carbonyls. Chelate formation occurs prior to addition of the organometallic to the carbonyl group. This subsequently occurs to the less hindered face of the chelate – this may result in induction that is opposite to that predicted by the simple Cram's Rule.

(i) pre-chelation of the carbonyl and alpha substituent by the metal
(ii) Nucleophilic attack on the less hindered face of the chelate
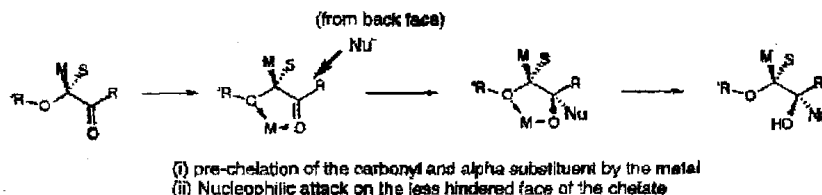
Chelation (a) enhances the electrophilic nature of the carbonyl and (b) prevents rotation about the C-C bond and compels the nucleophile to add from the least hindered face.

In general this is more powerful than the simple Cram Model, and chelation controlled reactions proceed with very high levels of asymmetric induction, e.g.


MEM = CH$_2$O(CH$_2$)$_2$OCH$_3$ >95%yield   diastereoselectivity >99:1
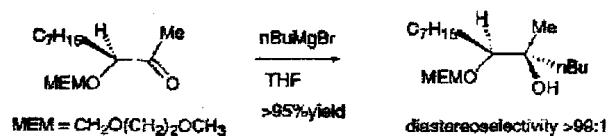
(iii)   **Felkin-Anh** Model. The most satisfactory explanation based on theoretical calculations:

Disfavoured   Favoured
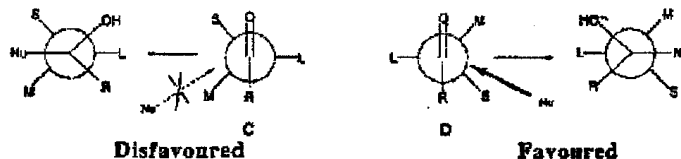
Molecular modelling showed that in fact the two lowest energy conformations are C and D. An important point was the realisation that nucleophilic attack does not occur perpendicularly to the carbonyl group as was previously thought. Thus, preferred reaction occurs via a transition state like D where the nucleophile attacks next to the small (S) group rather than via C where nucleophilic attack is disfavoured by the increased bulk of the medium (M) group.

Allylic 1,3 Strain and use for 1,2 and 1,3 Asymmetric Induction

Torsional strain between allyl substituents produces a conformational preference:


RELATIVE ENERGY   0   +0.73 kcalmol^{-1}
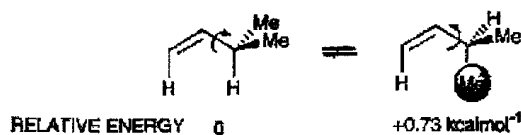
NB: only a couple of lowest energy conformers drawn.

Z substitution of an alkene increases this conformational preference to a size where it allows high levels of asymmetric induction. If the neighbouring allylic centre is chiral this can allow stereocontrol of addition reactions to the alkene providing groups R$_1$ and R$_2$ differentiate the faces of the double bond.
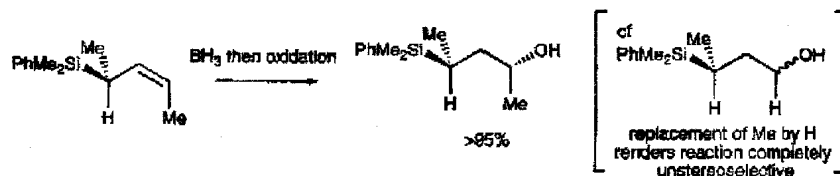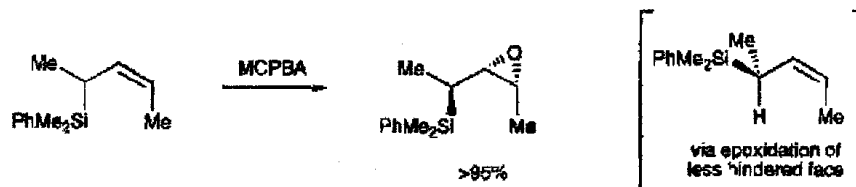

Preferred conformation

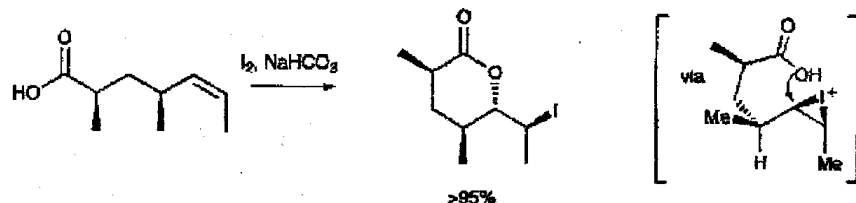

RELATIVE ENERGY   0   +4 kcalmol^{-1}
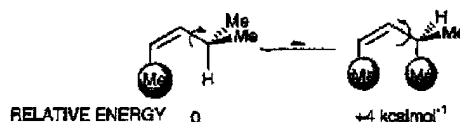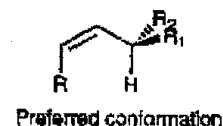
Examples:

Wittig Rearrangement –

100% diastereoselective
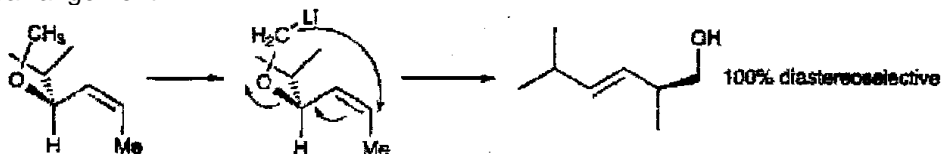
Hydroboration –

Epoxidation –

Iodolactonisation –

Summary of Some Commonly Used Hydride Reducing Agents

LiAlH$_4$	Lithium aluminium hydride	Very reactive, non-selective reagent, used in non-protic solvents.
LiBH$_4$	Lithium borohydride	Intermediate reactivity between LiAlH$_4$ and NaBH$_4$. Again, used in non-protic solvents.
NaBH$_4$	Sodium borohydride	More selective reagent, e.g. reduces aldehydes/ketones but not esters (apart from methyl). Note use in protic solvents and in combination with Cerium Chloride for chemoselective reductions.
DIBAL	Diisobutylaluminium hydride	Reactive reducing agent that shows high chemoselectivity when used at low temperature in non-polar solvents. Reagent of choice for transformations such as ester to aldehyde, lactone to lactol, nitrile to aldehyde, etc.
NaBH$_3$CN	Sodium cyanoborohydride	More selective and mild reducing agent than NaBH$_4$. For use in acidic solution for reduction of protonated species, e.g. during reductive aminations, imines, iminium ions, tosylhydrazones, etc.
LiAlH(OBu^t)$_3$	Lithium tert-butoxyaluminium hydride	Bulky reagent of lower reactivity than LiAlH$_4$ for selective reduction of aldehydes/ketones in presences of esters, lactones, amides, nitriles, epoxides, azides, etc. Reduces acid chlorides to aldehydes. Shows high levels of stereoselectivity.
L-Selectride (LiBH(s-Bu)$_3$)	Lithium tri-s-butylborohydride	Higher reactivity than LiBH$_4$, though ketones can be reduced in the presence of esters and lactones. Bulky: shows high levels of diastereoselectivity
Superhydride (LiBHEt$_3$)	Lithium triethylborohydride	Source of extremely nucleophilic H$^-$. Reagent of choice for dehalogenation, deoxygenation of tosylates/mesylates. Rapidly reduces aldehydes/ketones, esters, epoxides, etc.

Substituted Borohydrides –

- o Electronic effects of R substitution changes efficiency of hydride donation.
- o Inductive withdrawal of CN reduces e-density on B, resulting in a less potential (more stable) hydride donor.
- o Electron density on B increased – more potent source of hydride.
- o The counter-ion is also important. $LiBH_4$ is more reactive than $NaBH_4$ – explanation: Li is a Lewis Acid which activates the carbonyl to attack.

In Synthesis:

a)

$$\xrightarrow[\text{catalyst}]{H_2}$$

Pd, Pd on C, Pd(OH$_2$), PtO$_2$, Wilkinson's Catalyst.

b)

$$\xrightarrow[\text{(no EtOH)}]{Na/NH_3}$$

dissolving metal reduction w/ no more than 1 equiv of proton donor. >1 equiv ⇒ alcohol.

c)

$$\xrightarrow{DibalH}$$

(or NaBH$_4$ w/ CeCl$_3$)
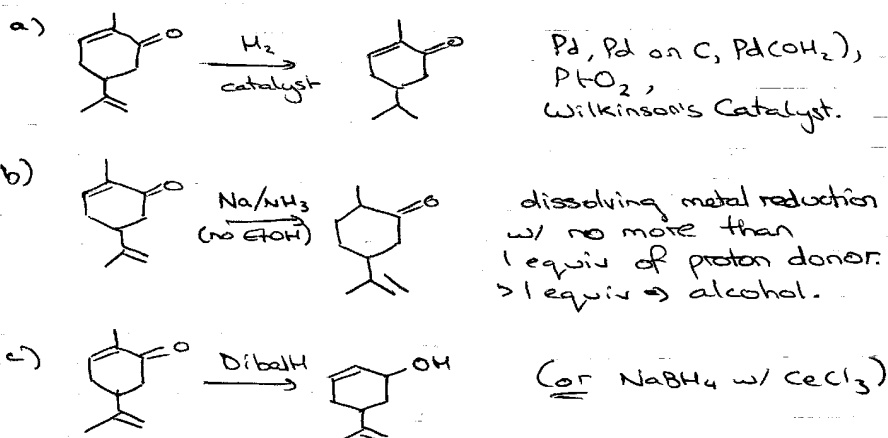
Stereoselectivity:

Reduction of C=C
Heterogeneous ➔ H_2 delivered SYN to alkene.

Can be directed by e.g. OH groups to one face, particularly if homogeneous.

For acyclics, may be controlled by 1,3-allylic strain:

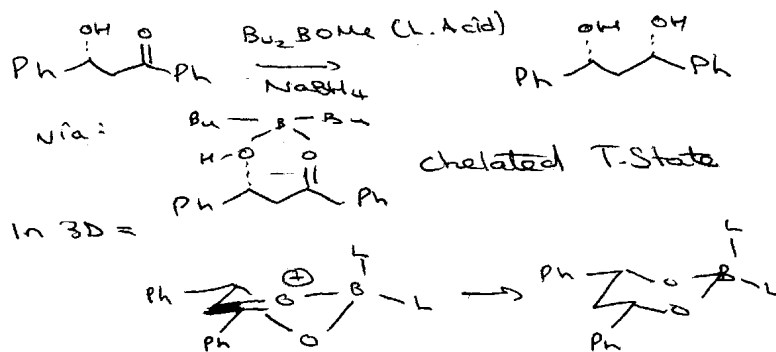via
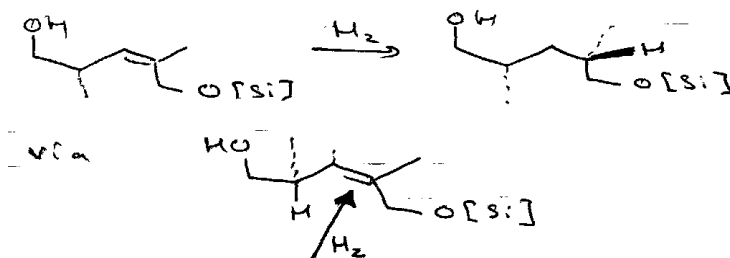
Reduction of C=O
Often chelation controlled, e.g.

$$\xrightarrow{LiAlH_4}$$

blocks attack from otherwise least hindered face.
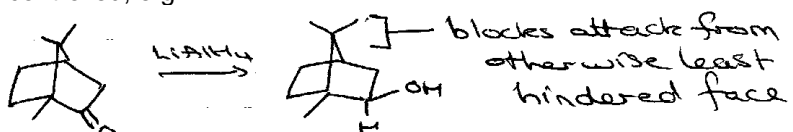
Acyclic Cases often have 1,2 Induction with α chiral centre (Cram's Rule).
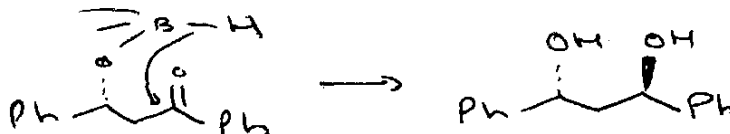
$$\xrightarrow{Li AlH_4}$$
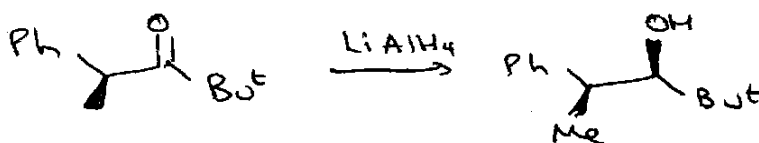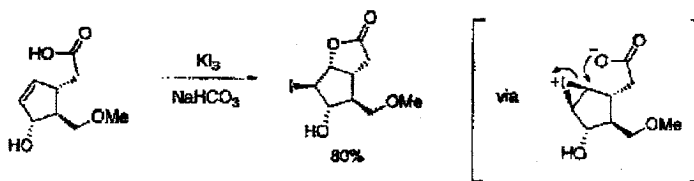
Felkin-Anh Model ➔
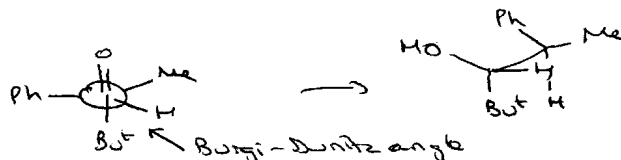
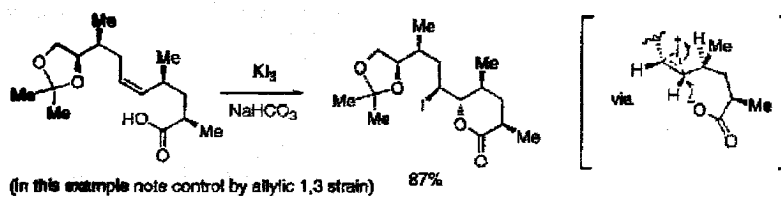Also, 1,3-induction by chelation control, e.g.
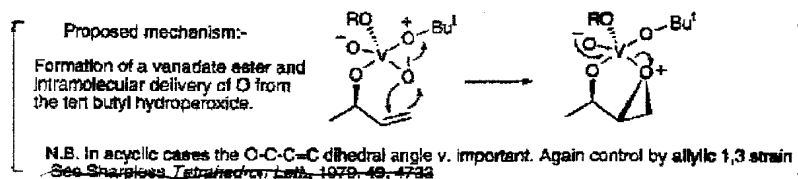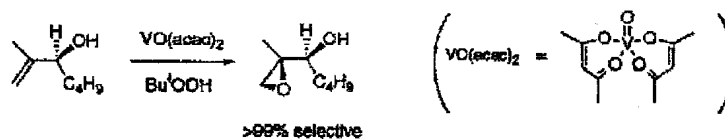

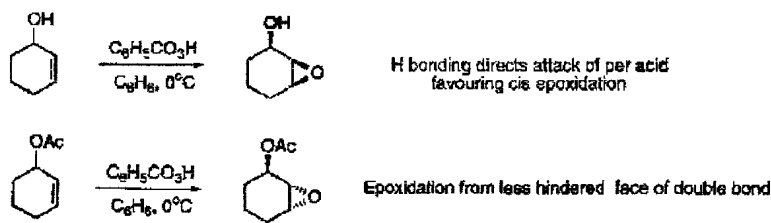Intramolecular delivery – no Lewis Acid ➔

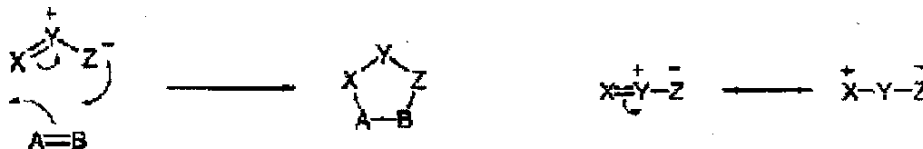(not restricted to hydroxyls either).

Iodolactonisation

Trans addition of I and O across a double bond
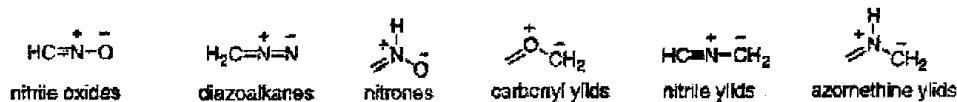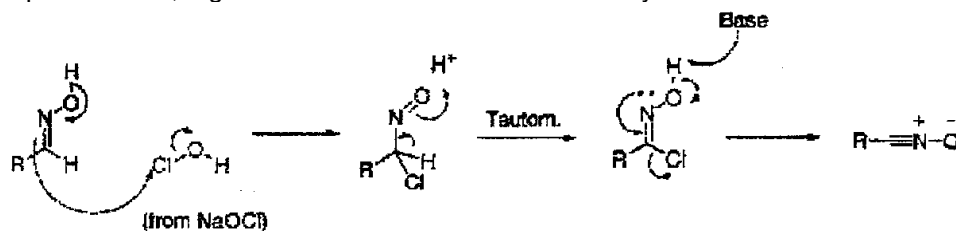O attack intramolecular and thus stereodefined

(in this example note control by allylic 1,3 strain)   87%

Stereoselective Epoxidation

H bonding directs attack of per acid favouring cis epoxidation

Epoxidation from less hindered face of double bond

>99% selective

Proposed mechanism:-

Formation of a vanadate ester and intramolecular delivery of O from the tert butyl hydroperoxide.

N.B. In acyclic cases the O-C-C=C dihedral angle v. important. Again control by allylic 1,3 strain. See Sharpless *Tetrahedron Lett.*, 1979, 49, 4733

Some Synthetic Applications of 1,3 Dipolar Cycloaddition Reactions

A few common 1,3 dipoles:

| nitrile oxides | diazoalkanes | nitrones | carbonyl ylids | nitrile ylids | azomethine ylids |

Often prepared in situ, e.g. nitrile oxides from oximes of aldehydes:

(from NaOCl)

Also, Nitrones from substituted hydroxylamines and carbonyls:
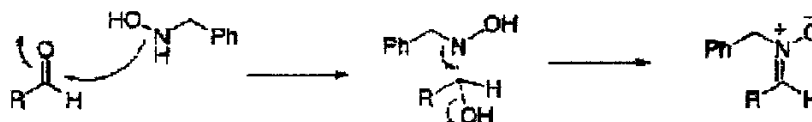
Stereospecific SYN addition. High degree of regioselectivity is also possible, though best when reaction is performed intramolecularly – form the most stable / least strained ring system.
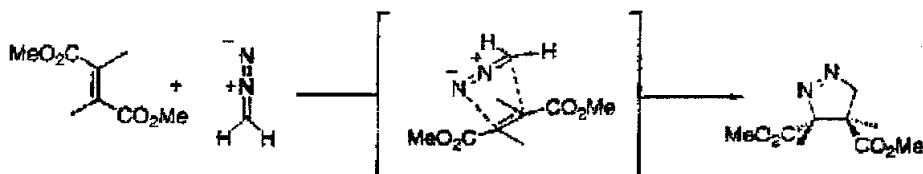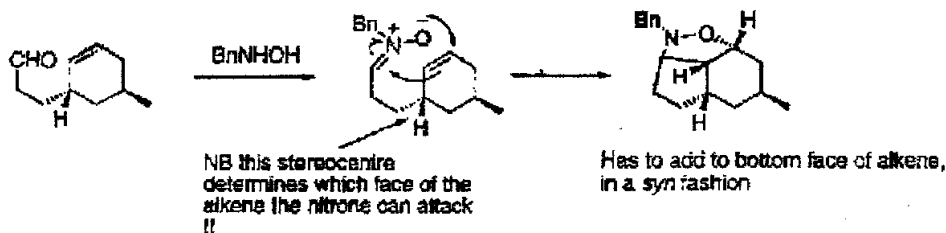
Diastereoselective Alkene Formation

The Salt-Free Wittig Reaction

With non-stabilised ylids under salt-free conditions, Z-1,2-disubstituted olefins are favoured with RCHO.

In the salt-free Wittig reaction, the ylid is generated from the phosphonium salt with a base such as sodium amide. The NaX salt that is formed is filtered off to leave the naked extremely highly reactive phosphorane.
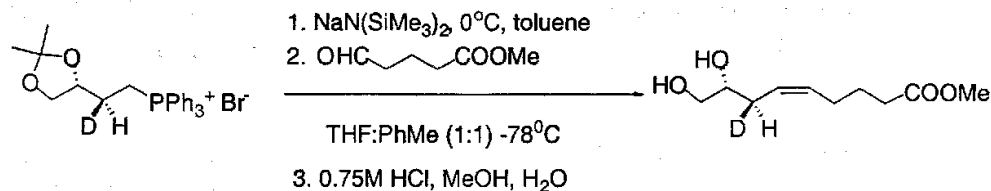
### The Wittig-Schlosser Reaction

Methodology for obtaining E-alkenes from non-stabilised phosphorus ylides.
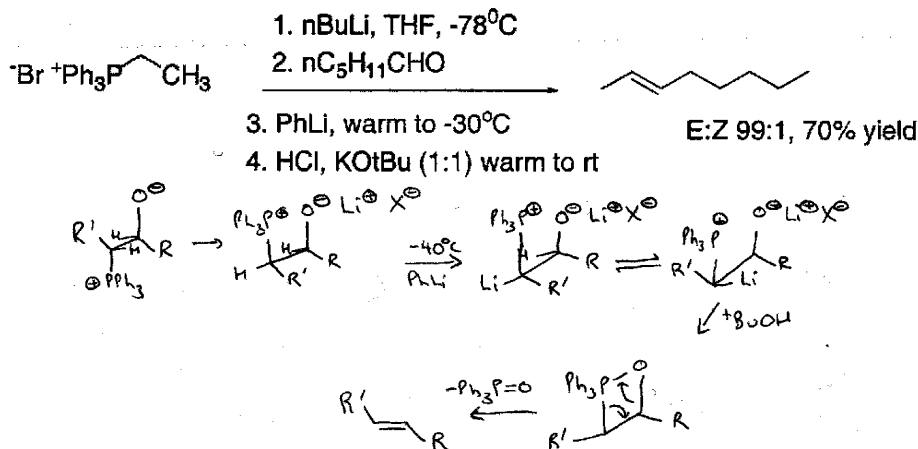
Horner-Emmons-Wadsworth modification

With stabilised phosphorus ylides in the presence of salts, E-disubstituted olefins are favoured with RCHO.

A stabilised ylide is an one in which the carbanion adjacent to the phosphorus substituents is additionally stabilised by the presence of an electron attracting group on the same carbon.
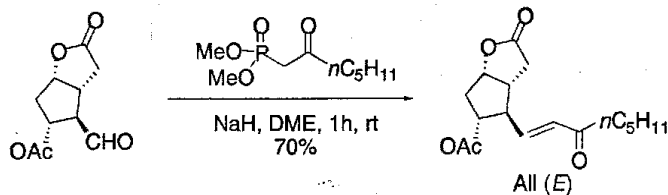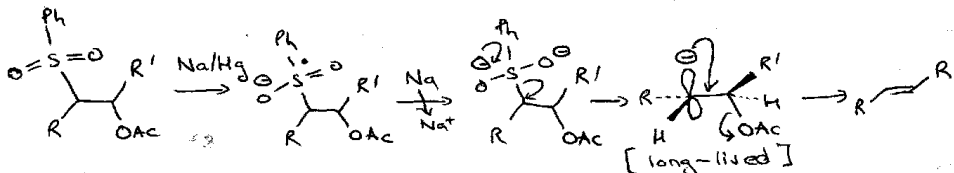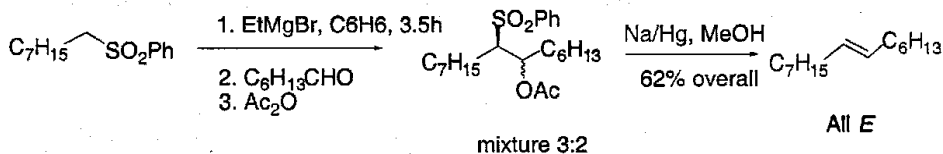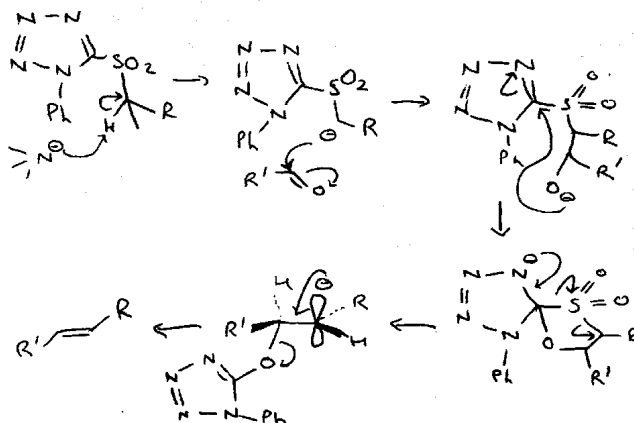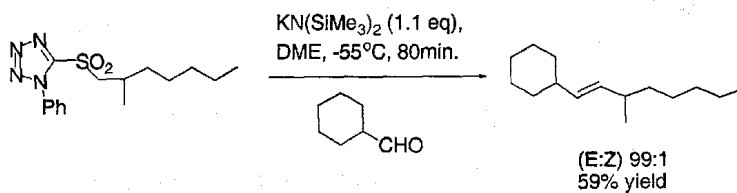

The Peterson Reaction
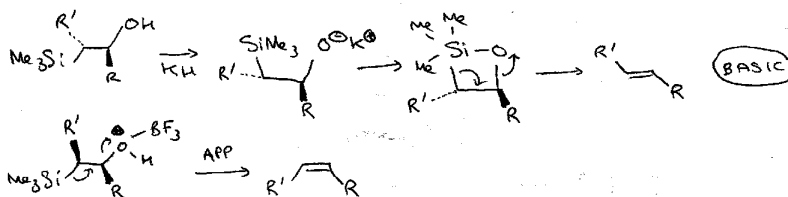
The Julia Reaction

One of the best methods available for forming E-1,2-disubstituted olefins from aldehydes in complex systems.
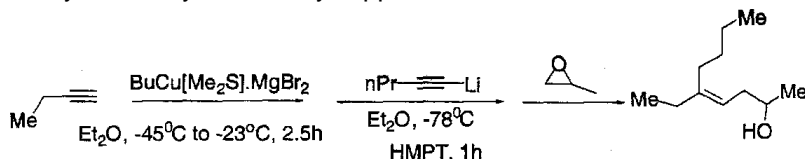

Kocienski's Modification

Carbocupration of Alkynes – *Synthesis of trisubstituted alkenes.*

One of the most valued properties of $RCu.MgX_2$ reagents is their ability to add across the triple bond of terminal acetylenes. Such processes are termed carbocupration reactions and they lead to the formation of synthetically useful vinylcopper intermediates.


Hydro- and Carboalumination of Terminal Alkynes *– Synthesis of di- and trisubstituted alkenes*

Alkynes undergo cis-addition in hydrocarbon solvents to give E-vinyl alanes which can be converted to the corresponding reactive ate complexes. These complexes react readily with many different electrophiles with complete preservation of the E-vinyl alane geometry.
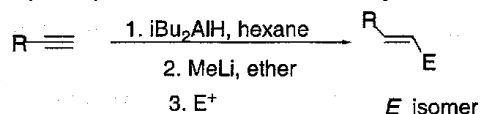

In the presence of zirconocene dichloride, trimethylaluminium will add cis across terminal alkynes to give methyl E-trisubstituted vinylalanes. These can be converted to the more reactive ate complexes through reaction with an alkyllithium which can then be trapped with a variety of electrophiles with retention of vinyl geometry.
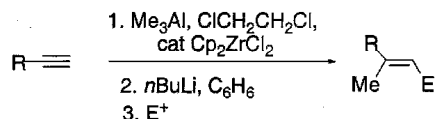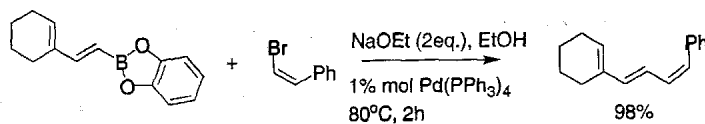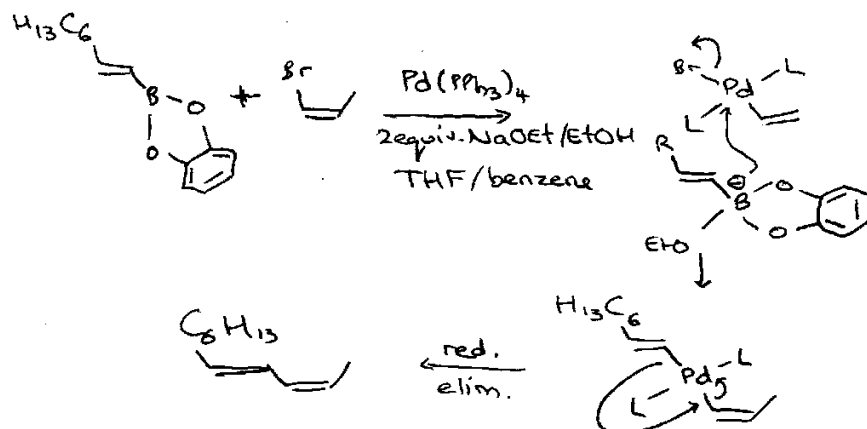

The Heck Reaction

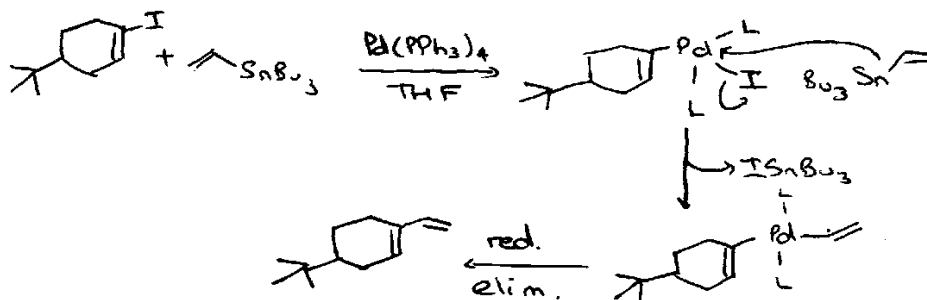Note how the Heck coupling proceed at a terminal alkene:
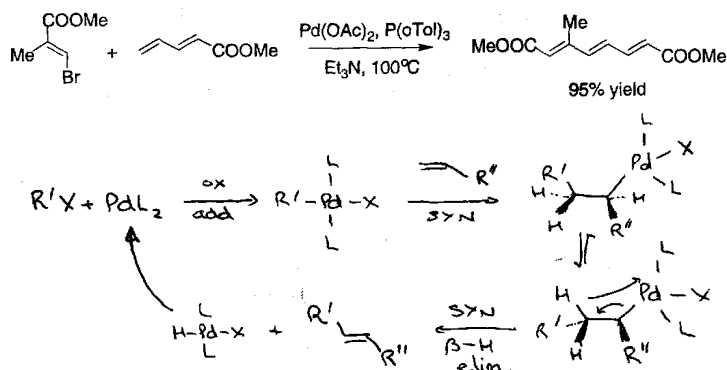
The Suzuki Reaction

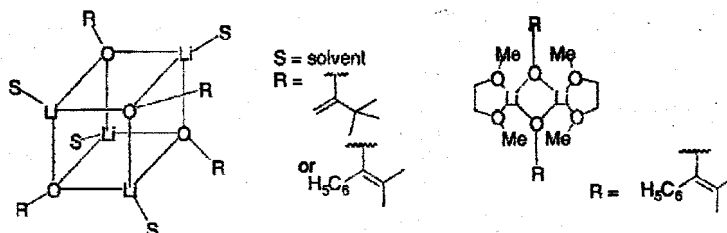Thallium hydroxide can dramatically increase the rate of this coupling.

The Stille Reaction

<u>Alkylation of Enolates</u>

Enolate Reactivity

The reactivity of an enolate is very sensitive to its state of aggregation, which in turn is influenced by the reaction medium.

Polar aprotic solvents are good cation solvators and poor anion solvators, and therefore provide a medium in which enolate-metal ion pairs are dissociated to give a less encumbered more reactive enolate.

Polar protic solvents are less favourable as solvents in enolate alkylation because they can coordinate to both the metal cation and the enolate ion.

THF and DME are slightly polar solvents, which are moderately good cation solvators but these solvents, because of their low dielectric constants, are less effective in separating ion pairs, and higher aggregates than are the polar aprotic solvents.

The reactivity of enolates is also affected by the metal counterion. The order of reactivity is generally: $Mg^{2+} < Li^+ < Na^+ < K^+$.

Oxygen vs. Carbon as the Reactive Centre

Effect of the electrophile – HSAB Principle

Of the two nucleophilic sites in an enolate ion, oxygen is harder than carbon. The hard-hard combination is favoured by an early transition state where the charge distribution is the most important factor. Therefore, conditions that favour a dissociated more reactive enolate favour O-alkylation.

The soft-soft combination is favoured by a later transition state where partial bond formation is important. The product of C-alkylation is more stable than the product of O-alkylation.

$X = OMs, OSO_2, {}^+OMe_2$ $X = I > Br > Cl$

Effect of the Solvent

Polar aprotic solvents (HMPA, DMF) promote O-alkylation (the enolate is most free) and ethereal solvents promote C-alkylation (aggregation and ion clustering). In polar protic solvents such as t-Butanol, C-alkylation is more favourable.

Effect of the Counterion

Larger alkali metals give more separated ion pairs, which are harder and therefore favour O-alkylation.
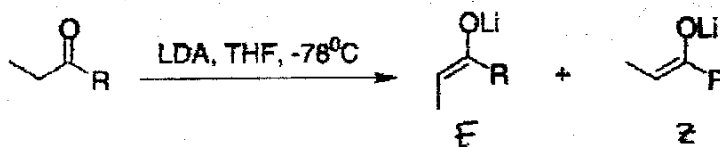
Stereoelectronic Effects

For intramolecular alkylation of enolates, Baldwin's Rules are followed.

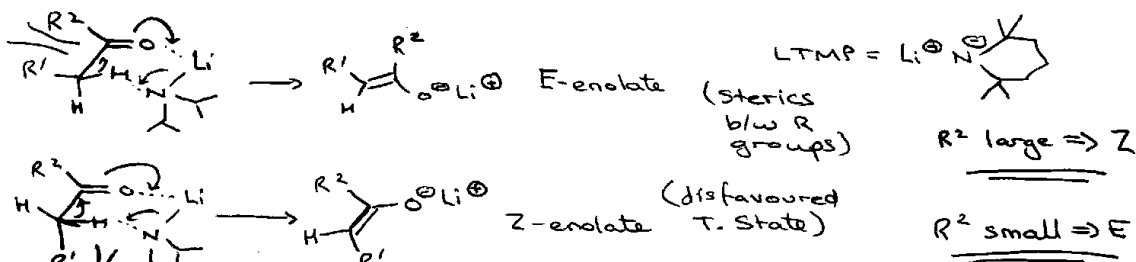**Stereochemistry of Enolate Formation**

The E:Z ratio depends on the reaction conditions and the nature of the substituents.

E enolates are often formed preferentially under kinetic conditions (except if R is large). Z enolates are generally thermodynamically more stable.
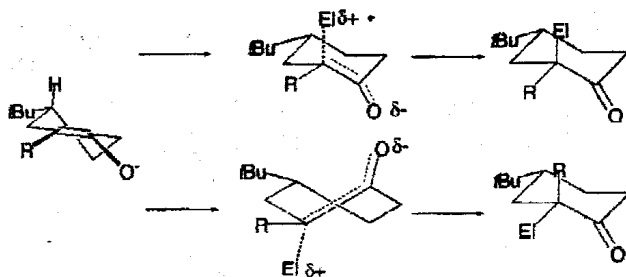

R	Base	E (trans)	Z (cis)
Et	LDA	77	23
Et	LTMP	86	14
Et	LTMP (HMPT)	8	92
Et	$LiN(Si(CH_3)_2C_6H_5)_2$	0	100
OMe	LDA	95	5
O^{t}Bu	LDA	95	5
S^{t}Bu	LDA	90	10
NEt$_2$	LDA	3	97
C(CH$_3$)$_3$	LDA	2	98
Ph	LDA	2	98

These trends could be rationalised in terms of the six-centered chair-like transition state models:

LTMP = Li⊕ N⊖ (structure)

E-enolate (sterics b/w R groups)

Z-enolate (disfavoured T. State)

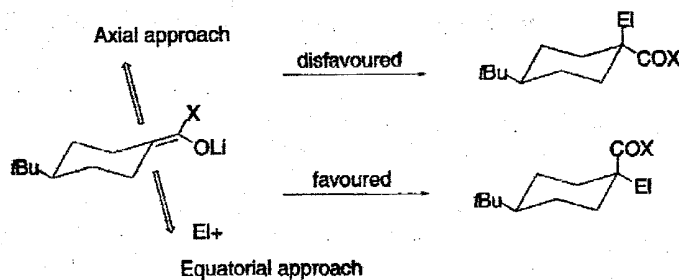R^2 large $\Rightarrow$ Z

R^2 small $\Rightarrow$ E

Electrophilic Reactions of Enolates – Stereoselectivity

Alkylation of Endocyclic Enolates –

Alkylation of Exocyclic Enolates –
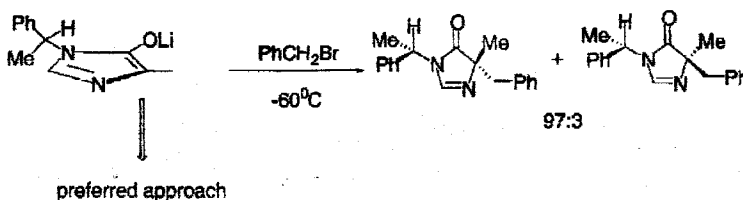

Axial approach — disfavoured

Equatorial approach — favoured

Chelate Enforced Control

LDA / EtI

92:8

LDA / EtI

22:78

LDA, -78°C

prevents rotation – intramolecular chelation

large → Z-enolate

97%   3%
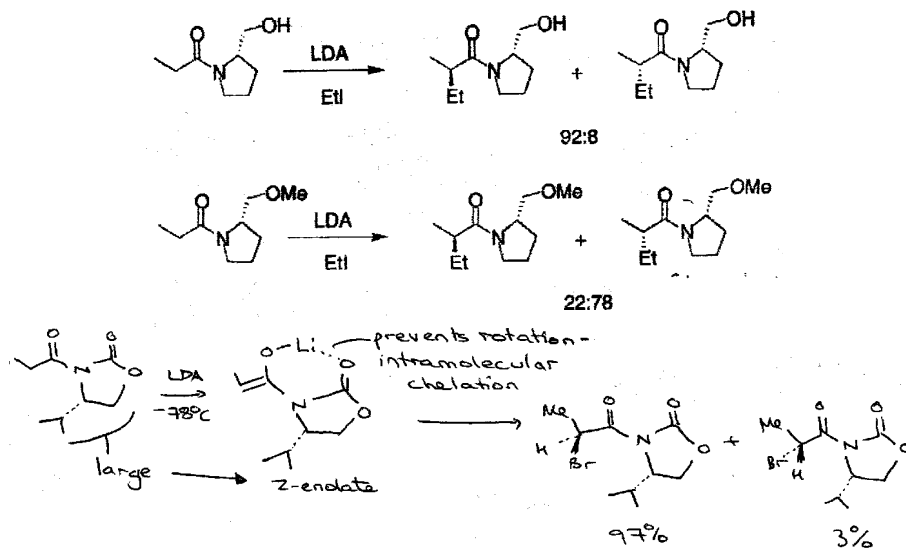
Extra-Annular Control Elements

97% de

92% de

Ar =
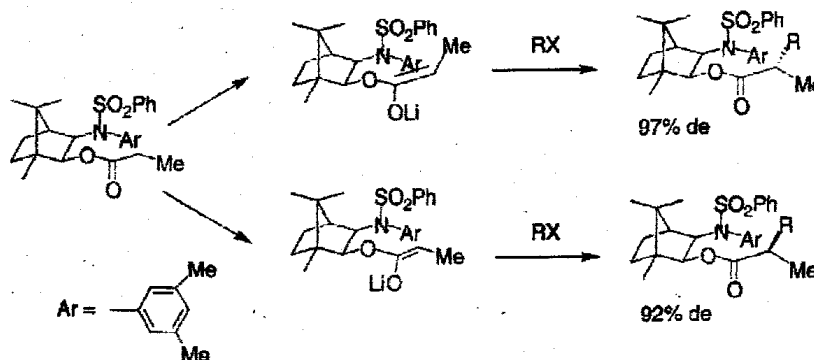
Alkylation of an imidazole derived enolate under extra-annular stereocontrol:

PhCH₂Br
-60°C

97:3

preferred approach

π-*Facial selectivity based on the minimisation of allylic strain $^{A(1,3)}$:*

A¹·³ strain –
avoided by having
smallest group
aligned.

large group is
stereo-directing.
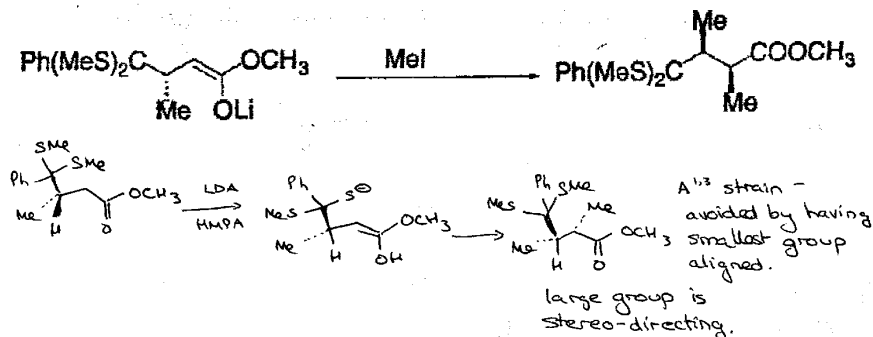
The Aldol Reaction

The name Aldol is given to a whole class of reactions between enol (or enolates) and carbonyl compounds even though in most cases the product is not a hydroxyl-aldehyde.

For cross-aldol reactions, several "levels" of control need to be addressed. Two methods are known that allow to control the *product outcome* of the reaction – in other words to ensure that one carbonyl group gives only one enol or enolate as the nucleophilic partner in the Aldol reaction, while only one carbonyl compound acts as the electrophilic partner.

In the **equilibrium method**, the reagents must be treated with weak (usually aqueous or alcoholic) acid or base and allowed to equilibrate with all possible enols or enolates. Either only one product is possible (this might be due to symmetry or blocking of the α-positions) or some thermodynamic factors (such as the formation of the more stable conjugated enone) ensure that the reaction proceeds along one preferential reaction pathway.

In the **directed Aldol**, one component is premodified and converted into a specific enol equivalent (such as lithium enolate, silyl enol ether, enamine, aza-enolate, zinc enolate) and only then combined with the electrophilic partner. If the ketone is unsymmetrical and presents two possible reactive sites (regioisomeric enol equivalents), the regioselectivity can be controlled in the step involving the conversion of the ketone into an enol equivalent.

lithium enolate   silyl enol ether   boron enolate

aza enolate   enamine
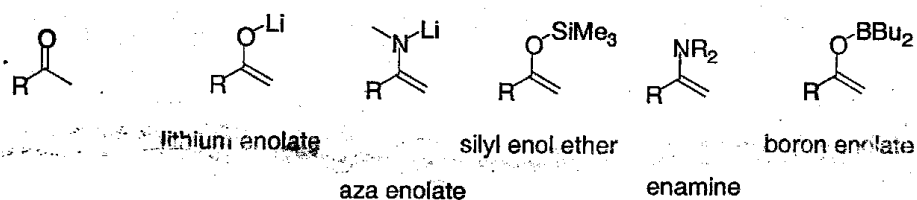
In addition to the product outcome and the control of regioselectivity (if any), there are two major stereochemical issues that must be addressed. The first is the relative configuration of the two newly created stereogenic centers. The second issue concerns diastereofacial selectivity and arises from the addition of achiral enolates to chiral aldehydes or the vice versa.

Relative Configuration (Simple diastereoselectivity) – *Addition of achiral enolates to achiral aldehydes*
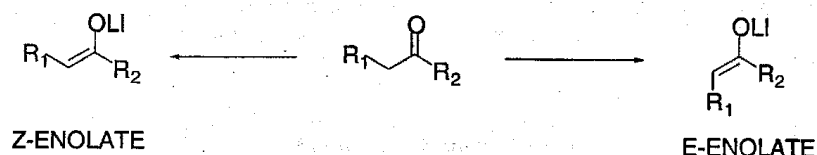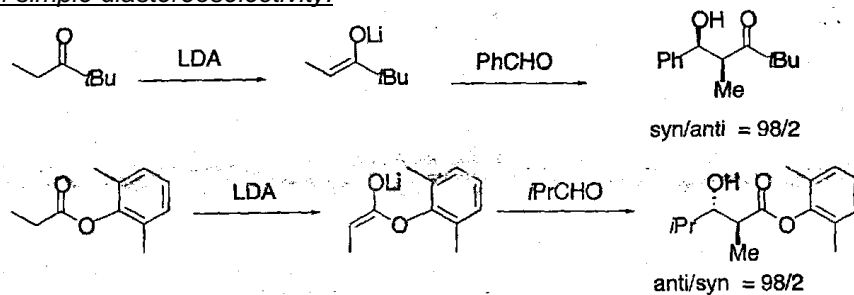

Z-ENOLATE   E-ENOLATE

Zimmerman-Traxler Transition State Structures for the Aldol Reaction
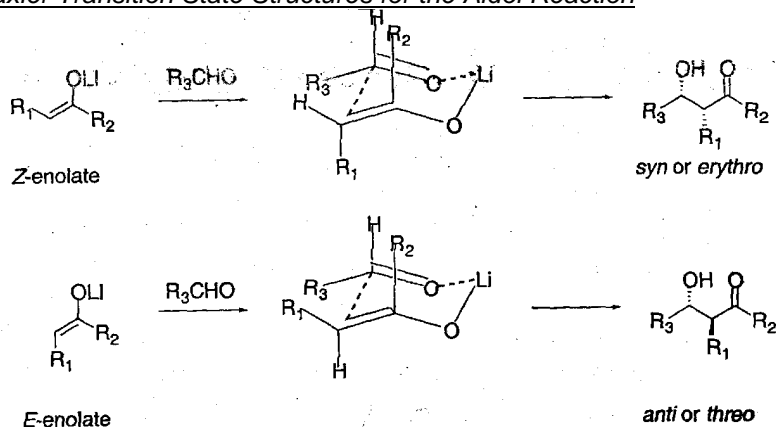
R_3 adopts a preferential equatorial position. The position of R_1 is predetermined by the enolate geometry.

Examples of simple diastereoselectivity:

syn/anti = 98/2

anti/syn = 98/2

When the Aldol reaction is carried out under reversible conditions, it is generally found that the anti isomer predominates. If it is assumed that chelated products are more likely to be thermodynamically more stable than non-chelated products, this stereochemical outcome might

be rationalised by consider the Newman projections for the two possible aldolates. Aldol products can undergo syn/anti isomerisation more commonly by reverse aldolisation.
In most cases however, reactions are **kinetically controlled**.

Diastereofacial Selectivity in Aldol Reactions
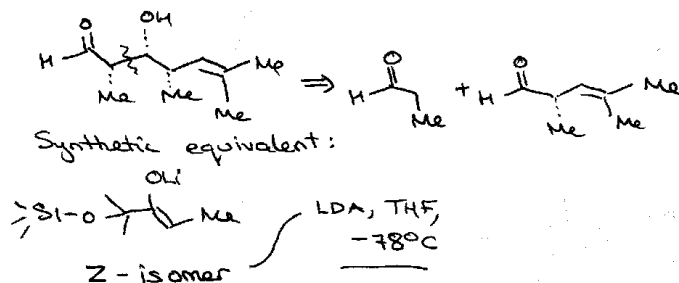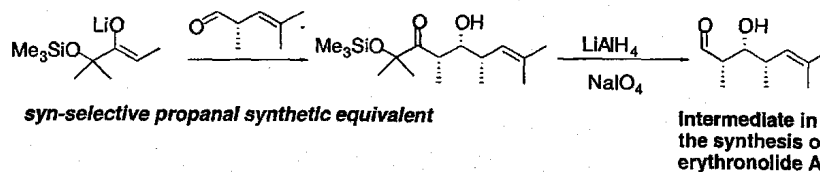
Chiral aldehyde with achiral enolate
The two faces of the chiral aldehyde are diastereotopic. Therefore the reaction of a chiral aldehyde with an achiral enolate gives rise to a mixture of diastereoisomers. The major product can be predicted in line with Cram's model.
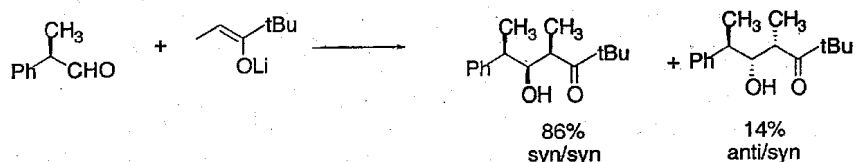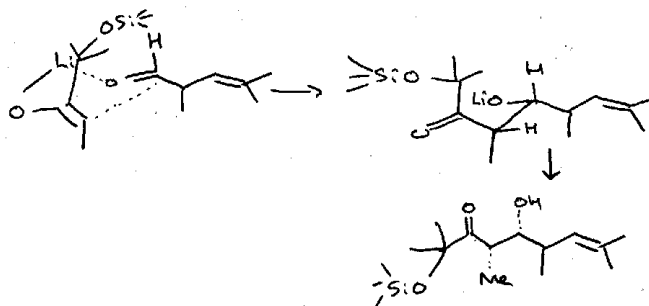

- The 2,3 relative stereochemistry is determined by the enolate geometry.
- The 3,4 relative stereochemistry is determined by the diastereofacial selectivity of the addition of the aldehyde.
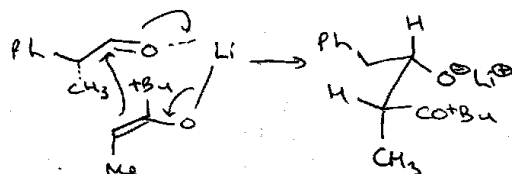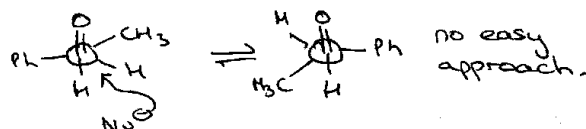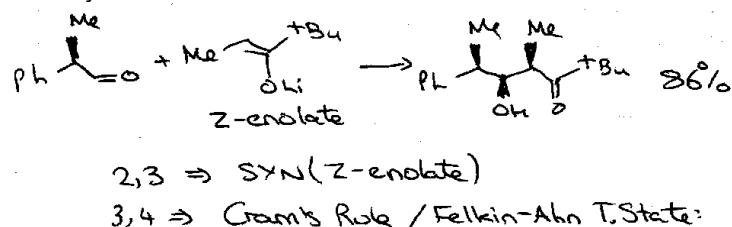
Case Study: control of enolate geometry, diastereoselectivity and diastereofacial selectivity:

syn-selective propanal synthetic equivalent

**Intermediate in the synthesis of erythronolide A**

Achiral Aldehyde with chiral Enolate

The two faces of the enolate are diastereotopic. Preferential addition of the aldehyde will occur on the less hindered face of the enolate leading again to some degree of diastereofacial selectivity. Usually excellent levels of selectivity have been obtained for many chiral enolates derived from ketones, amides and imides.
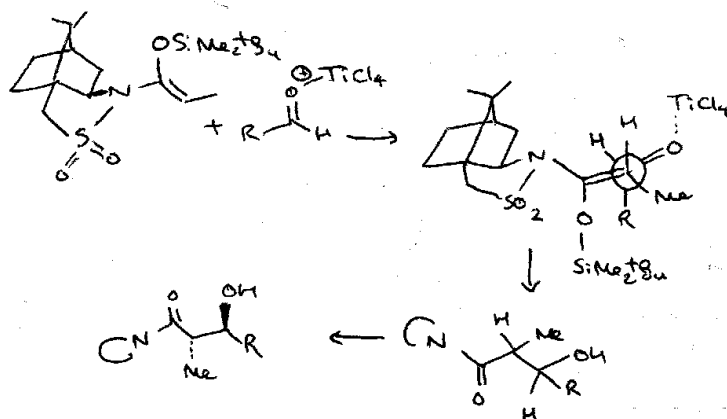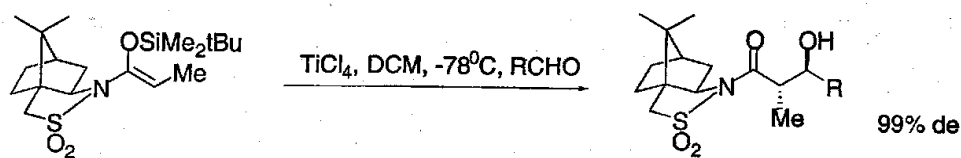
Examples of diastereofacial selectivity with chiral enolates:
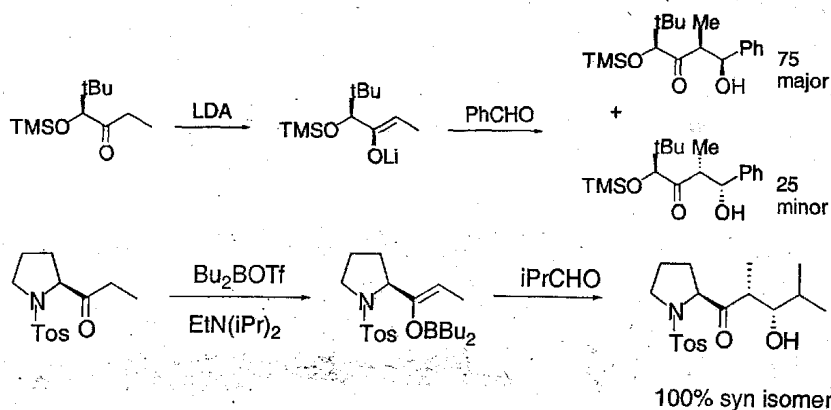
Another example of syn-selective Aldol process: the use of Evans Oxazolidinone:

de>99%
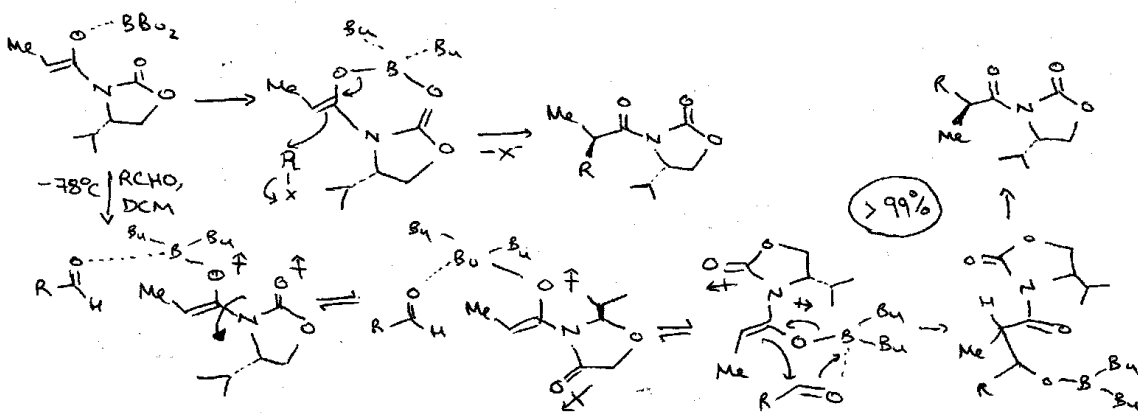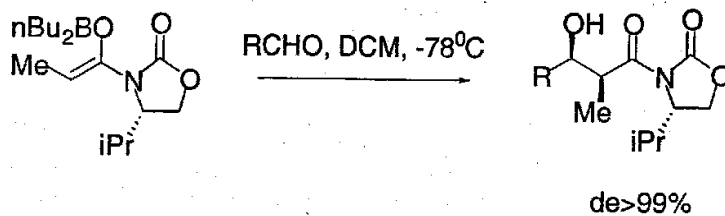
Example of anti-selective Aldol reaction: the use of Oppolzer chiral auxiliary:

Chiral Aldehyde with Chiral Enolate – Double Stereodifferentiation

When more than one participant is chiral, the stereochemical outcome will depend to a degree on the relationship between their respective absolute configurations and the proximity of stereogenic elements in the transition state structures.

In the case of the Aldol reaction, both the aldehyde and the enolate have their own inherent diastereofacial selectivity. If the pair is matched, then these selectivities will act in unison (synergic effect). Often very high levels of diastereofacial selectivity can be observed. This combined interaction between the chiral centres in both the aldehyde and the enolate is termed double stereodifferentiation.

If the diastereofacial selectivities of the two partners are in the same sense (matched pair), then the two effects reinforce each other and very high selectivity can be observed.

Complementary Selectivity:
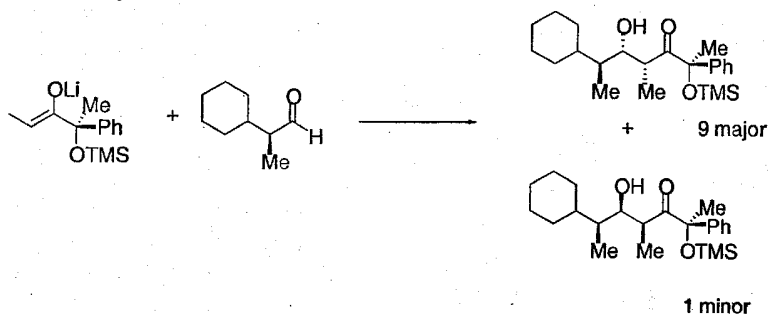
If the diastereofacial selectivities of the two partners are in opposite senses (mismatched pair) then the two effects oppose each other and reduced selectivity will be observed.

Opposed Selectivity:
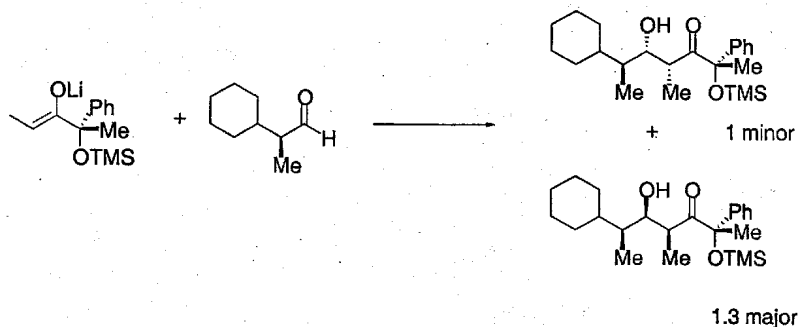
Asymmetric Synthesis

What do we mean by asymmetric synthesis – a reaction that creates one configuration of new stereogenic elements by the action of a chiral reagent or auxiliary acting on heterotopic (enantiotopic or diastereotopic) faces, atoms or groups of a substrate.

Why we always need a chiral component to achieve asymmetric synthesis? Let's consider the three possible scenarios for a model reaction, the addition of a nucleophile to a carbonyl compound:
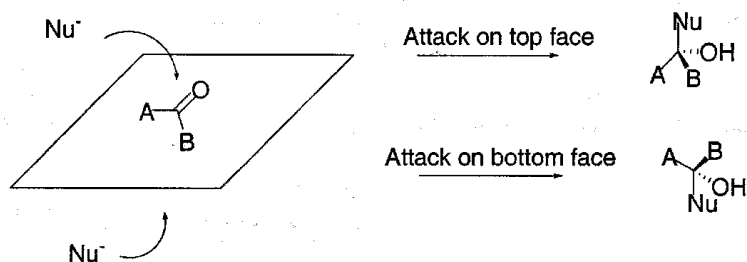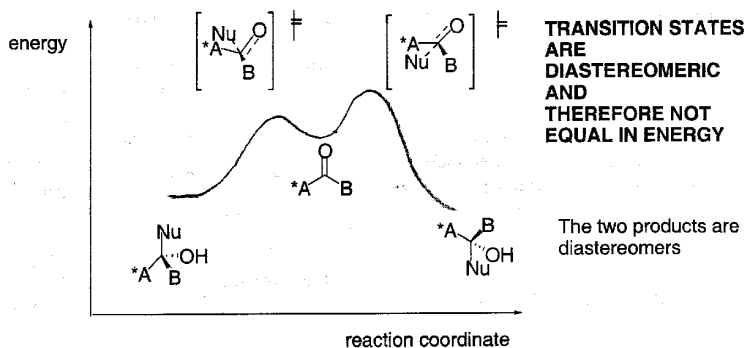

Achiral carbonyl compound in the presence of an achiral nucleophile:
The two faces (Re and Si) of the achiral compound are enantiotopic. The nucleophile can attack either face leading to two possible transition states. If the nucleophile is itself achiral then these two transition states are enantiomeric and therefore equal in energy. The two enantiomeric transition states lead to the formation of the two enantiomeric products in equal amount, in which case a racemic mixture is formed. In other words, if there is no chiral information in the reaction, then a racemic mixture will always result.
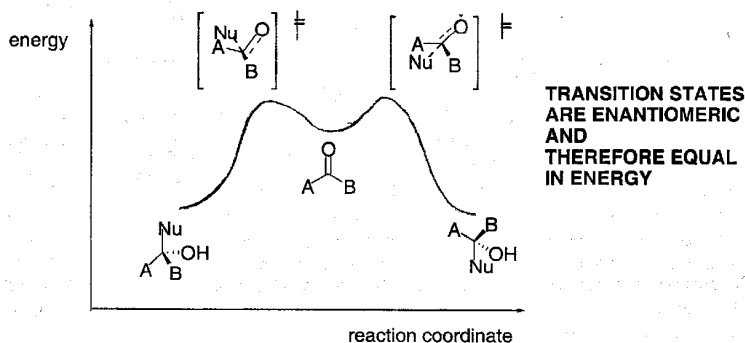
*Chiral carbonyl compound in the presence of an achiral nucleophile:*
This is related to the Cram Rule / Felkin-Ahn model. If the carbonyl compound is including within its structure a stereogenic centre, the two faces of the carbonyl group are now diastereotopic and no longer enantiotopic.

If the group A* denotes a group containing a stereogenic centre, an achiral nucleophile can attack either face of the carbonyl compound, but the two transition states are no longer enantiomeric but diastereomeric. Therefore these two transition states are different in energy and consequently, one of the two diastereomers will be formed preferentially.

Achiral carbonyl compound with a chiral nucleophile:
The two faces of the carbonyl compound are enantiotopic and the nucleophile can attack either one. However since the nucleophile is chiral, the two transition states for these two reactions must be diastereomeric. Therefore the reaction leads to the preferential formation of one diastereomer as the two diastereomeric transition states are not equal in energy.
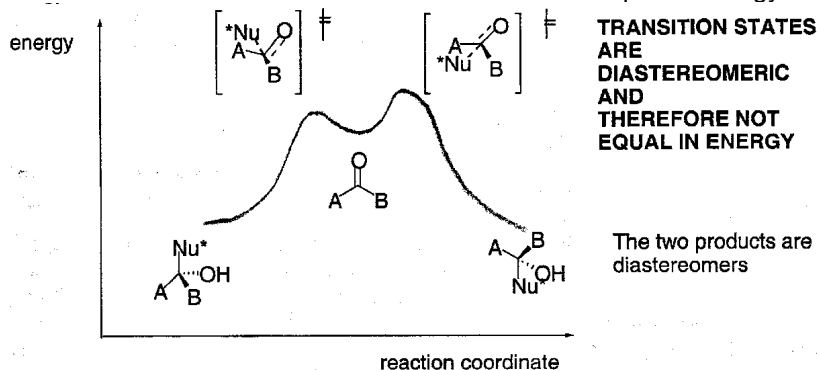
Conclusion: Asymmetric synthesis takes place via diastereomeric transition states and takes advantage of the difference in energy between these two transition states in order to obtain preferentially one product.

## Chemical separation of enantiomers via diastereomers

The largest number of recorded resolution has been affected by conversion of a racemate to a mixture of diastereomers. In this type of reaction, the substrate to be resolved is treated with one enantiomer of a chiral substance (the resolving agent). The vast majority of resolutions mediated by diastereomers (diastereomeric salt mixture in particular) have been based on solubility differences of solids. However, chromatography has freed resolutions from the constraint of dependency on crystallisation as the technique on which diastereomer separation has traditionally depended. Resolving agents are currently available for acids and lactones, bases, amino acids, alcohols, diols, thiols, dithiols, phenols, aldehydes, ketones, etc.
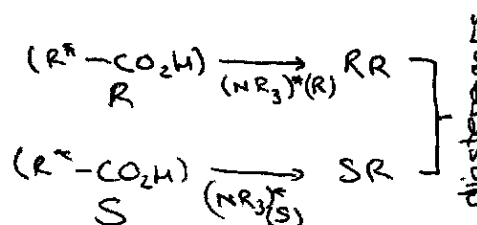
Kinetic Resolution and Dynamic Kinetic Resolution –
The enzymatic resolution of racemic amino acid derivatives is a fairly common kinetic resolution method wherein one enantiomer of the racemate is recovered as the unhydrolysed derivative while the other may be recovered from the hydrolysate as a pure amino acid or as a new amino acid derivative. In this case, the maximum yield of the desired enantiomer cannot exceed 50%.

A dynamic kinetic resolution allows in theory the formation of the desired enantiomer with a chemical yield of 100% as the kinetic resolution process is coupled with the spontaneous racemisation of the starting material (but not the product!) under the reaction's conditions:


(S)-(-)-Ketorolac
anti-inflammatory and analgesic agent
92% yield, ee 85%
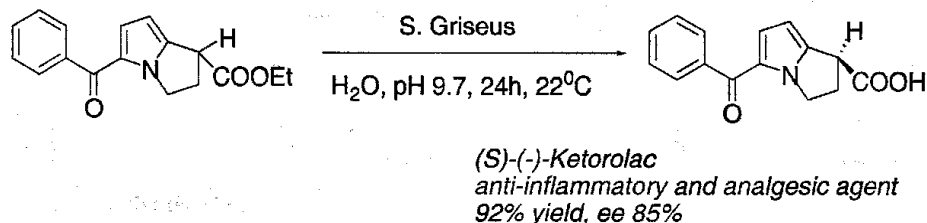
The Use of Chiral Reagent
One typical example is the use of chiral hydride reagents that might afford good level of enantioselection in the reduction of ketones. Much of this has centered on lithium aluminium hydride modified by the attachment of chiral ligands such as diols, diamines, aminocarbinol, etc. One of these reagents so-called BINAL-H (BINAL is the complex formed from equimolar amounts of lithium aluminium hydride, 2,2'-dihydroxy-1,-1'-binaphtyland ethanol) which is available as either enantiomer provided excellent result with enantiomeric excesses up to 95% - 100% from the reduction of a reasonable range of ketones. In general poor enantiomeric excesses are obtained when both groups attached to the carbonyl group are alkyl groups.

The Use of a Chiral Auxiliary
This principle will be illustrated with the asymmetric alkylation of a homochiral oxazoline as developed by Meyers et al. In this strategy, the prochiral substrate is attached to a chiral non-racemic group known as the chiral auxiliary, and this is done prior to the reaction, here an alkylation. The two possible products become now diastereomeric and one should be formed in excess providing that the difference in energy between the two diastereomeric transition states is sufficiently large. The major diastereomer can be isolated and then the chiral auxiliary is cleaved to afford the desired enantio-enriched / pure product. After cleavage, the chiral auxiliary can be recycled.

masked
carboxylic acid
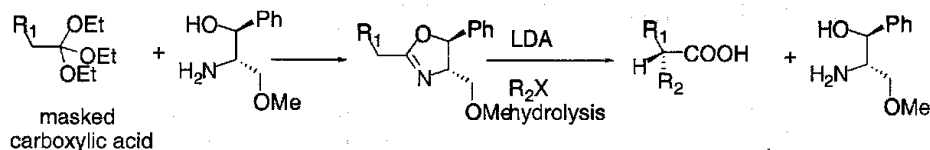
The Use of a Chiral Catalyst
This type of asymmetric synthesis is extremely attractive as a small amount of the homochiral catalyst leads to stoichiometric amounts of the desired enantiomer. In the laboratory, both enzymes and synthetic catalysts are used to achieve asymmetric synthesis. Up to now, many examples were based on the use of an organometallic catalyst such as the Sharpless Epoxidation:

$$iPr \diagup\!\!\!\diagdown OH \xrightarrow[\text{5-10\% (+)-DET}]{\text{tBuOOH, 5-10\% Ti(OiPr)}_4} iPr \diagup\!\!\!\diagdown OH$$
94% ee
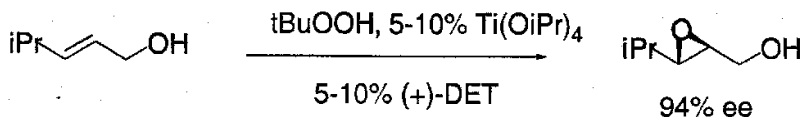
More recently it has been demonstrated that small organocatalysts are suitable candidates for various asymmetric catalytic transformations such as Aldol reactions or Diels-Alder reactions.

Product Analysis

Enantiomeric excess (or e.e) = % major enantiomer formed - % minor enantiomer formed. If a reaction gives 75% of the R enantiomer and 25% of the S enantiomer, then the e.e. 75% - 25% = 50%. Enantiomeric excesses are almost always quoted after reactions as a guideline to how enantioselective a particular process is. The key problem is therefore "how do you work out just how much of each enantiomer you have?"

Polarimetry
Chiral compounds rotate the plane of polarised light. The oldest and simplest method of analysis therefore relies on measuring the optical activity of the sample (how much the plane of light is rotated) and comparison of this value with the value obtained for the pure single enantiomer. The sign of the rotation reflects the absolute configuration (R or S) of the sample whereas the value (size) of the rotation represents the optical purity of the sample.

Specific Rotation – $[\alpha]^T_D = {}^{100\alpha}/_{l.c}$

α = measured optical rotation.
l = path length of cell.
c = concentration of the sample.
T = temperature of the sample.
d = defines the wavelength as the sodium D line (590nm), other wavelength light may be used.

% optical purity = ${}^{\text{measured specific rotation x 100}}/_{\text{specific rotation of the pure enantiomer}}$
This is usually equal to the e.e.

Derivatisation
Reaction of a mixture of enantiomers with a chiral entity produces a mixture of diastereomers. Analysis or separation of this diastereomeric mixture is then straightforward. However there are several important drawbacks. It is crucial that the derivatisation reaction goes to completion so that the diastereomeric ratio accurately reflects the original enantiomeric ratio. Any kinetic resolution must be avoided and of course the reaction conditions for derivatisation must not cause racemisation. A typical reagent to achieve the derivatisation of secondary alcohols is the Mosher acid. NMR ^{1}H, ^{13}C or ^{19}F can be used to observe the diastereomeric mixture.

MTPA = methoxytrifluoromethylphenylacetic acid

(R)-MTPA   (S)-MTPA

mixture of two enantiomers
unknow ratio
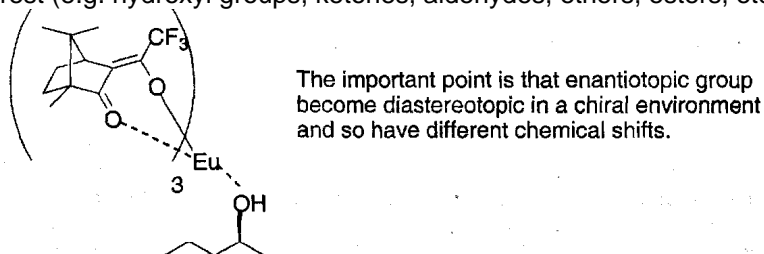
diasteromeric mixture produced
analysis by NMR
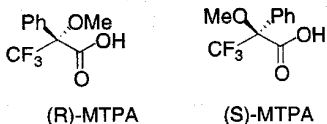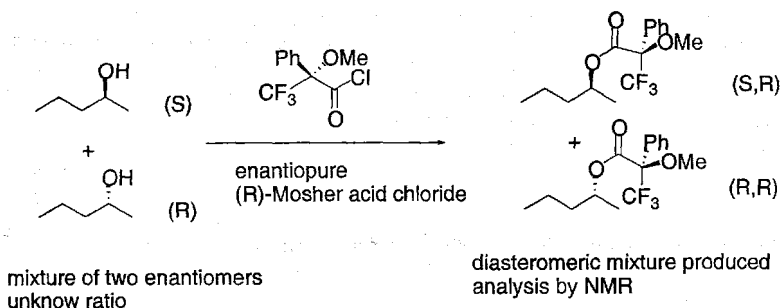
Chiral Shift Reagents

In situ NMR analysis of enantiomeric ratios can be achieved by the use of chiral shift reagents (CSA's). These are chiral complexes of lanthanide metals, usually europium, ytterbium or praseodymium with chiral β-dicarbonyl compounds. Two of the most common ligands are TFC or HFC:
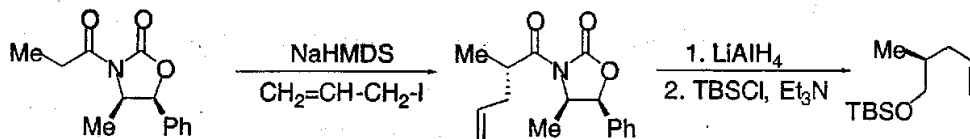

The complexes are in fact trimeric i.e. Eu(tfc)$_3$, Yb(hfc)$_3$

tfc   hfc
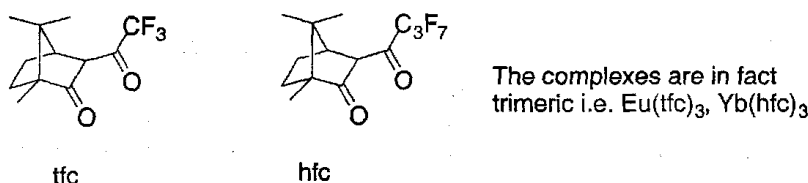
The lanthanide metals are hard Lewis Acids and coordinate to any hard Lewis base sites on the molecule of interest (e.g. hydroxyl groups, ketones, aldehydes, ethers, esters, etc.)

The important point is that enantiotopic group become diastereotopic in a chiral environment and so have different chemical shifts.

Separation through chiral media (chiral GC or HPLC)

Principle of column chromatography: one stationary phase and one mobile phase. In gas chromatography, the stationary phase is a liquid and the mobile phase is a gas. In high pressure liquid chromatography, the stationary phase is a solid and the mobile phase is a liquid. If the stationary phase is chiral, the interaction between the stationary phase and the two enantiomers that are being eluted become diastereomeric and therefore could be separated.

Evans Oxazolidinones
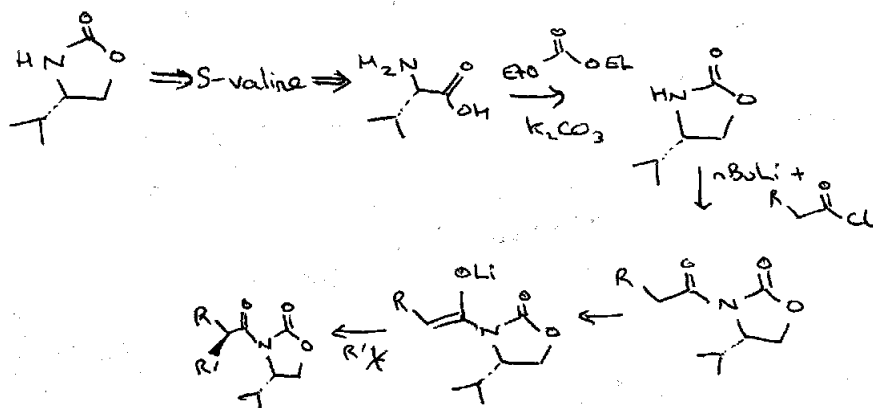
Oppolzer Sultams
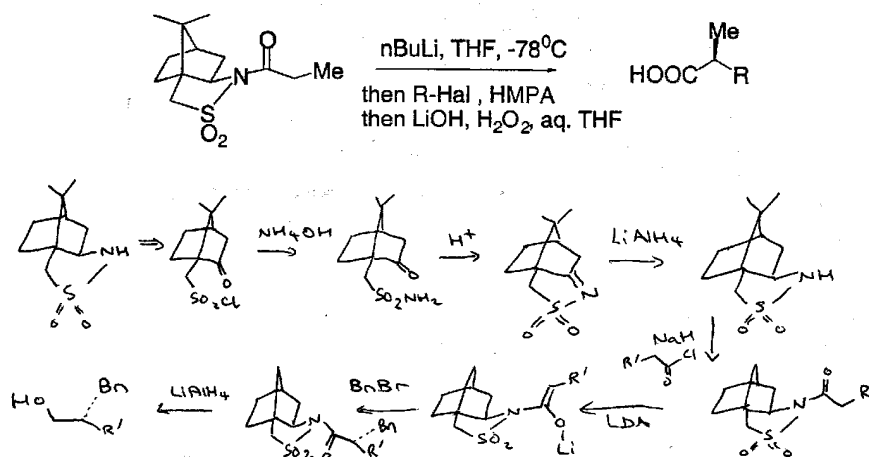
Davies Iron Acetyl Complexes

96% de
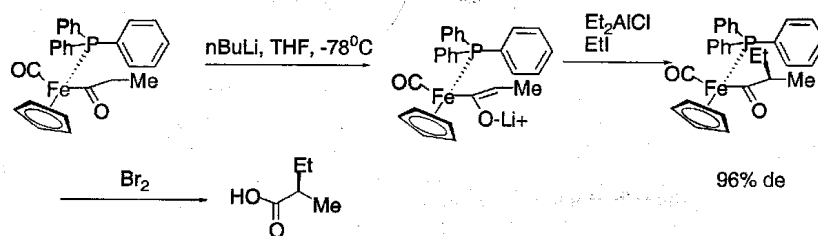
Enders SAMP and RAMP Hydrazones

SAMP
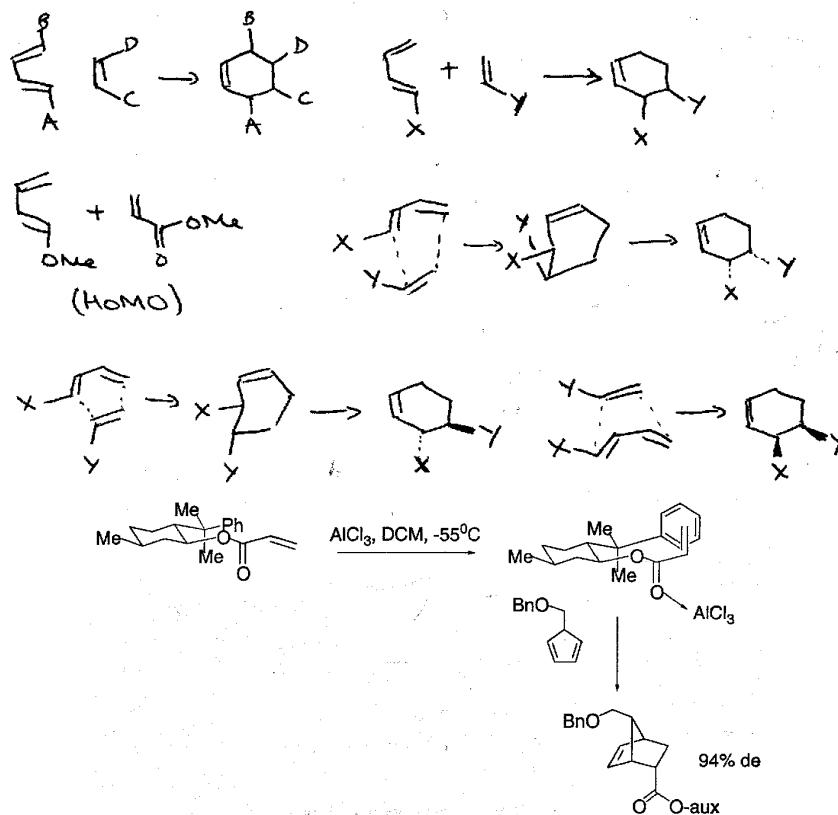
RAMP

O₃, DCM, -78⁰C, 30s
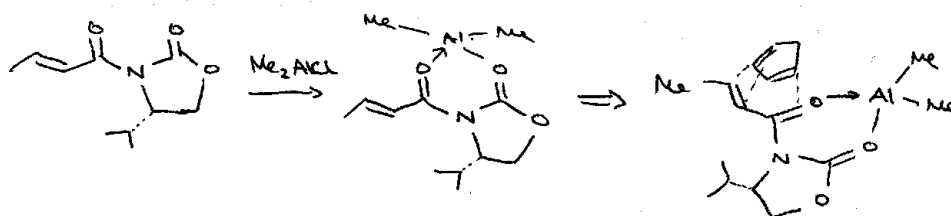
Ph₃P=CHCOOMe, DCM

LiOH, MeOH-H₂O
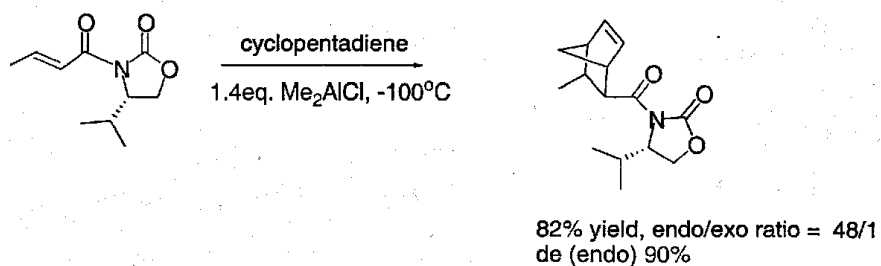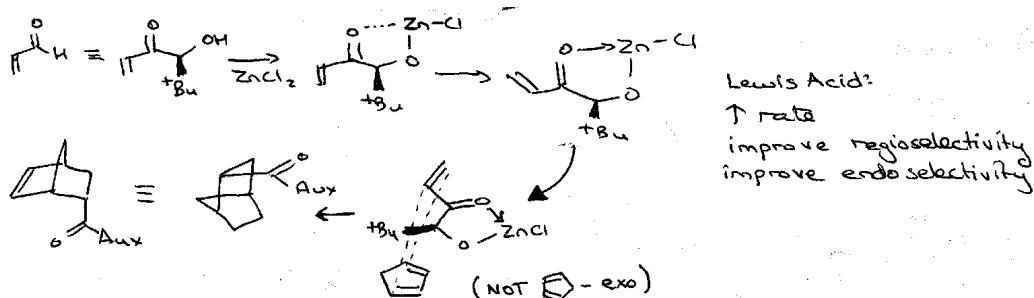27% overall yield
92% de
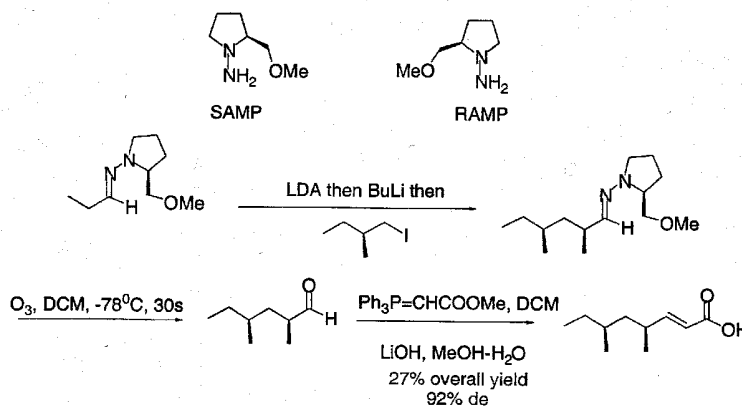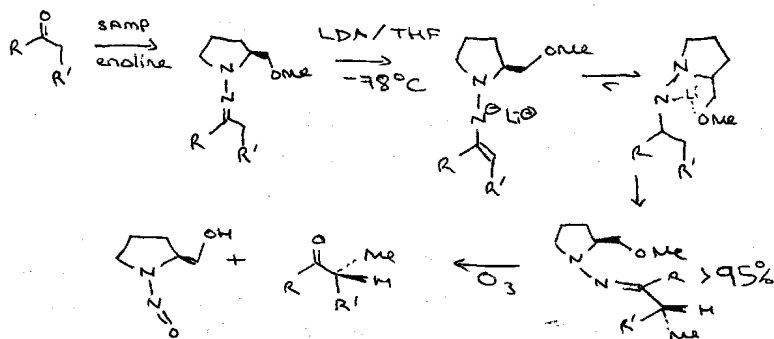
Asymmetric Diels-Alder Reactions

Many examples with strategies including attachment of the chiral auxiliary on the dienophile, on the diene or by using a homochiral catalyst.

- o Control of regio-, diastereo- and enantioselectivity.
- o Formation of up to four stereocentres.
- o More often, but not always, concerted mechanism.

Lewis Acid:
↑ rate
improve regioselectivity
improve endo selectivity

82% yield, endo/exo ratio = 48/1
de (endo) 90%

Only recently, asymmetric Diels-Alder reactions have been reported, which employ organic molecules as organic catalyst despite the widespread availability of organic chemicals in enantiopure form and the accordant potential for academic, industrial and economic benefit.
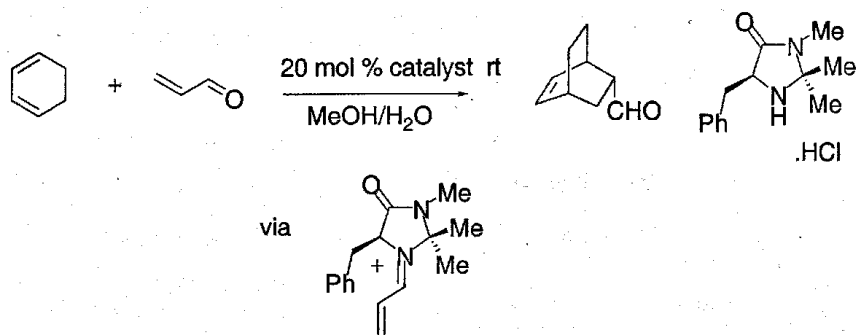

Asymmetric Allylations: The Use of Chiral Allyl Boranes
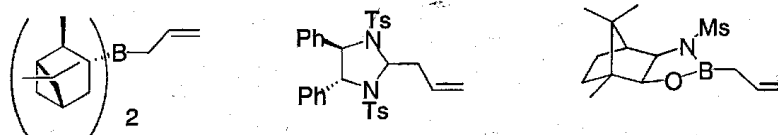
For allylboranes bearing a substituents at the terminal position, two stereogenic centres could be created upon addition of these allylboranes onto aldehydes.
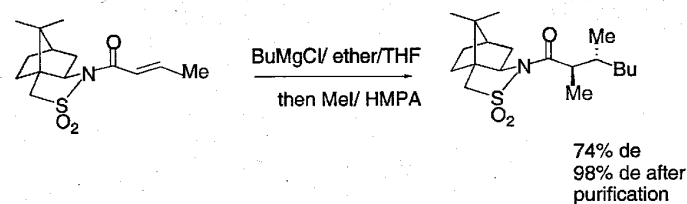**Z-allylboranes give syn products.**
E-allylboranes give anti products.
If chiral ligands are attached to boron, high level of enantioselectivity can be achieved since the two transition states are no longer enantiomeric but diastereomeric.
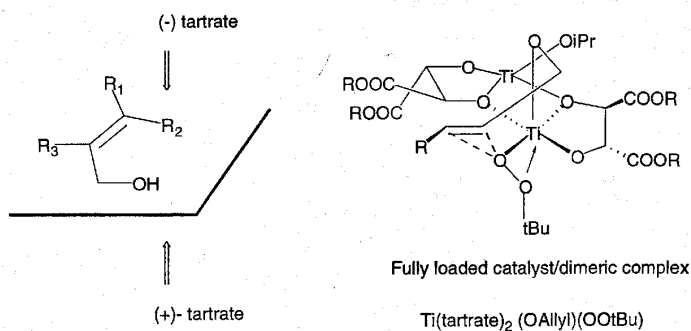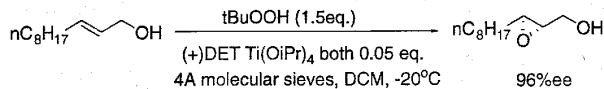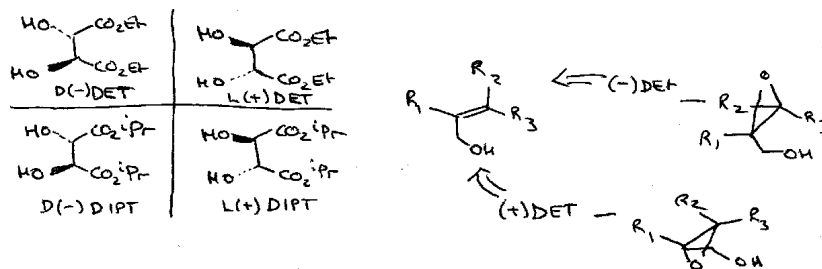
anti/syn 95/5
ee 73%

anti/syn 1/99
ee 70%

ee 95%

ee 95%

Z ⇒ syn
E ⇒ anti
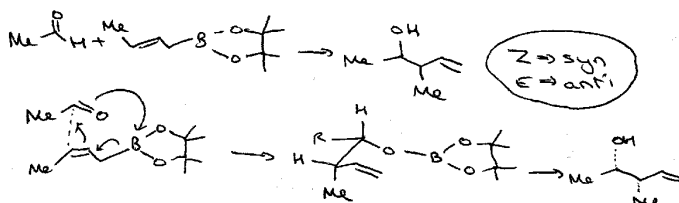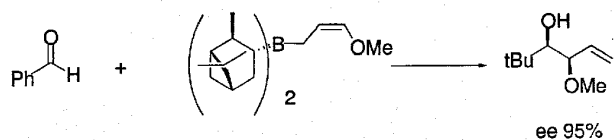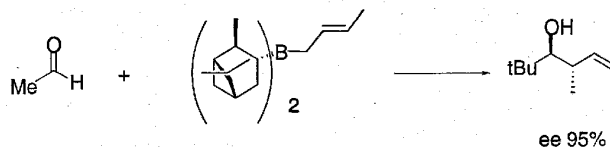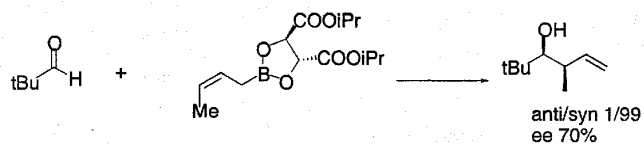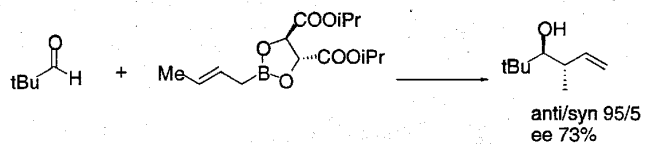
Asymmetric Michael Additions

BuMgCl/ ether/THF

then MeI/ HMPA

74% de
98% de after
purification

Asymmetric Oxidations

The Sharpless Asymmetric Epoxidation of Allylic Alcohols

tBuOOH (1.5eq.)

(+)DET Ti(OiPr)$_4$ both 0.05 eq.

4A molecular sieves, DCM, -20°C

96%ee

(-) tartrate

(+)- tartrate

Fully loaded catalyst/dimeric complex

Ti(tartrate)$_2$ (OAllyl)(OOtBu)

Kinetic Resolution of Racemic Secondary Alcohols

yield 41%
ee 92%

yield 35%
ee 95%
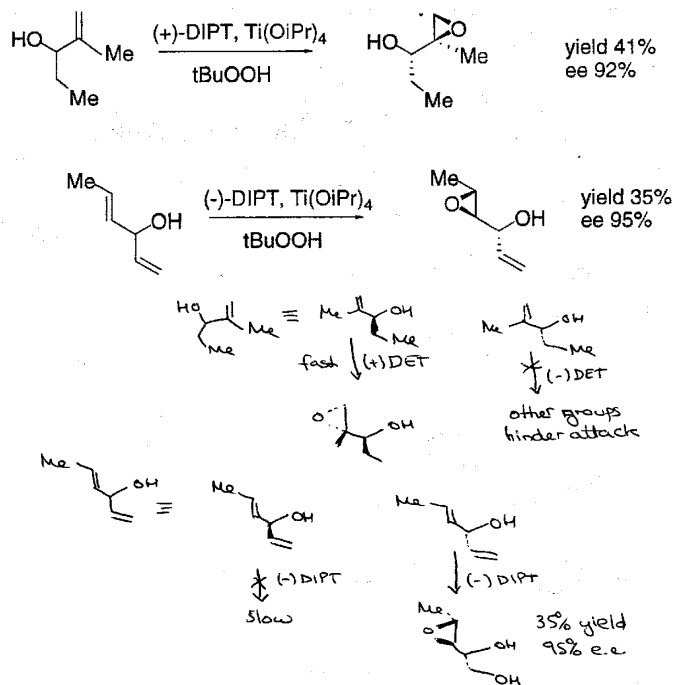
The Sharpless Asymmetric Dihydroxylation (AD)

AD mixβ   (DHQD)₂-PHAL

AD mix α   (DHQ)₂-PHAL

alkaloid-O —[PHAL]— O-alkaloid

PHAL (phthalazine class)

Dihydroquinidine
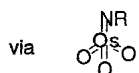(DHQD)

Dihydroquinine
(DHQ)
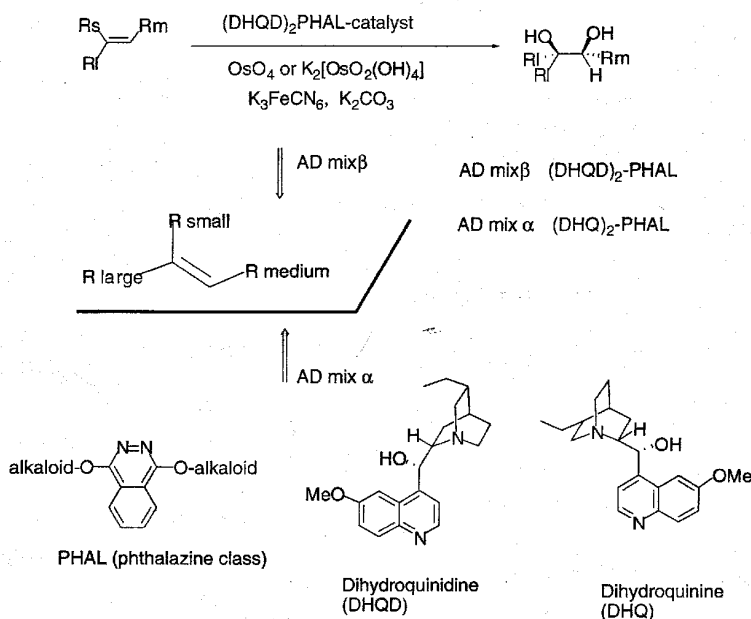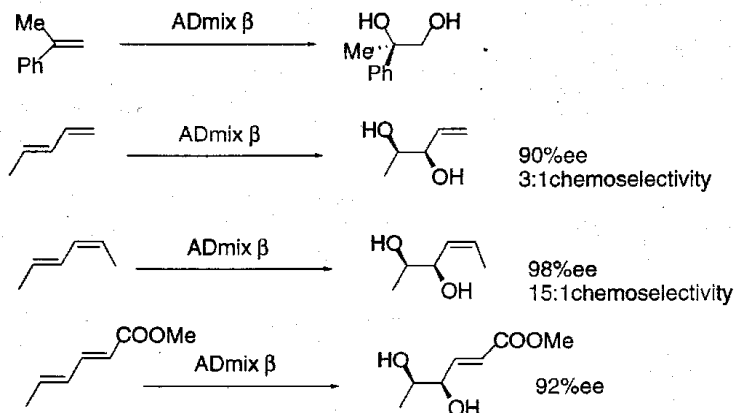
Examples:

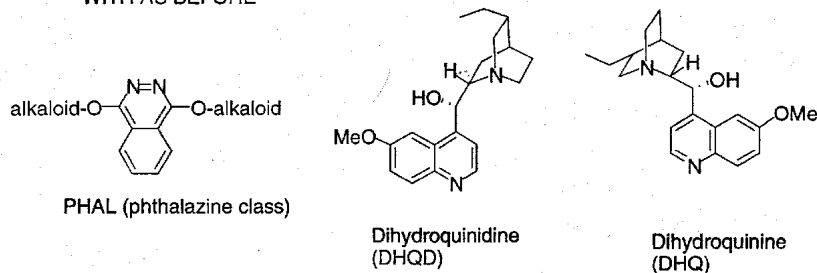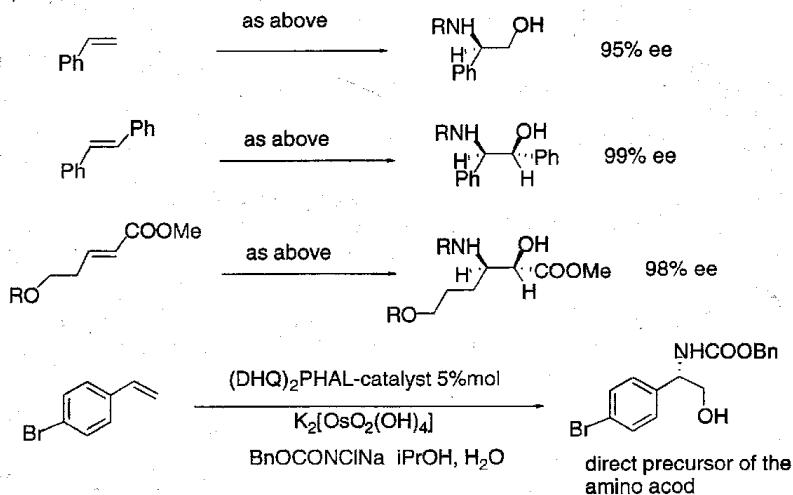## *The Sharpless Asymmetric Aminohydroxylation*
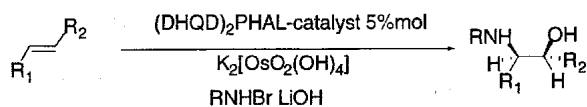
with R = COOR or COMe or Ts or Ms

via

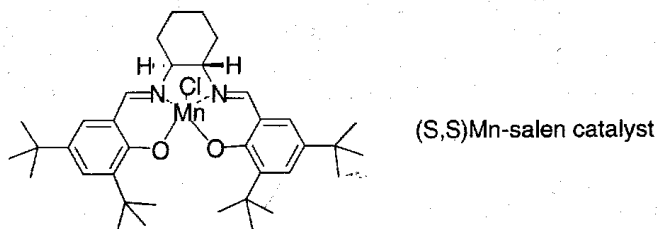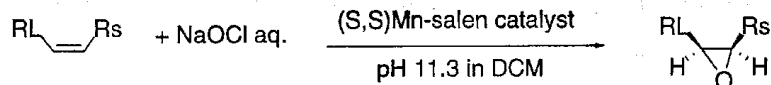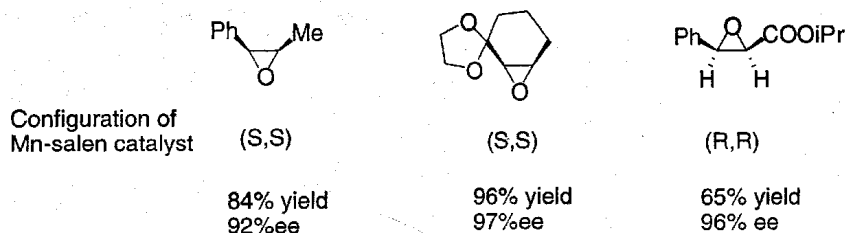WITH AS BEFORE

PHAL (phthalazine class)

Dihydroquinidine (DHQD)

Dihydroquinine (DHQ)

Examples:

The Jacobsen Asymmetric Epoxidation

Examples:

Configuration of Mn-salen catalyst	(S,S)	(S,S)	(R,R)
	84% yield 92%ee	96% yield 97%ee	65% yield 96% ee

## Stereoselective Glycoside Formation

Fischer Glycosidation
The terms glycosidation and glycosylation are frequently used interchangeable.
A glycoside is a carbohydrate substituted at the anomeric centre, usually with alcohols. In the presence of an acid catalyst, an alcohol can react with a sugar lactol hemiacetal to form an acetal that is called a glycoside. This is an equilibrium reaction and therefore treatment of a glycoside with aqueous acid can reverse this reaction and give the parent carbohydrate. The reaction is under thermodynamic control and therefore the thermodynamic product is formed preferentially.
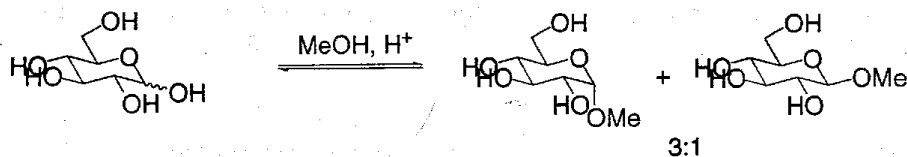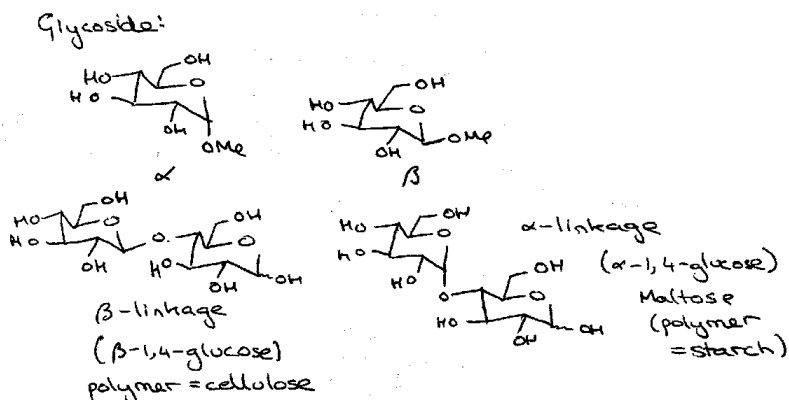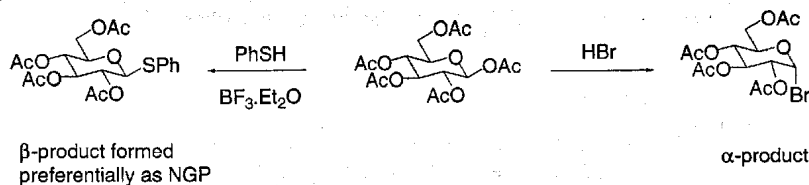
Nucleophilic Substitution at the Anomeric Centre

Acetylation is often the first step of synthetic sequences involving sugars. Conversion of the hydroxyl group at the anomeric position into an acetate is useful as the acetate can readily act as a leaving group under the appropriate conditions and therefore many other anomeric substituents may be introduced by nucleophilic substitution reactions.

β-product formed preferentially

α-product formed preferentially
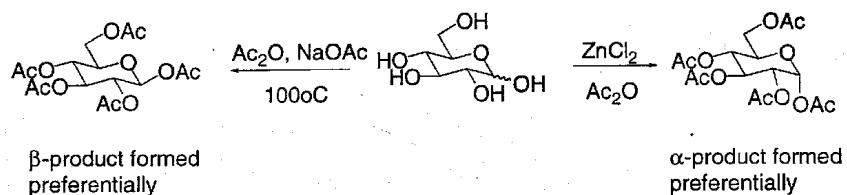
Anomeric acetates are themselves precursors for the introduction of other substituents at the anomeric position. Two important synthetic intermediates that could be prepared from anomeric acetates are glycosyl bromides or thioglycosides.

β-product formed preferentially as NGP

α-product

Mechanism of nucleophilic substitution at the anomeric centre – S_N1 or S_N2 –

SN1 pathway
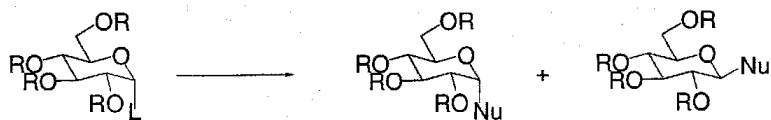

SN$_2$ pathway

Neighbouring Group Participation

There are several strategies to control the stereochemical outcome of nucleophilic substitution reactions at the anomeric centre. One of the most successful strategies is by neighbouring group participation of an ester protecting group such as acetate or benzoate on the 2-hydroxyl group. The net result is that the newly formed anomeric linkage is necessarily *trans* to the 2-hydroxyl group.
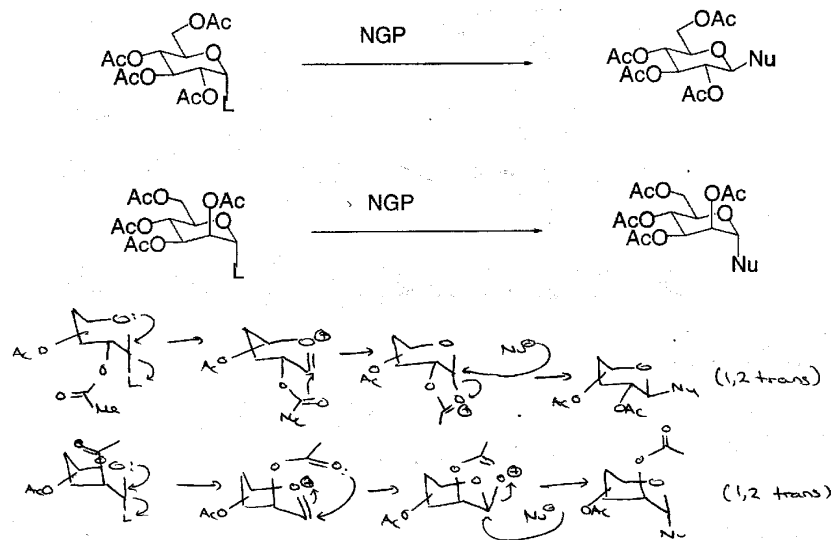
Solvent Effect

The reaction solvent can have a marked effect on the stereochemical outcome of the reaction. A good example is the stereoselective formation of β-linked disaccharides from glycosyl donors that do not possess a participating group at the 2-position. An example is presented below and involves the direct participation of the solvent in the reaction mechanism:

β:α = 24:1
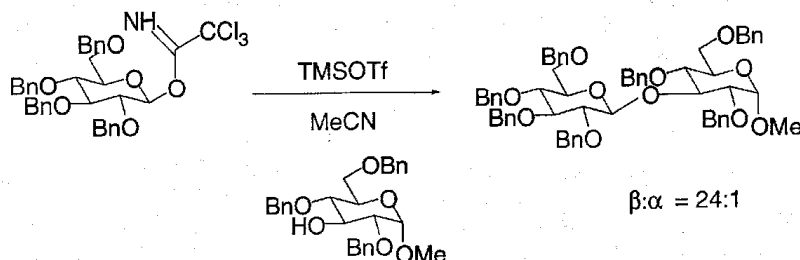
Molecular Tethering – Intramolecular aglycon delivery

How can we form stereoselectively 1,2-cis glycosidic linkages? Overcome this synthetic problem by temporarily tying together the donor and acceptor before the glycosylation reaction is performed – molecular tethering. Subsequent activation of the donor glycoside is then followed by **intramolecular** delivery of the acceptor:
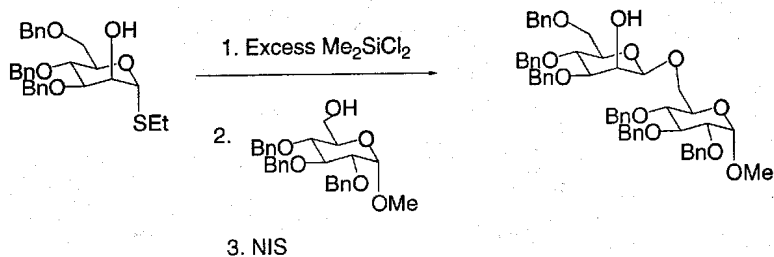
Chemical Disaccharide Formation

The glycosyl acceptor is the nucleophile. The glycosyl donor is the electrophile.

glycosyl donor   glycosyl acceptor   disaccharide

Lg = Br, F, SR , SOR etc