

FREE RADICALS NOTES

Definitions

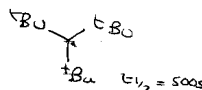
Free radical – organic species with an unpaired electron, not including carbenes and certain photochemically excited compounds.

Stabilised – include carbon-centred radicals, R^\cdot , for which the R-H bond strength is less than that for the corresponding C-H in ($1^\circ/2^\circ/3^\circ$) alkane. Usually transient.

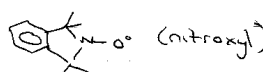
Persistent – radicals with a lifetime significantly greater than methyl under the same conditions. Not necessarily stabilised. Lifetimes range from seconds to years.

Examples:

Non-stabilised, persistent



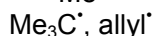
Stabilised, persistent



Transient, non-stabilised

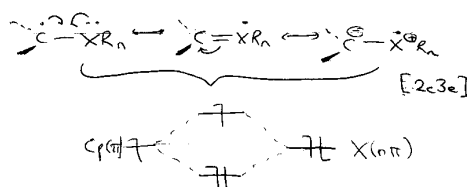


Transient, stabilised



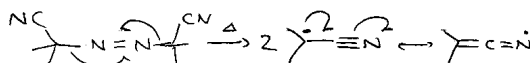
Valence Bond Picture of Heteroatom Stabilisation

Dative:



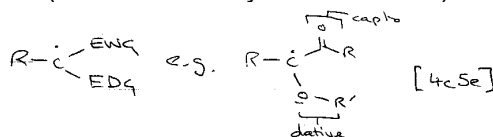
Therefore stabilised.

Capto:



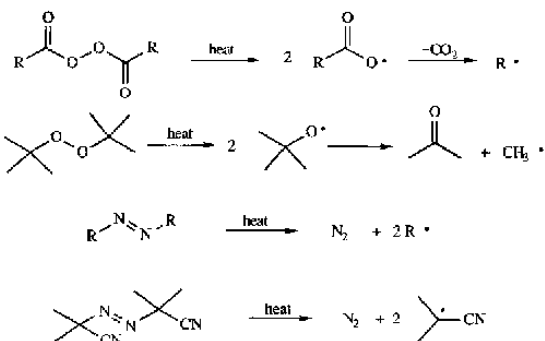
Captodative:

Only radicals can do this (ionic \rightarrow one way is destabilised).



Generation of Free Radicals

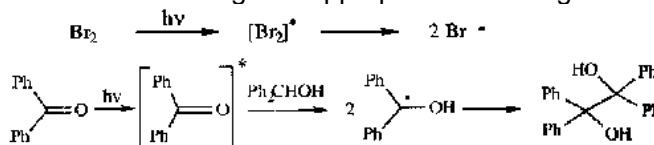
Thermal cleavage of weak bonds



Photochemical cleavage of weak bonds

Useful as heat can destabilise compound.

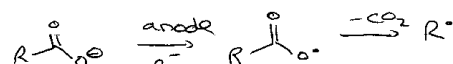
Initiating compound must absorb light of appropriate wavelength to cleave the bond.



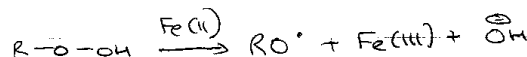
Note that the latter reaction is technically a "phototransformation".

Electron Transfer

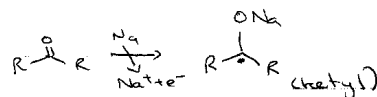
Electrolytic –



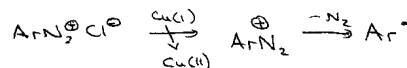
Redox (Fenton) –



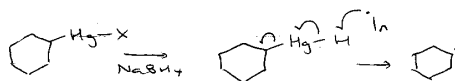
Dissolving Metal –



S_{RN}' (Sandmeyer) –

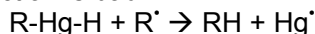


Giese's Mercury Method –



- Room temperature.
- No UV initiation.
- Clean - Hg⁺ by-product.

But, competing direction reduction is bad:



Birch Reduction –

1 electron process.

Regiochemistry applies when substituted.

See other notes (e.g. Oxidation and Reduction Notes) for the mechanism.

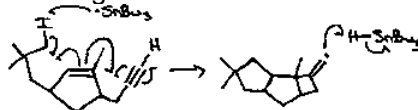
Simple Reactions

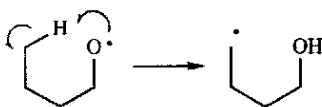
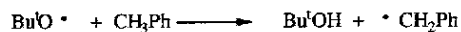
Radical Combination –

Combining two radicals to terminate a chain reaction, R[•]+R[•] → R-R. Often slow due to low concentrations of radicals generally. Only really viable for long-lived radicals or via solvent cages (can be rapid in the latter case).

Radical Abstraction –

Attack often on a H atom or Halogen atom.





Can be thought of as displacement reaction.

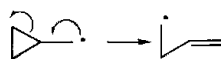
Radical Addition –

Radicals can add to double or triple bonds, and it is often the case that anti-Markovnikov product can be obtained by this route. For example:



Fragmentation –

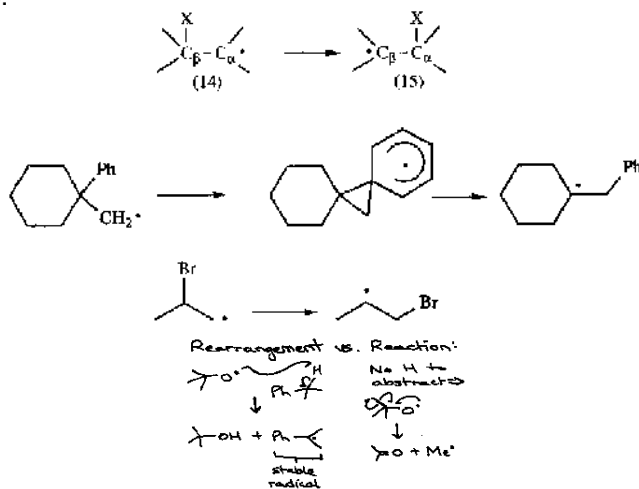
This is the reverse of radical addition, and often occurs as β -elimination. An example would be:



Rearrangements –

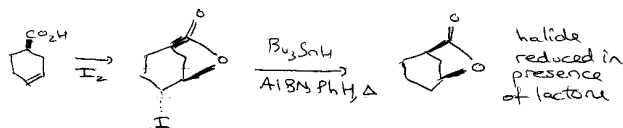
These are radical reactions that occur intramolecularly (often abstraction). It can lead to cyclisation of long chain compounds.

Some examples:

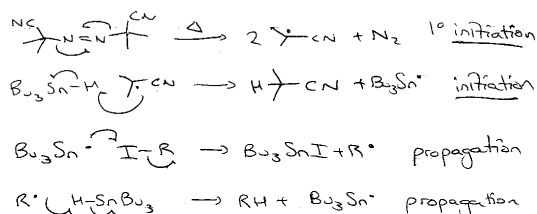


Chain Reactions

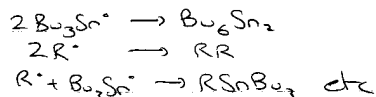
Example:



Series of events:



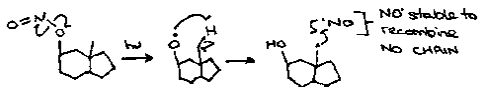
Termination:



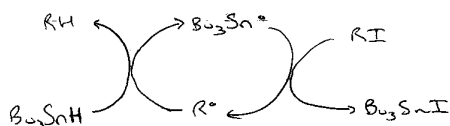
At low concentration, this is unlikely. Minimising termination thus involves:

- Low concentration of radicals \rightarrow steady initiation (AIBN).
- Fast propagation \rightarrow 2 x weak bonds to give 2 x strong bonds (e.g. $\text{Sn-H} + \text{R-I} \rightarrow \text{Sn-I} + \text{R-H}$).

Note that sometimes chain reactions do not occur, particularly with stable radicals or those that are trapped in solvent cages, for example:



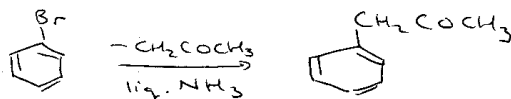
Cyclic Representation –



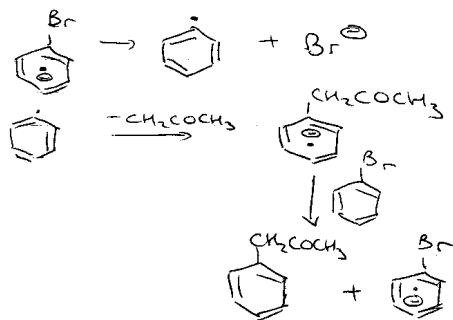
Radicals Ions & the SET Mechanism

Examples of reactions involving radical ions – pinacol, acyloin (see other notes).

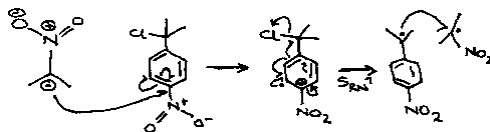
S_{RN1} Mechanism:



Chain propagation –

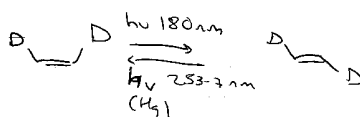


This is another example of Single Electron Transfer, then the S_{RN1} mechanism:



Biradicals and Radical Pairs

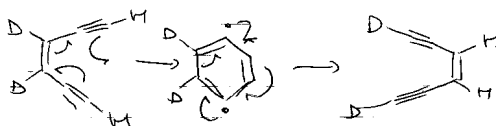
e.g.



Also, benzene is a biradical in the triplet state.

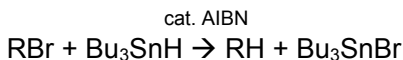
Example reactions – Wittig & Stevens Rearrangements (see Rearrangements Notes).

Also, Bergman Cyclisation –

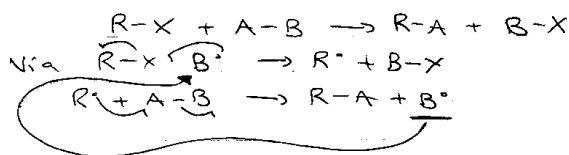


Free Radical Substitution

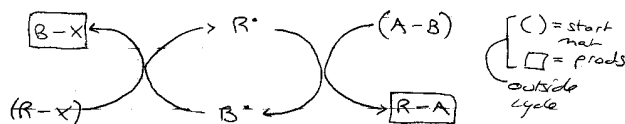
Homolytic bimolecular substitution. Most common is H-abstraction.



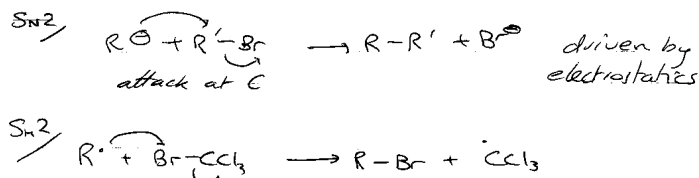
Generally,



In cyclic form:



Comparison with (ionic) nucleophilic substitution –



Attack at halogen instead. Driven by availability of the atom and bond strengths (particularly breaking).

Determination of Reactivity and Regioselectivity

Bond Breaking

$$k = A e^{-E/RT}$$

In $A \approx$ same values for different R in $\text{CH}_3^\bullet + \text{H-R} \rightarrow \text{CH}_4 + \text{R}^\bullet$.

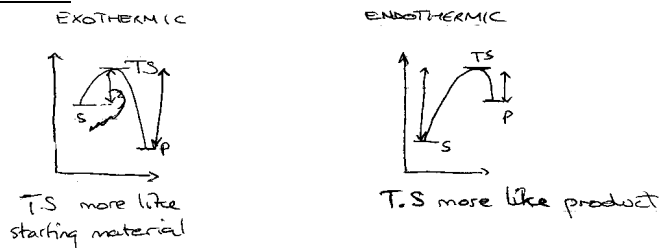
Thus, similar entropy for bimolecular process. Hence, E_a is proportional to $D(\text{R-H})$. In k is also proportional to $D(\text{R-H})$ as a result [linear correlation], which implies bond breaking is important in the rate determining step.

Bond Forming

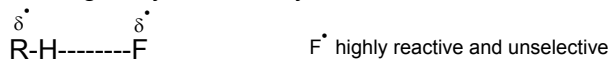
In A similar, so E_a is proportional to $D(\text{X-H})$. Dominates as in bond breaking.

In k vs. $D(\text{X-H})$ is non-linear, i.e. bond forming may or may not be important \rightarrow early or late Transition States (Hammond Postulate).

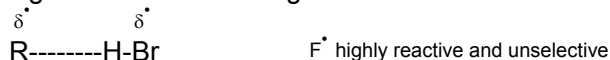
Hammond Postulate -



Thus, for H[•] abstraction by X[•], when X = F reaction is very exothermic → early transition state (like starting materials), therefore little R-H breaking. Hence, T. State is not greatly affected by R:

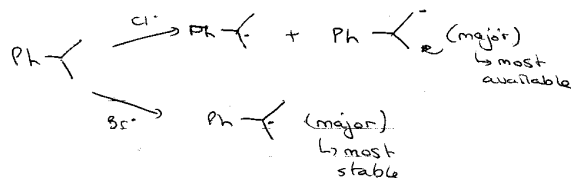


When X = Br reaction is endothermic → late transition state (like products). Thus significant R-H breaking. T. State will be sensitive to the nature of R:



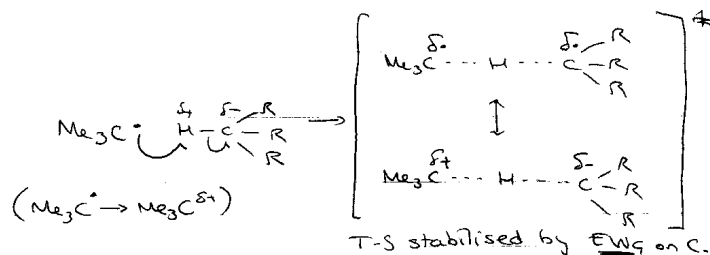
In general, halogens become less discriminating in H-abstraction in the order:
I > Br > Cl > F

e.g.

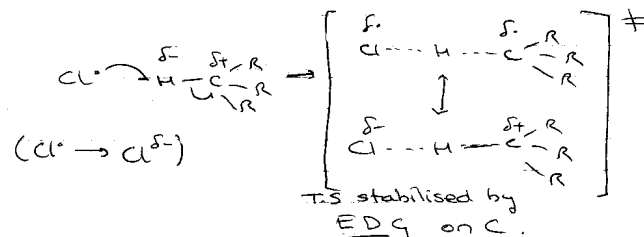


Polarity Effects

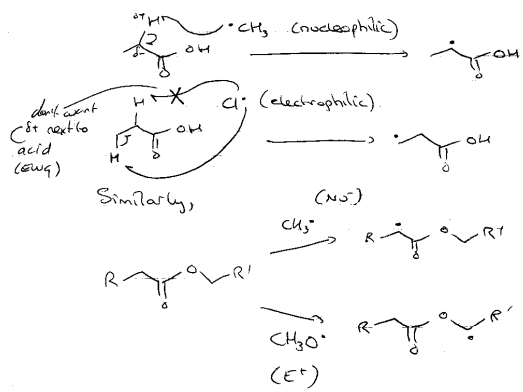
Nucleophilic:



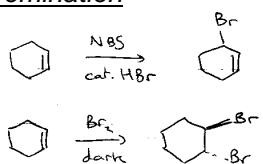
Electrophilic:



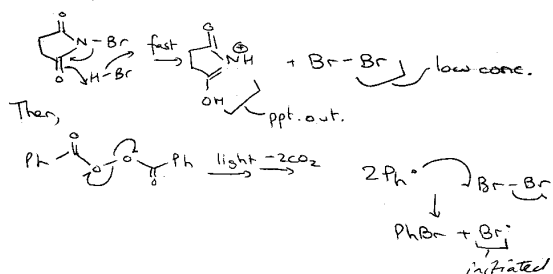
Explains the position of H-abstractions, e.g.



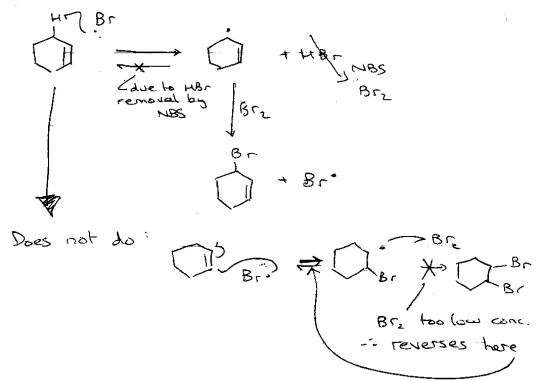
Wohl-Ziegler Allylic Bromination



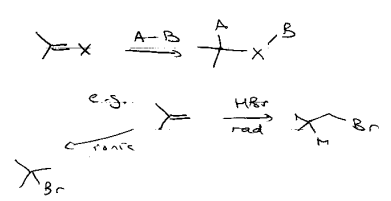
Goldfinger mechanism:



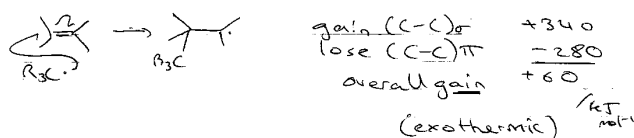
Then,



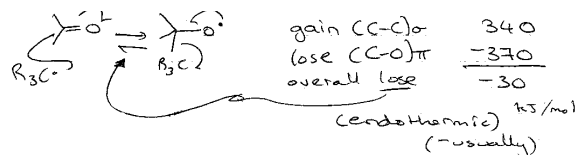
Addition to Multiple Bonds



Consider:

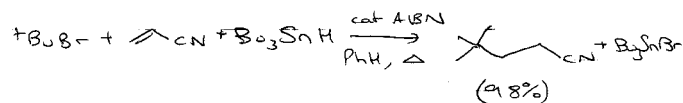


But,

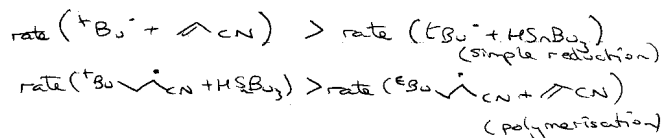


Selectivity

Consider:



For this to occur:

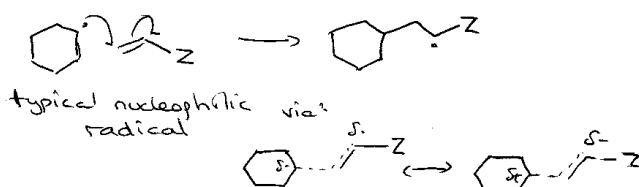


$t\text{Bu}\cdot + \text{HSnBu}_3$ is very fast ($3 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$) so set $[\text{Bu}_3\text{SnH}]$ to be as low as possible. Also set $[\text{H}_2\text{C}=\text{CHCN}]$ as high as possible. Reason why there's no polymerisation? See below.

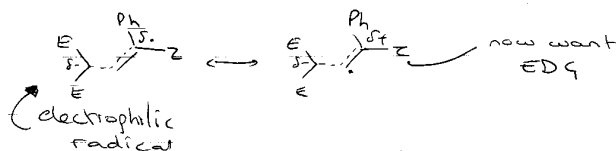
Substituent Effects



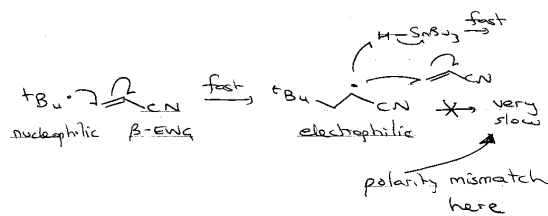
β -effects



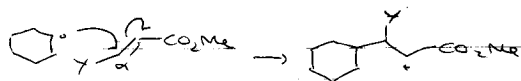
i.e. want electron withdrawing Z to stabilise T. State when nucleophilic radical.



Consider:



α -effects



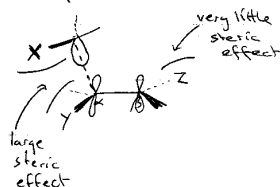
Electron withdrawing group Y favours Nucleophilic radical a little, but sterics usually the dominant factor – often offset any electronically favourable effects operating.

Radical Substituents

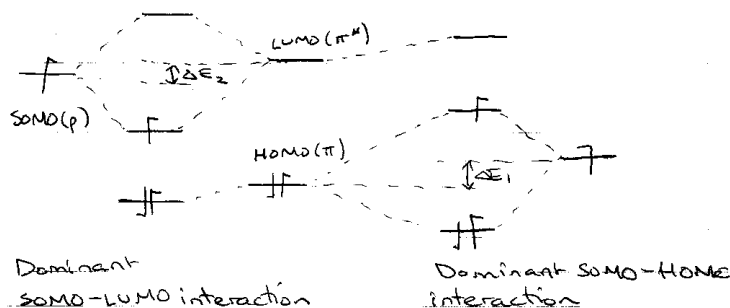
Comparable to α -effects – generally slow addition.

Mechanism

Exothermic \rightarrow early transition state (Hammond Postulate).

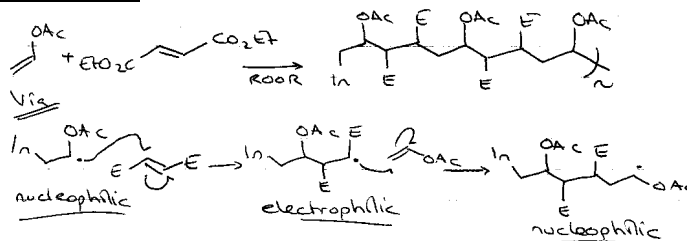


Molecular Orbital Description –

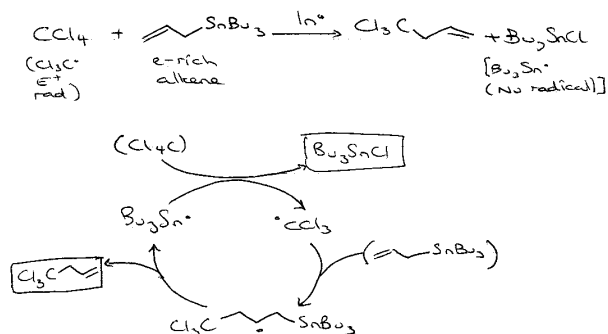


EWG on alkene: lower HOMO and LUMO $\rightarrow \Delta E_2 < \Delta E_1$.
 EDG on alkene: raise HOMO and LUMO $\rightarrow \Delta E_1 < \Delta E_2$.

Radical Copolymerisation



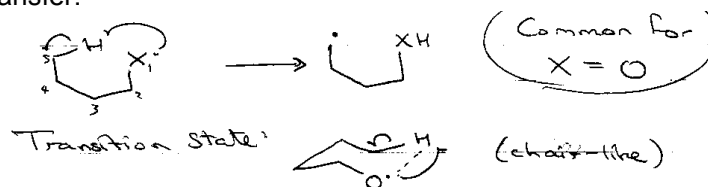
Allyl Transfer



Rearrangements

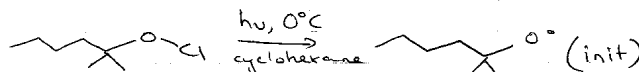
$R^{\cdot} \rightarrow R'^{\cdot}$ without change of molecular formula.

e.g. [1,5] H-transfer:

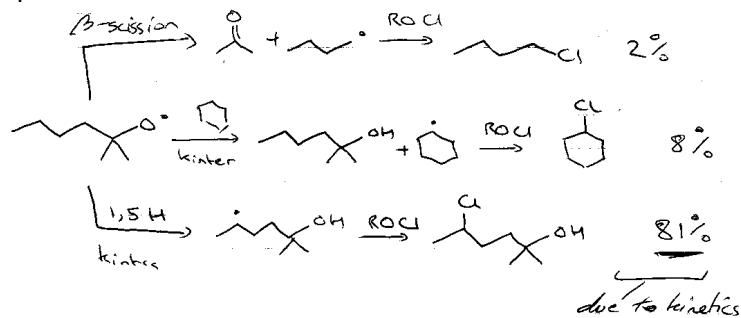


Favourable by $\sim 50-75 \text{ kJ mol}^{-1}$.

Mechanism

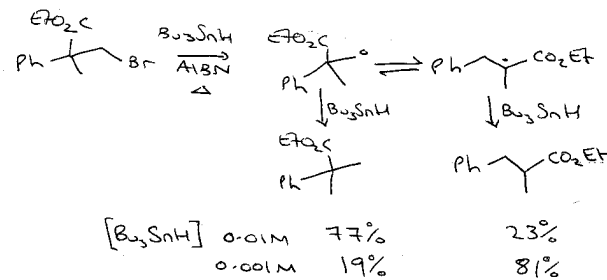


Then several paths available:



Homobenzylic Rearrangement

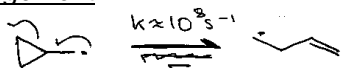
(1,2-phenyl shift).



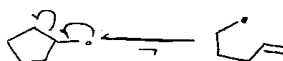
Via:



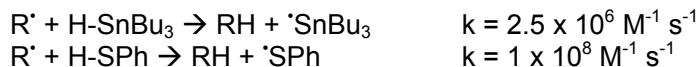
Cyclopropylcarbinyl Rearrangement



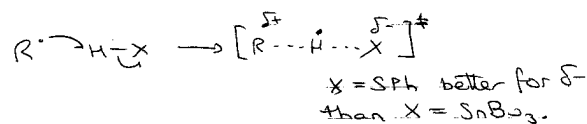
But,



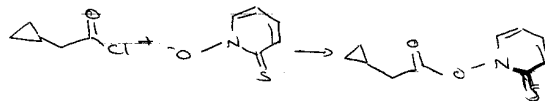
Rate of H-atom Transfer –



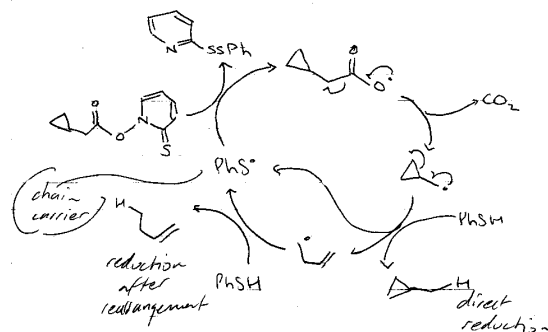
Reason:



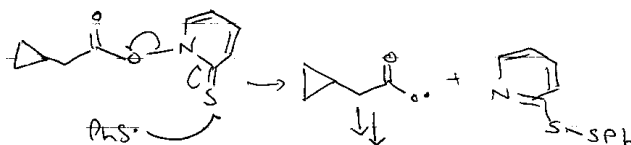
Barton's Pyridinethione Oxycarbonyl Esters (PTOC esters)



Consider:



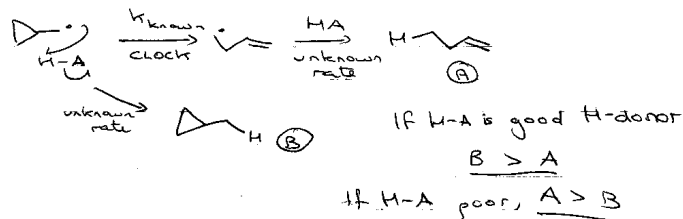
Via:



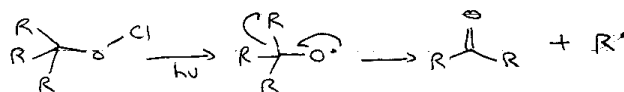
- C=S weak π -bond.
- PhS \cdot attacks S=C \rightarrow S-S bond.
- Aromaticity driven.

Radical Clocks

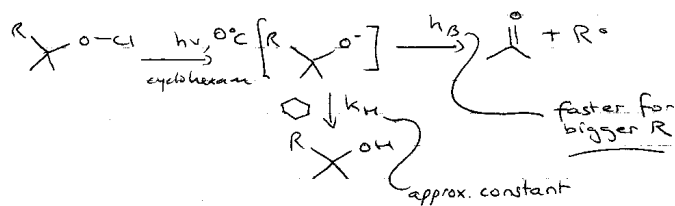
Free radical reactions having a known rate against which other reactions may be gauged (common is cyclopropylcarbinyl cleavage).



β -scission



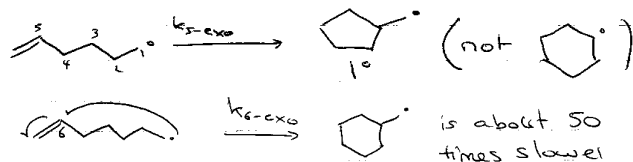
Effect of varying attached groups:



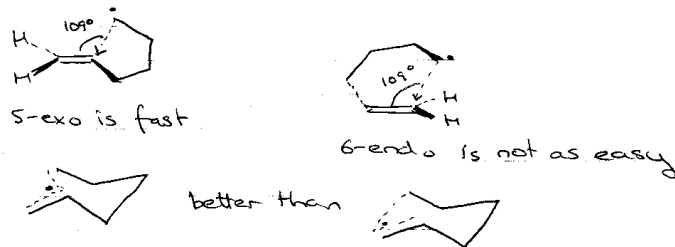
R = Ph → Me[•] ejected, as:

- 1) Phenyl destabilised wrt methyl, and
- 2) Favourable phenyl-carbonyl π -overlap may develop in the transition state.

Cyclisation



Follows kinetic control:

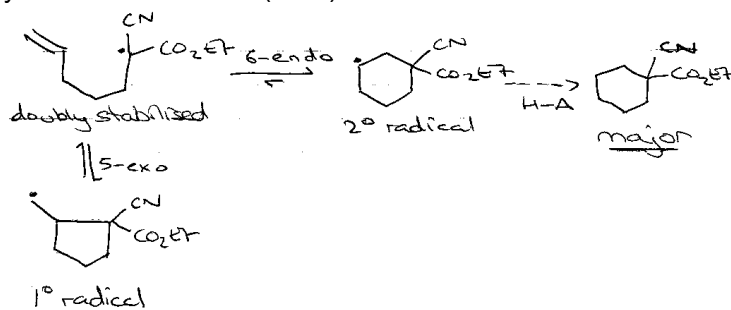


Baldwin's Ring Closure:

Most important here are the trigonal systems –

3 to 7-exo-trig	FAV
3 to 5-endo-trig	DISFAV
6 to 7-endo-trig	FAV

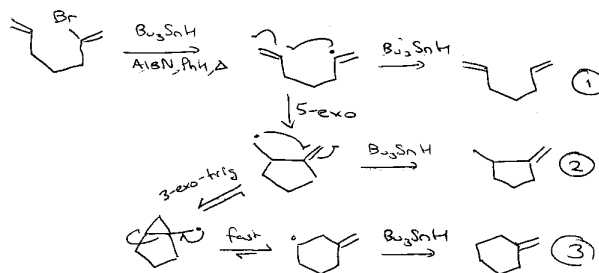
But thermodynamic control also? (Julia)



Balance of:

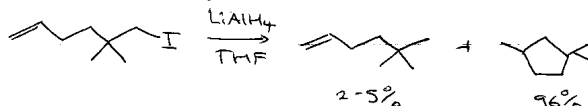
- Radical stabilisation, and
- σ vs. π C-C bond strength

5-exo-cyclisation followed by cyclopropylcarbinyl fragmentation also gives 6-membered rings:

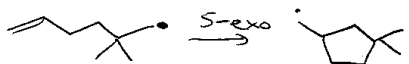


Depends on $[Bu_3SnH]$ – favours (1) \gg (2) $>$ (3).

5-exo-cyclisation as a mechanistic probe –

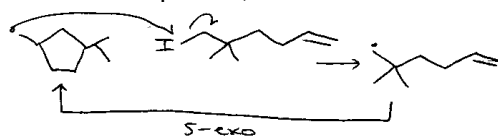


Ashby proposed:
SET by AlH_4^-



(Probably correct).

Newcomb proposed:
Iodine atom transfer / reduction sequence, via:

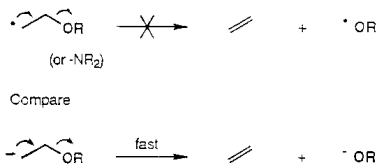


Radicals in Synthesis

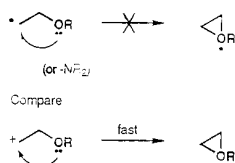
Functional Group Chemistry

General Points –

- C-centred radicals are extremely reactive, yet they can be generated under mild, neutral conditions and often undergo highly regio- and stereoselective reactions.
- Radical additions to $C=C$ are usually exothermic and irreversible with early, reactant-like Transition States. Kinetically controlled.
- Since radicals are not cluttered with counterions or solvation spheres, radical intermediates are ideally suited for synthesis at crowded bonds.
- C-centred radicals are inert to OH and NH, therefore no protecting groups for these. Exception: phenols (capto stabilised).
- Unlike carbanions, carbon radicals are not subject to β -elimination of OR or NR_2 .



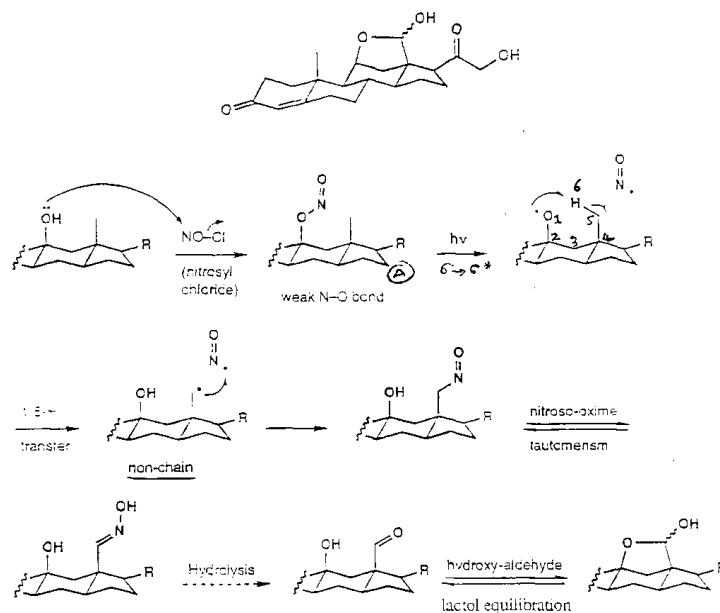
- Unlike carbocations, carbon radicals are not subject to capture by β -OR or NR_2 groups, nor are they usually prone to migration of β -H or $-CR_3$ groups. They are, however, subject to β -elimination of SR, SO_nR and SnR_3 groups.



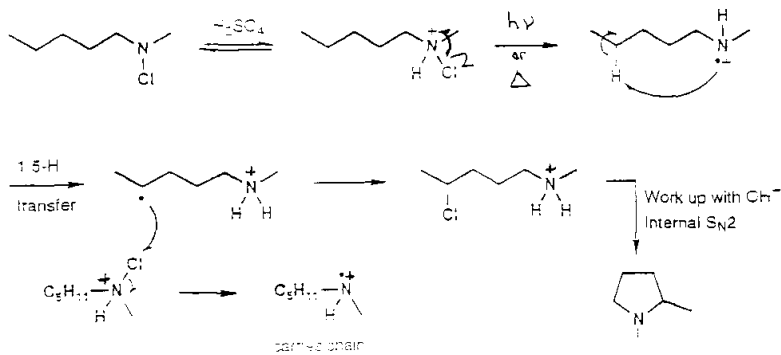
- Radical centres do not usually retain stereochemistry. Can be a drawback, but precursor synthesis is simplified (geometrically labile sp²-like radicals).

Examples

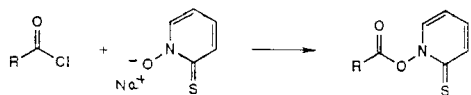
Barton Nitrite Ester Reaction



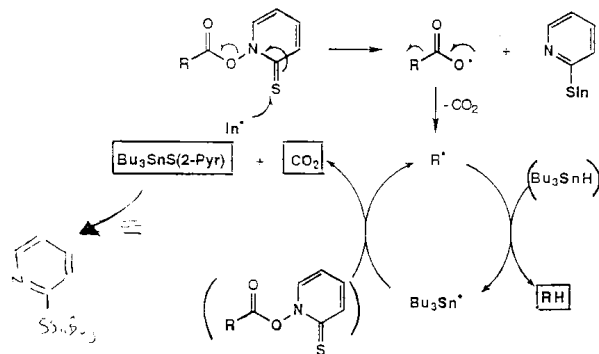
Hoffmann-Löffler-Freytag Reaction



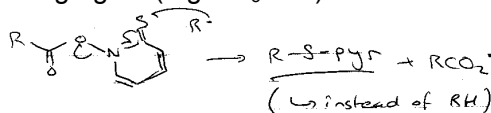
Barton's PTOC Esters



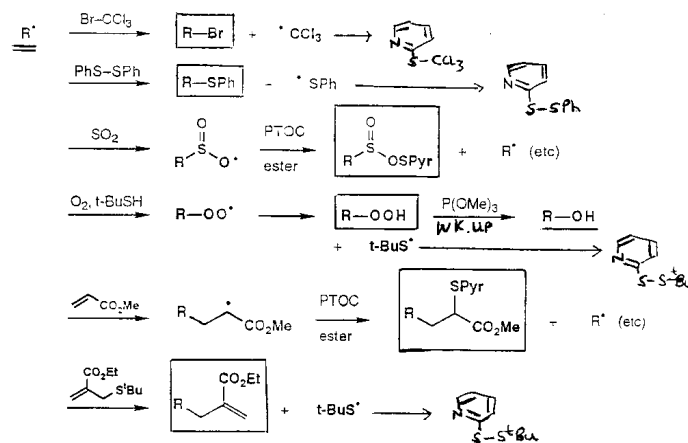
PTOC ester - weak N-O bond
 - weak C=S bond
 - potential aromatic system
 - potential to lose CO₂
 ⇒ thermodynamically unstable



If there's no added reducing agent (e.g. Bu₃SnH):

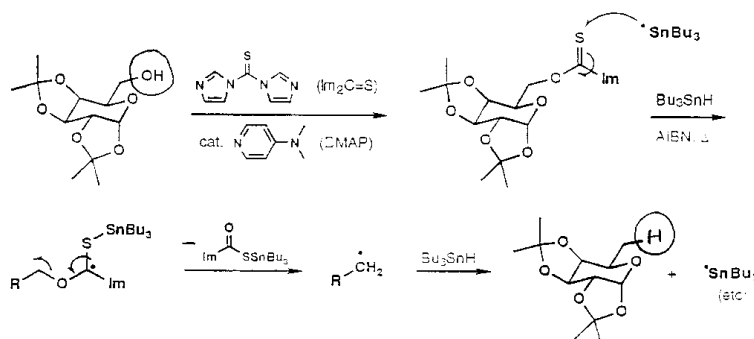


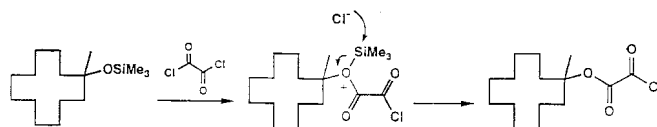
This leads to many possibilities for reaction:



Removal of OH

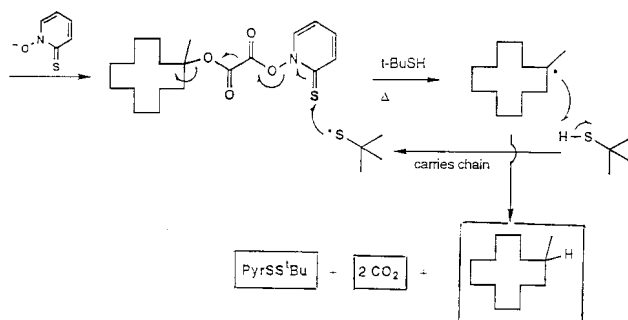
For 1° and 2° alcohols





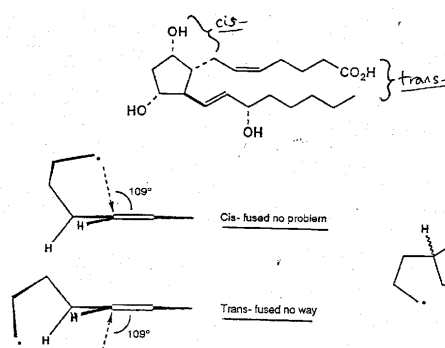
(can also be done on free alcohol)

Then...

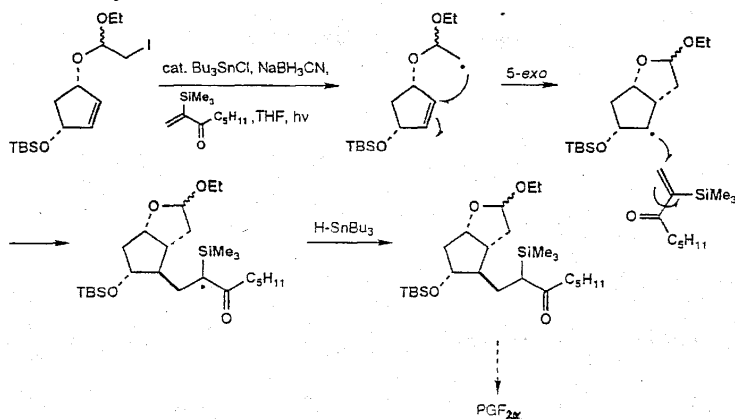


Free Radicals in Natural Product Synthesis

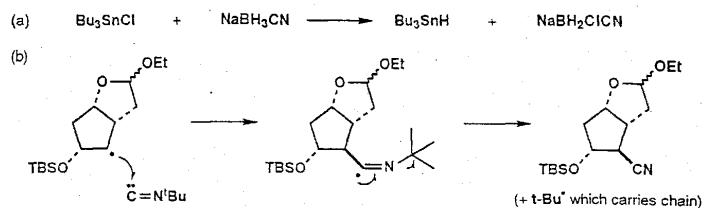
Prostaglandin F_{2α}



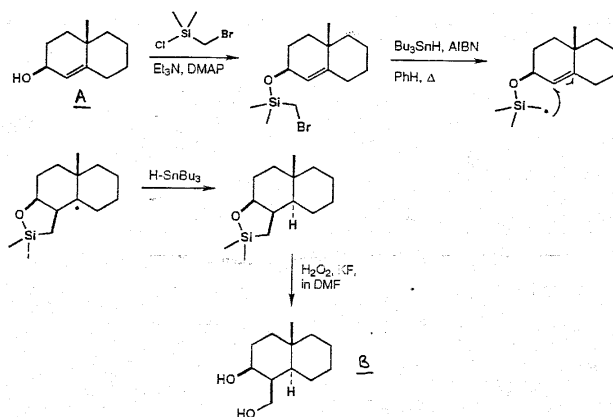
Iodoacetal tethered cyclisation –



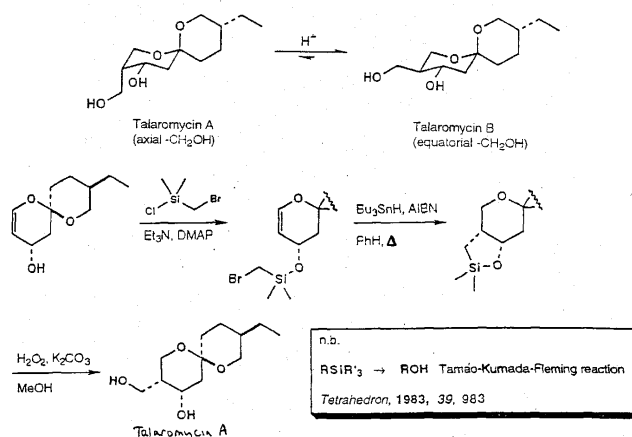
Notes:



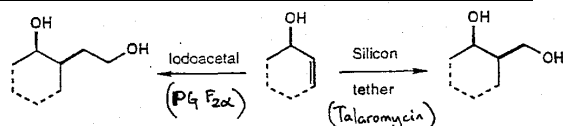
Also, Silicon Tethered free radical reactions –



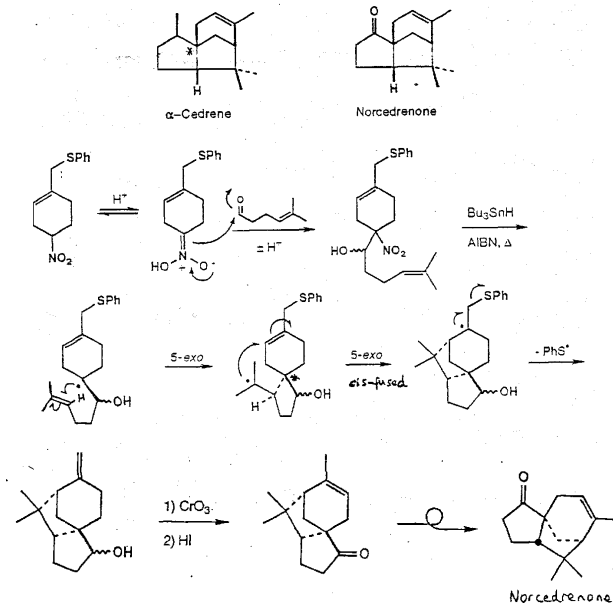
Talaromycin A



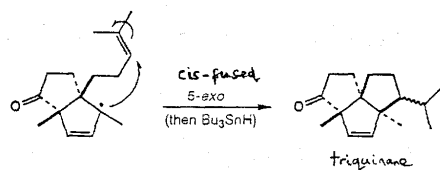
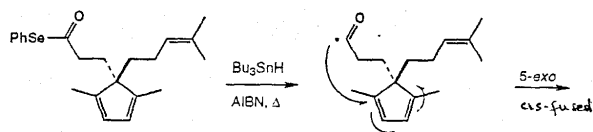
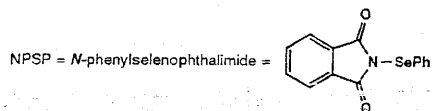
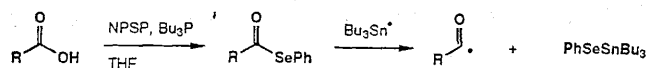
Comparison of iodoacetal and silicon tethered radical reactions



α -Cedrene

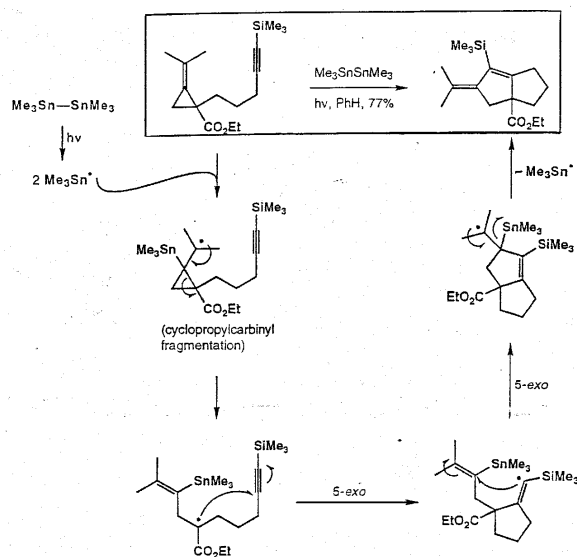


Acyl Selenides as acyl radical precursors



Fragmentation Chemistry in Synthesis

Intramolecular Annulation



Epoxide Fragmentations

Cyclopropylcarbonyl \rightarrow homoallyl



Epoxycarbonyl \rightarrow allyloxy



normally C-O cleavage observed

Incorporation into cascade sequences

