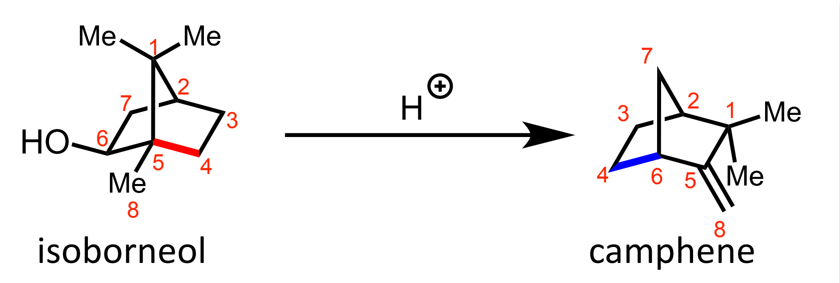
Rearrangements and Reactive Intermediates
Hilary Term

1A Organic Chemistry

Handout 1



- ■ *Polar Rearrangements*, Oxford Chemistry Primer no. 5; L. M. Harwood
- ■ *Organic Chemistry* J. Clayden, N. Greeves, S. Warren – Chapters 36-41
- ■ *Reactive Intermediates,* Oxford Chemistry Primer no. 8; C. J. Moody, G. H. Whitham

- ■ *Mechanism and Theory in Organic Chemistry*, T. H. Lowry, K. S. Richardson
- ■ *Advanced Organic Chemistry,* F. A. Carey, R. A. Sundberg
- ■ *Modern Physical Organic Chemistry*; E. Anslyn, D. Docherty

Synopsis

- **Carbocations and carbanions** NMR spectroscopy and X-ray structures of carbocations; aggregation and pyramidal inversion of carbanions. Reactivity, including S_E1, redox, hydride elimination and rearrangements: Wagner–Meerwein, pinacol, semi-pinacol.

- **Rearrangement of anions and carbocations** Orbital theory; Is 3c-2e structure TS or HEI? Stepwise versus concerted rearrangements; non-classical carbocations (carbonium ions), transannular hydride shifts.
Carbanions: Favorskii, Ramberg-Bäcklund, Stevens and Wittig rearrangements.

- **Carbenes** Structural features that influence stability. Methods of making them; carbenes versus carbenoids. General classification of the types of reaction that these species undergo. Rearrangements: Wolff, cyclopropanation, C-H insertion.

- **Rearrangements to electron-deficient nitrogen and oxygen** Structure of nitrenes; structural features that influence stability. Methods of making them. Types of reaction: aziridination, C–H insertion. Nitrene versus non-nitrene mechanisms. Rearrangements to electron-deficient nitrogen (Beckmann, Neber, Hoffmann, Curtius, Schmidt, Lossen). Baeyer–Villiger rearrangement.

- **Introduction to radicals** Structure; stability. General types of reaction involving radicals: homolysis, recombination, redox, addition, β-scission, substitution, disproportionation.

- **Problem class** relating to lectures 1–4.

- **Case studies** Elucidating mechanisms of rearrangements. Evidence for currently accepted mechanisms for the Baeyer–Villiger, Beckmann and Favorskii rearrangements.

- **Problem class** relating to lectures 5 and 7.

Types of High Energy Intermediates

■ Electron Deficient Cations

Two classes of carbocations

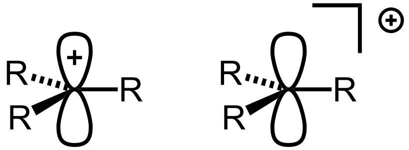
reactive towards

a) nucleophiles

b) bases

c) reducing agents

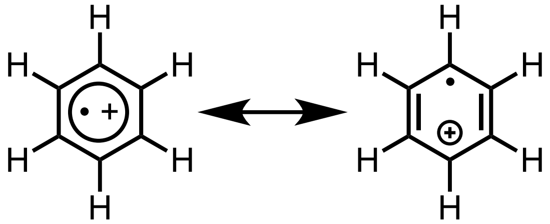
Carbenium ion (6 electrons)



Carbonium ion (8 electrons)

e.g. $\overset{\oplus}{CH_5}$

Radical cation



■ Neutral species

Carbenes (6 electrons)

singlet

triplet

■ Electron Rich Anions

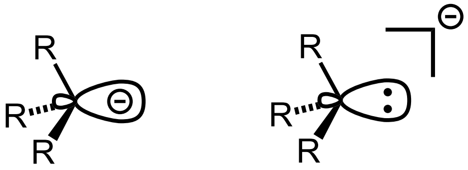
Carbanion (8 electrons)

reactive towards

a) electrophiles

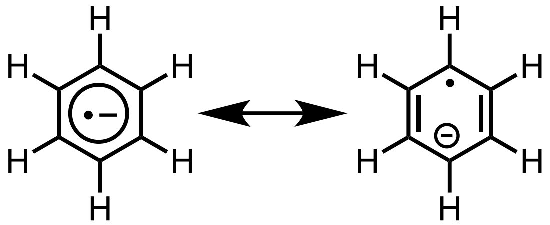
b) acids

c) oxidising agents



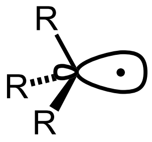
■ Electron Rich Anions

Radical Anion



■ Neutral species

Radical (7 electrons)



reactive towards

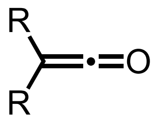
a) electrophiles or nucleophiles

b) other high energy agents

c) oxidising or reducing agents

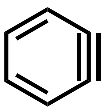
■ Neutral species

ketenes



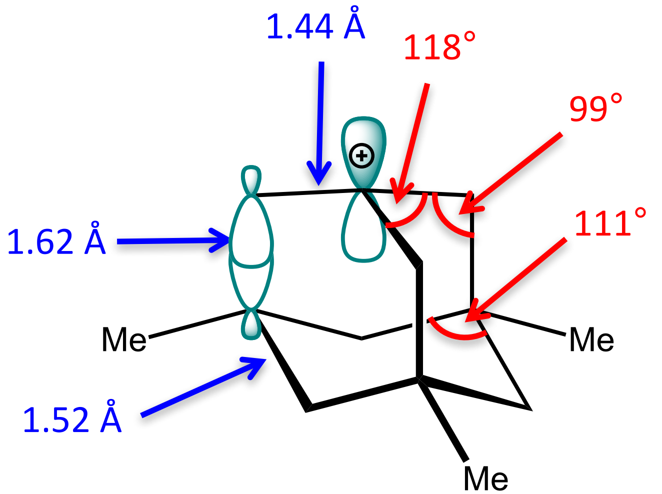
■ Neutral species

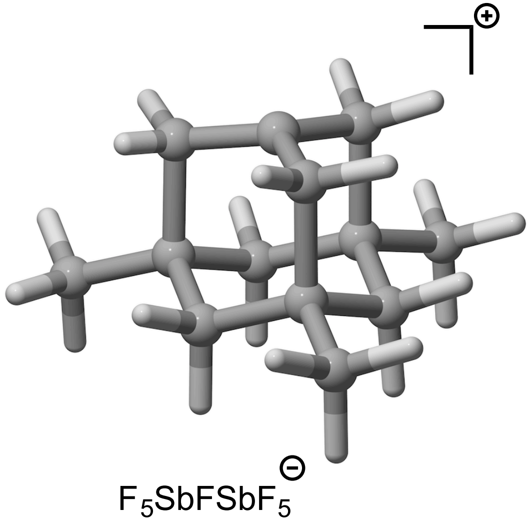
arynes

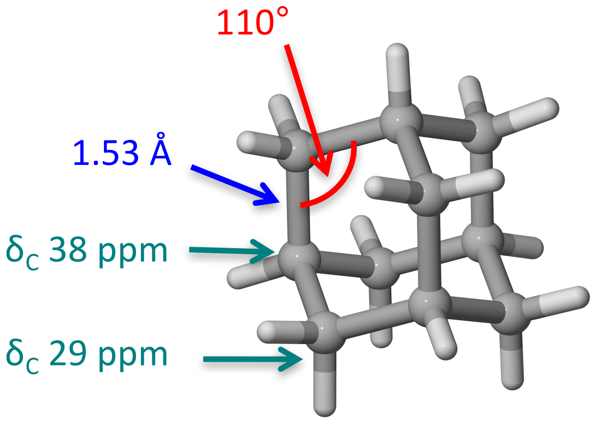


Stuctures of Carbocations

- Crystal structure of an adamantyl carbocation

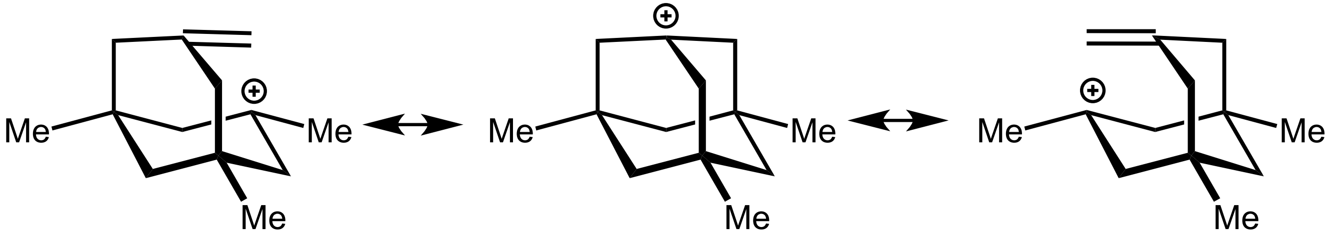




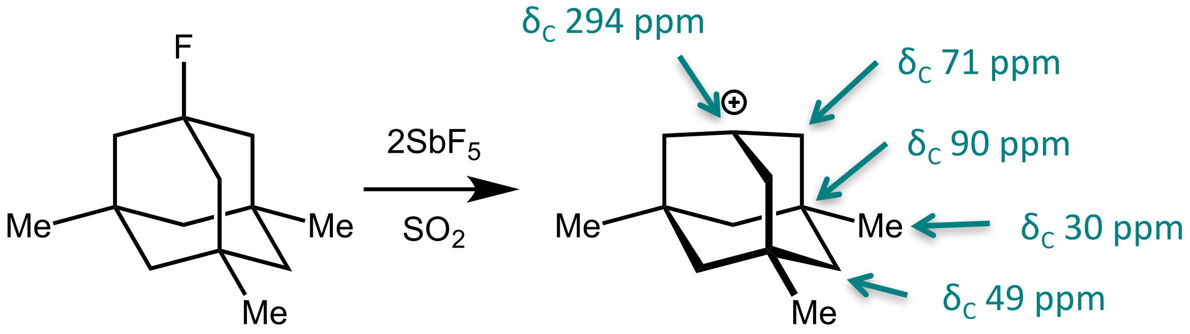


adamantane

- C-C σ to empty p



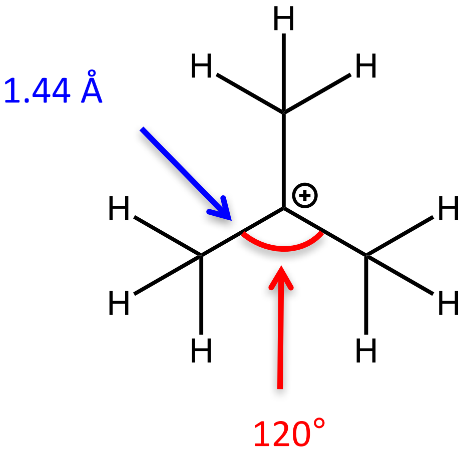
C-C	sp^3-sp^3	1.54 Å
C-C	sp^3-sp^2	1.50 Å
C-C	sp^2-sp^2	1.46 Å
C=C		1.34 Å

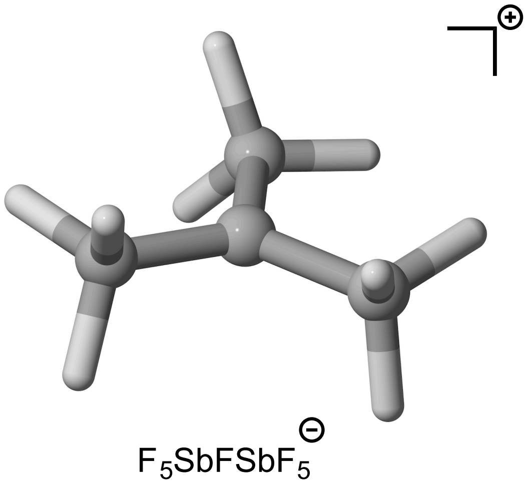


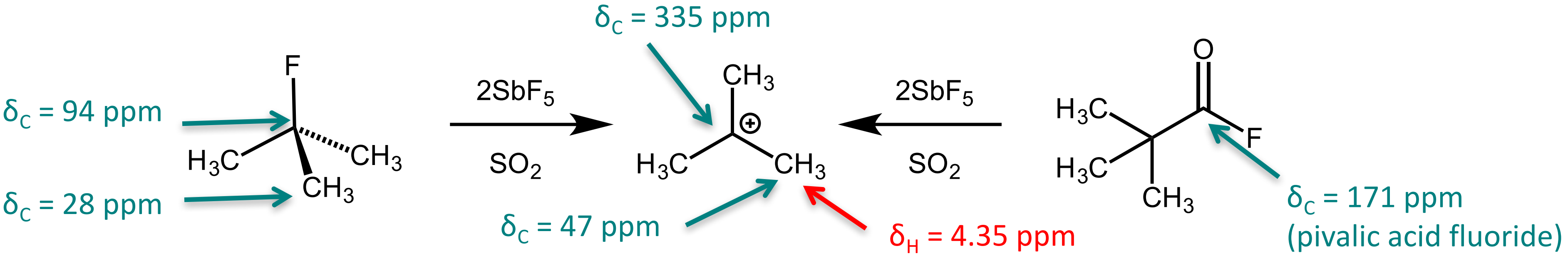
- Bond lengths and bond angles provide evidence of hyperconjugation (T. Laube, *Angew. Chem. Int. Ed.* **1986**, *25*, 349).

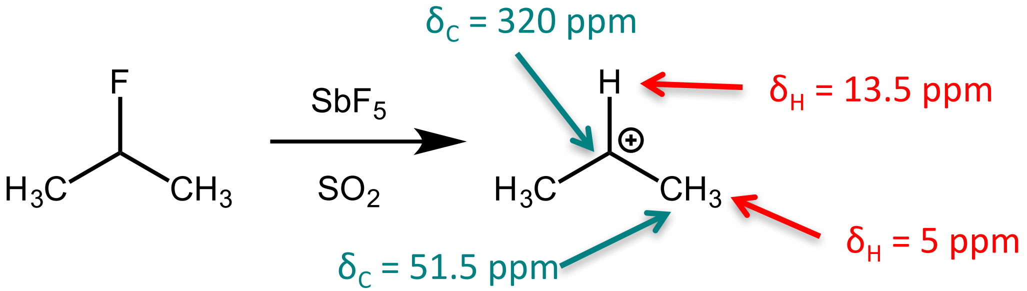
- Crystal structure of a *t*-butyl carbocation

C-C	sp^3-sp^3	1.54 Å
C-C	sp^3-sp^2	1.50 Å
C-C	sp^2-sp^2	1.46 Å
C=C		1.34 Å





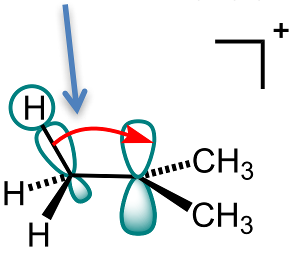


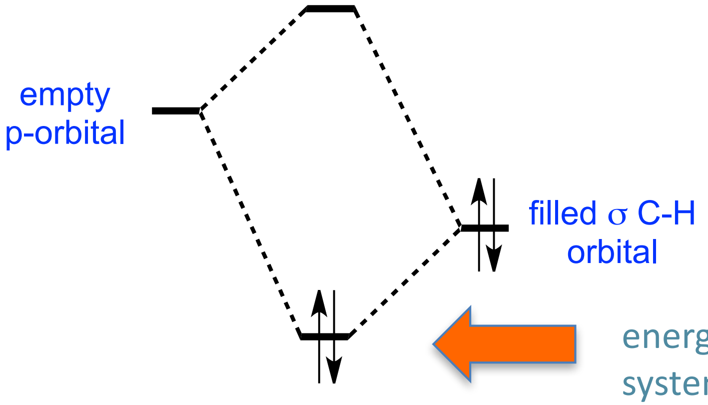


- Bond lengths provide evidence of hyperconjugation (T. Laube, *J. Am. Chem. Soc.* **1993**, *115*, 7240).

- Hyperconjugation

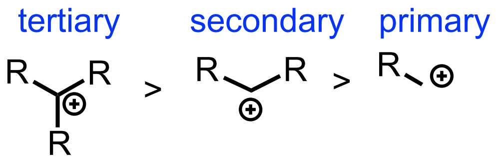
donation of C-H σ-bond (or C-C σ-bond) electrons into empty p orbital



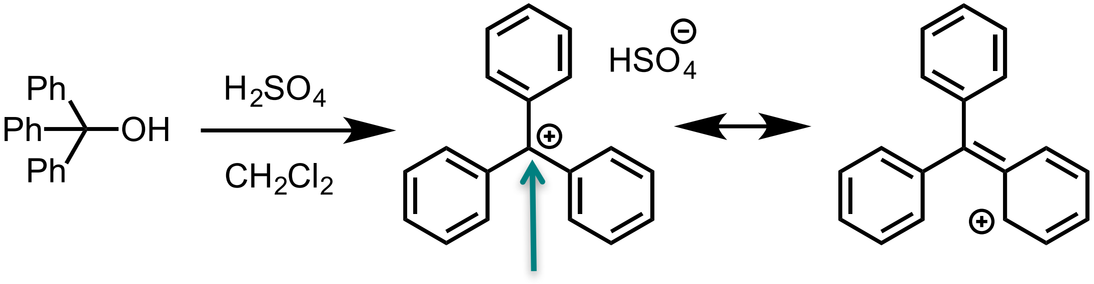


energy of the bonding electrons reduced
system stabilised

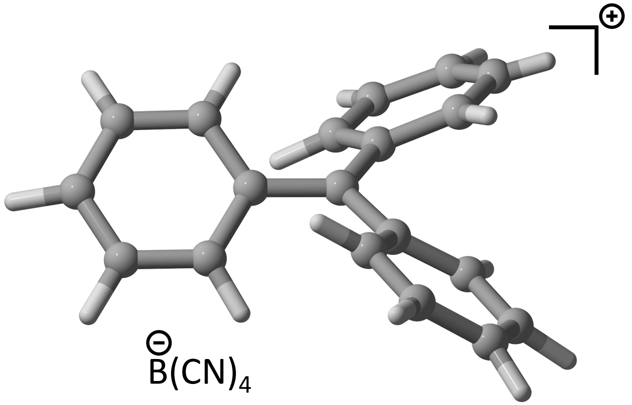
- greater number of C-H (or C-C) σ-bonds the greater the extent of hyperconjugation and the greater stabilisation
- carbenium ion stability therefore goes in the order:



- conjugation with alkenes, arenes and lone pairs, also stabilises carbenium ions
- most carbocations are fleeting reaction intermediates – the triphenylmethyl (trityl) cation persists - crystal structure of trityl cation demonstrates all the phenyl groups are twisted out of plane
- $Ph_3C^{\oplus}$ $BF_4^{\ominus}$ is a commercially available crystalline solid



δ_C = 212 ppm

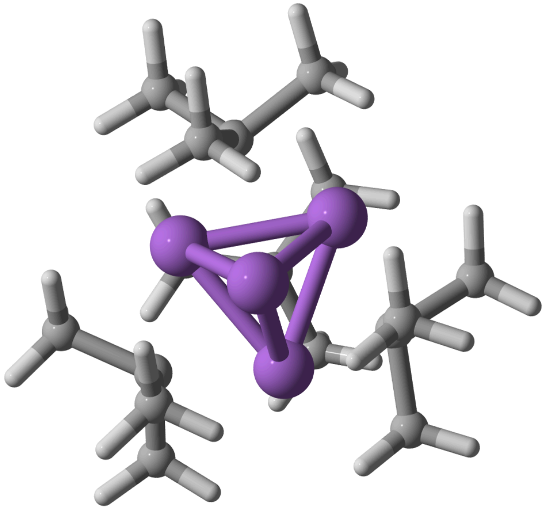


Structures of Carbanions

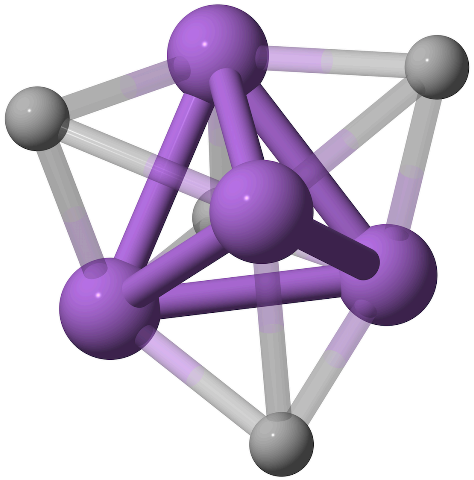
- generally aggregated in the solid state and in solution

- methyllithium is a tetramer $(MeLi)_4$ with CH_3 groups sitting above each face of a Li_4 tetrahedron — overall a distorted cube

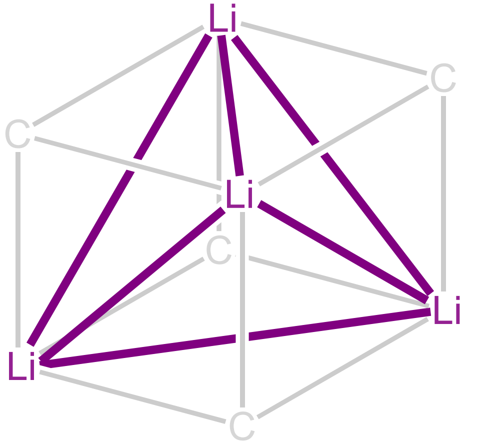
- *tert*-butyllitium is also tetrameric in the solid state (X-ray crystal structures below)



t-butyllithium
$(t\text{-}BuLi)_4$



methyllithium
$(MeLi)_4$
(H-atoms removed for clarity)

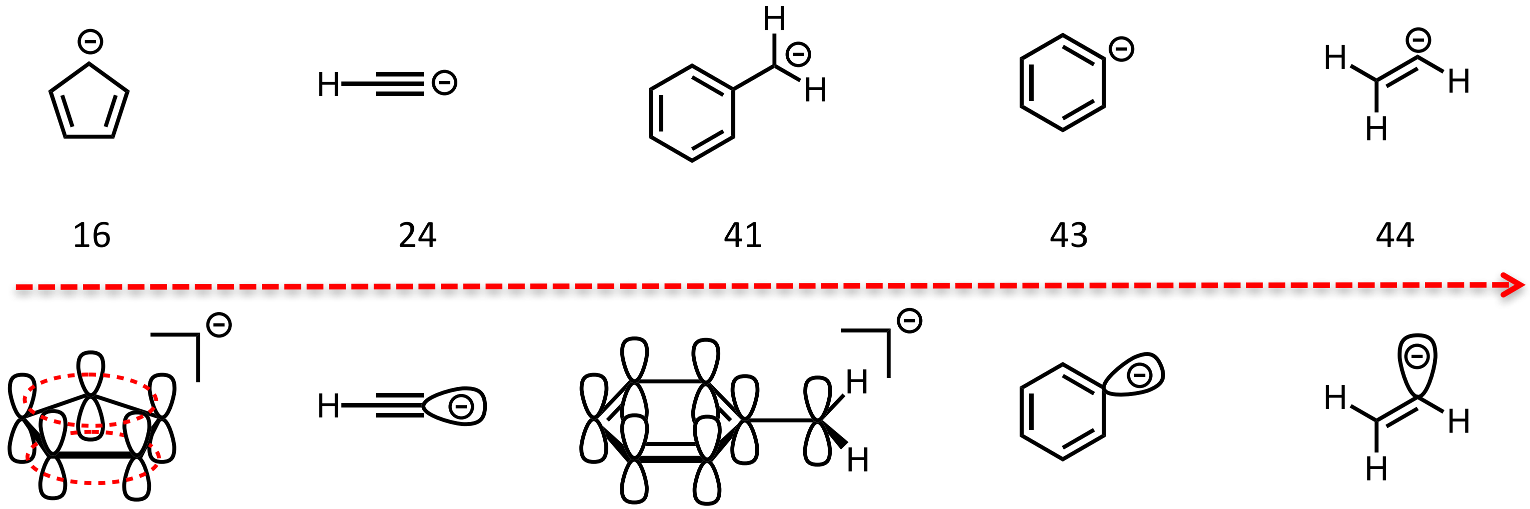


idealised arrangement of lithium and carbon atoms

- in coordinating solvents e.g. THF, Et_2O most organolithiums become less aggregated and hence more reactive

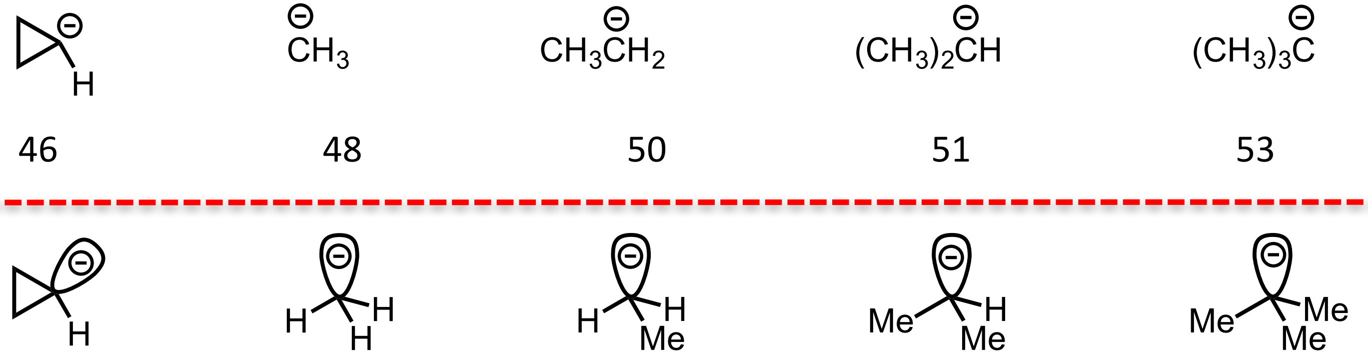
- stability of carbanions is related to the pKa of their conjugate acids

increasing pK_a of conjugate acid, increasing reactivity, decreasing stability



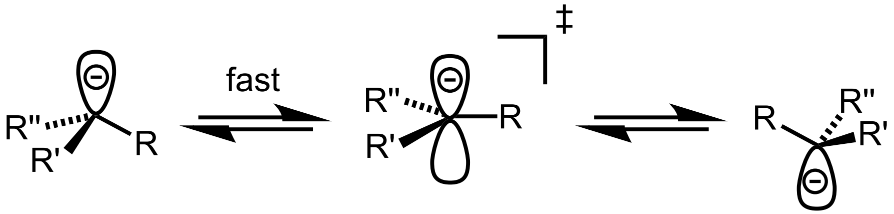
16	24	41	43	44
aromatic	sp-hybridised	conjugated	sp^2-hybridised	sp^2-hybridised

increasing pK_a of conjugate acid, increasing reactivity, decreasing stability

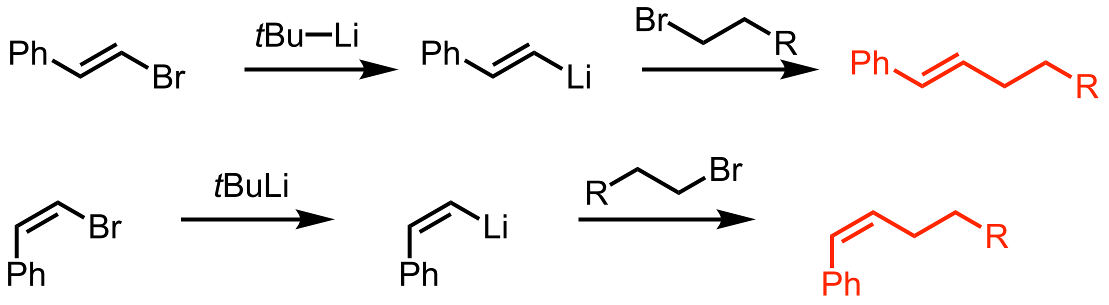


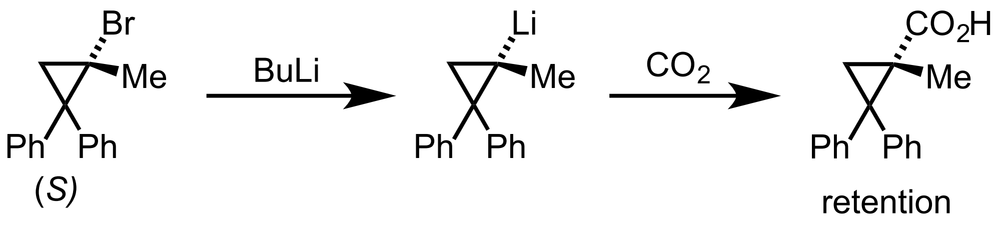
$\overset{\ominus}{\text{C}}$ (cyclopropyl)	$\overset{\ominus}{C}H_3$	$CH_3\overset{\ominus}{C}H_2$	$(CH_3)_2\overset{\ominus}{C}H$	$(CH_3)_3\overset{\ominus}{C}$
46	48	50	51	53
sp^2-hybridised	sp^3-hybridised	sp^3-hybridised electron donating alkyl group	sp^3-hybridised electron donating alkyl groups	sp^3-hybridised electron donating alkyl groups

- pyramidal inversion is generally fast for sp^3 hybridised carbanions (they are isoelectronic with NH_3) and hence chiral carbanions generally undergo rapid racemisation.

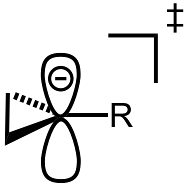


- vinyl anions and cyclopropyl anions are the exceptions and are generally considered configurationally stable
- lithium halogen exchange with alkenyl iodides and bromides is a stereospecific process



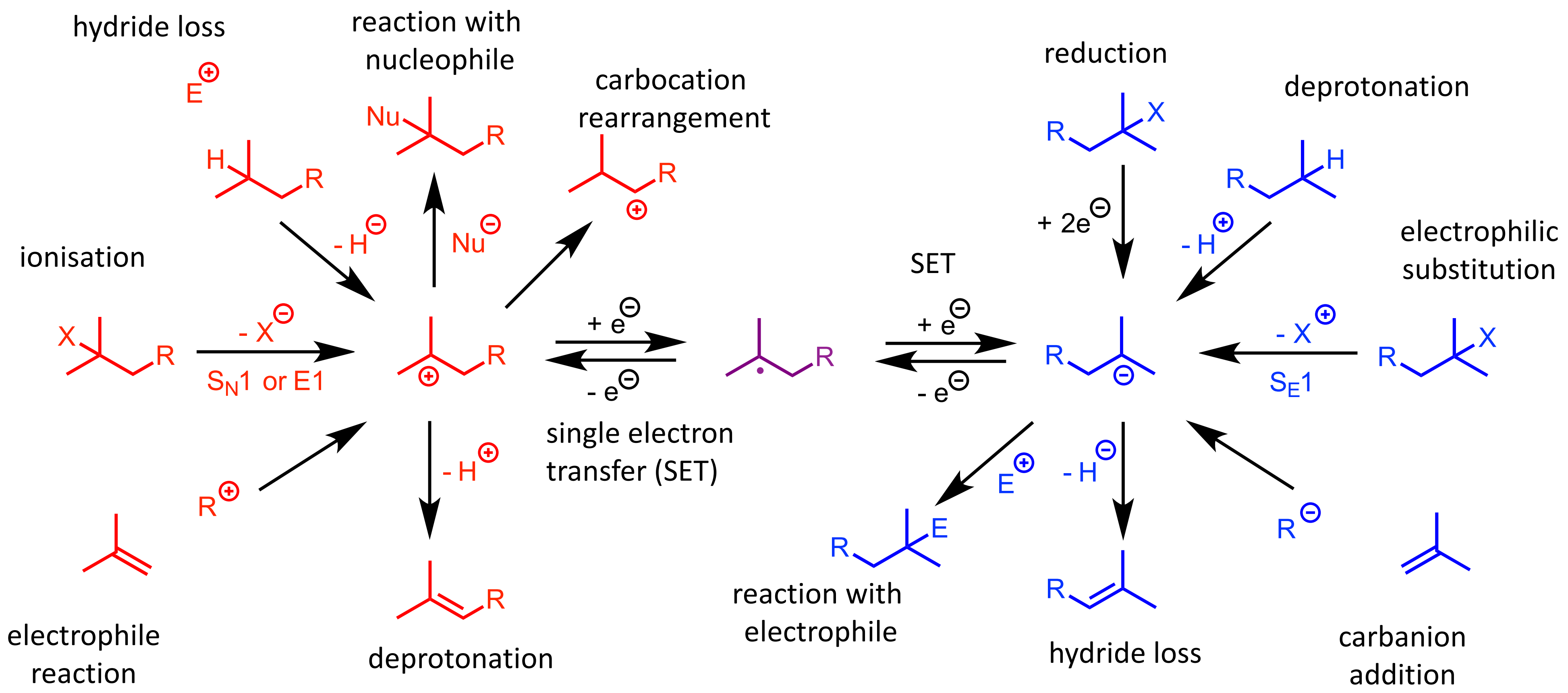


- sp^2 hybridisation at transition state for pyramidal inversion
- ideal 120 ° angles only ca. 60° for cyclopropane
- transition state highly strained therefore slow rate of inversion



Reactions of Carbocations and Carbanions

- Generic reaction map of carbocations and carbanions

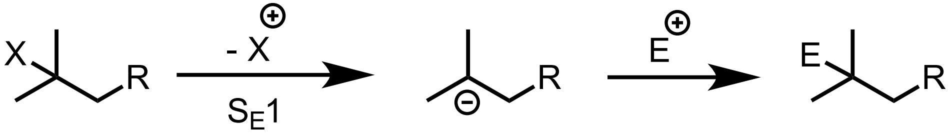


- most common reaction of carbanions is reaction with electrophiles (e.g. RLi or RMgBr plus $E^{\oplus}$) which is amply covered elsewhere

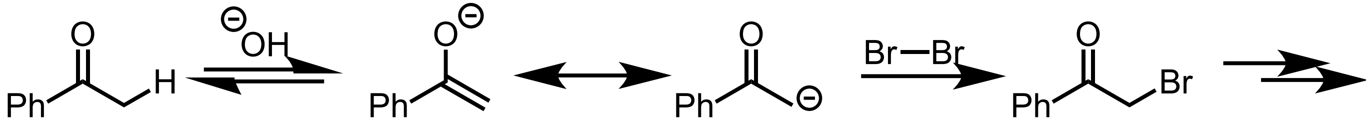
- some other reactions are shown below

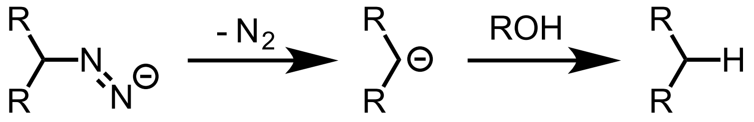
S_E1 – Substitution Electrophilic Unimolecular - formally related to a carbanion as S_N1 is to a carbocation

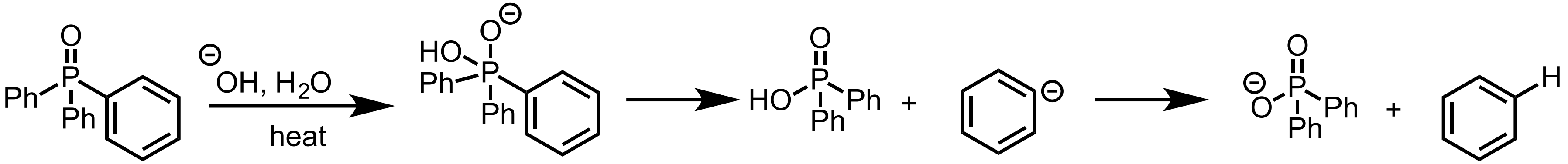
- generic mechanism



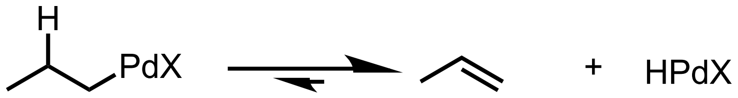
- examples

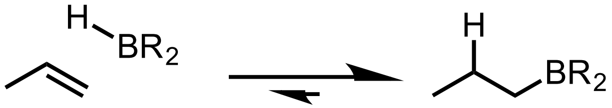




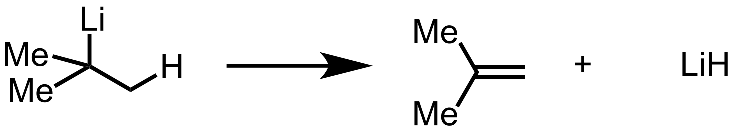


- β-hydride elimination from carbanions common for transition metals
- reverse reaction is hydrometallation – well known from hydroboration chemistry

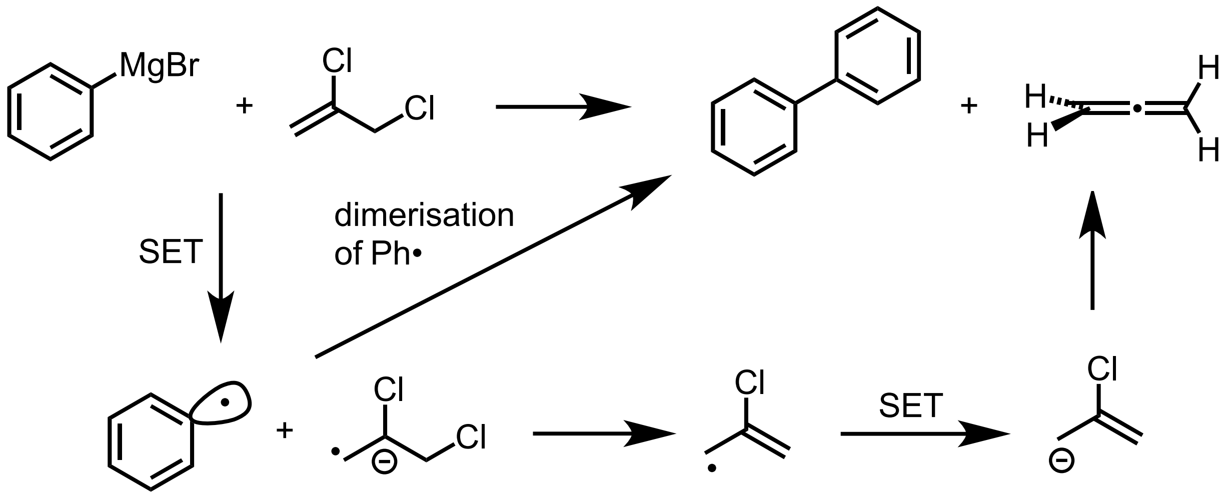




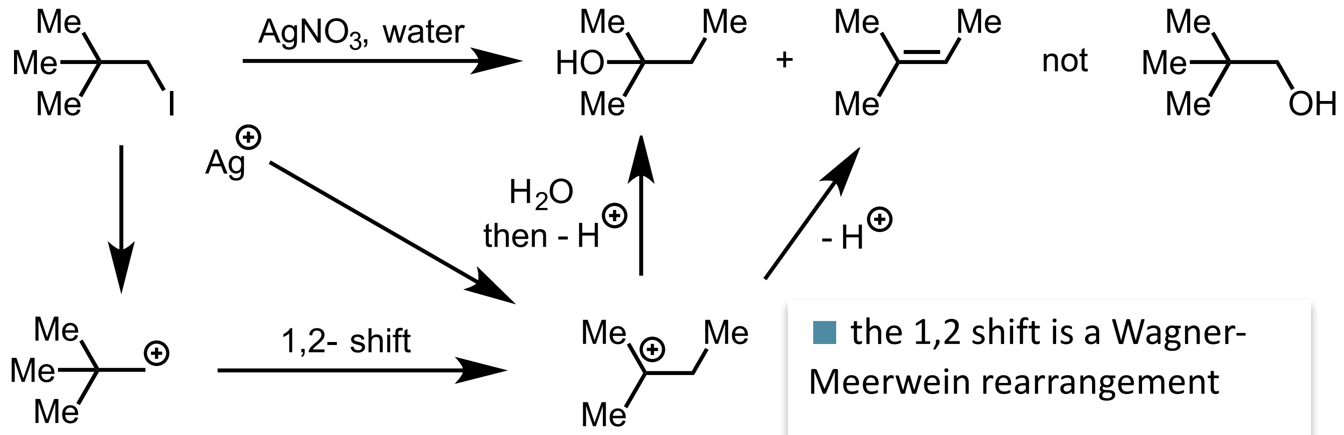
- not a common reaction for Grignard reagents or organolithiums; however, β-hydride elimination is a decomposition pathway for organolithiums and *tert*-butyllithium can act as a source of hydride



- redox reactions – Single Electron Transfer - SET

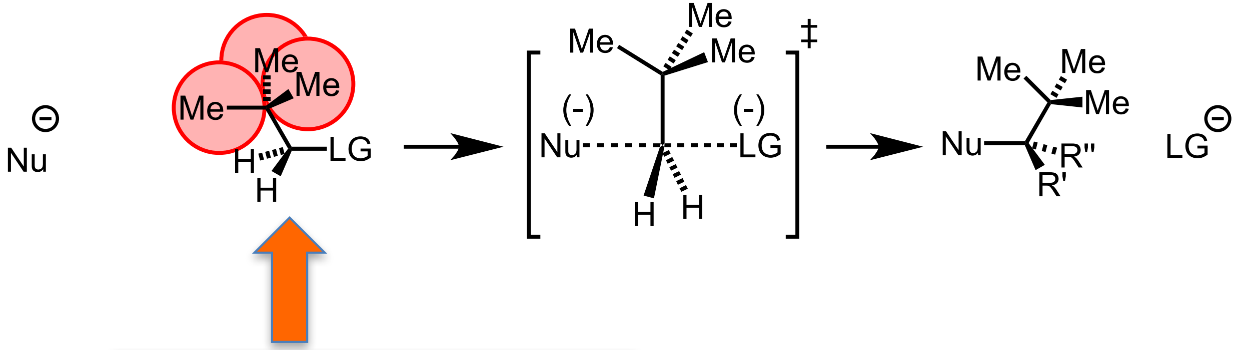


- rearrangement of carbocations
- the neopentyl system



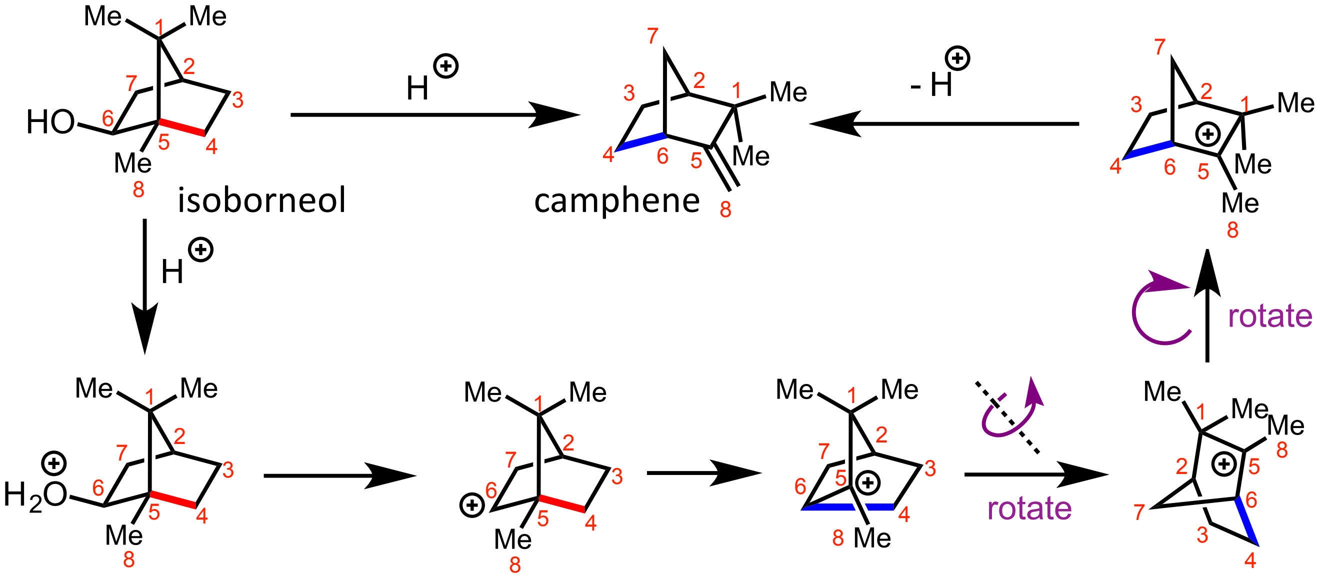
- the 1,2 shift is a Wagner-Meerwein rearrangement

- as an aside, remember that neopentyl systems, although primary, are unreactive under S$_N$2 conditions as the nucleophile is severely hindered from attacking the necessary carbon atom



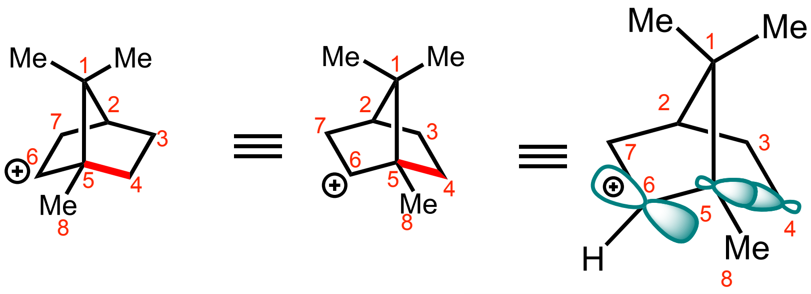
- staggered conformation requires nucleophile to approach passed one of the methyl groups

Wagner-Meerwein rearrangements exemplified



- secondary carbocation
- tertiary carbocation

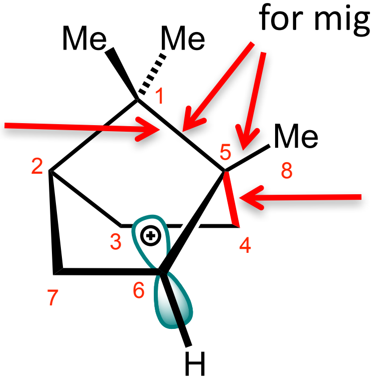
- overall red bond is broken and blue bond is formed
- in general alkyl shifts occur to yield a more stable carbocation
- best orbital overlap is also important in determining which group migrates



- orbital overlap $\sigma_{C\text{-}C}$ into empty p-orbital

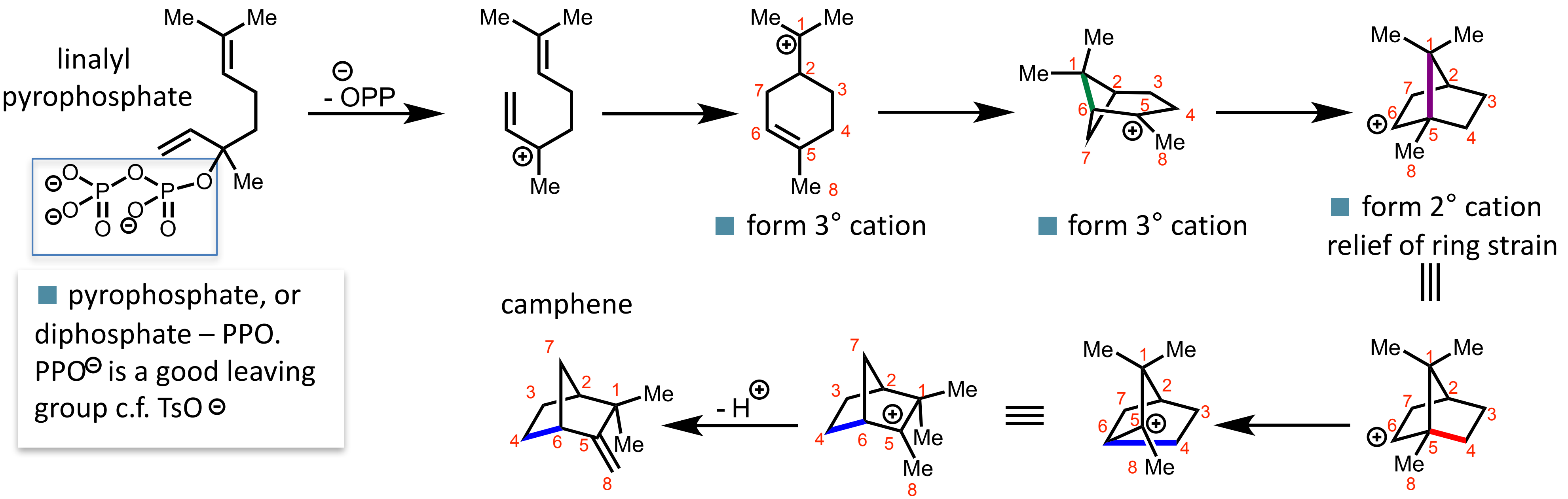
migration would lead to 4-membered ring

poor orbital overlap for migration



best orbital overlap for migration (ca. co-planar)

- Wagner-Meerwein rearrangements exemplified – Nature was here before us – biosynthesis of camphene



linalyl pyrophosphate

- form 3° cation

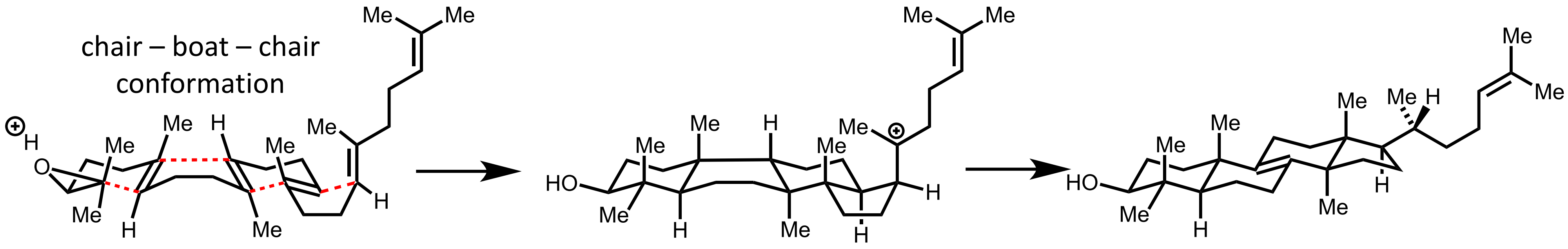
- form 3° cation

- form 2° cation relief of ring strain

camphene

- pyrophosphate, or diphosphate – PPO. PPO⊖ is a good leaving group c.f. TsO⊖

- Wagner-Meerwein rearrangements exemplified – Nature was here before us – biosynthesis of lanosterol (precursor of cholesterol)



chair – boat – chair conformation

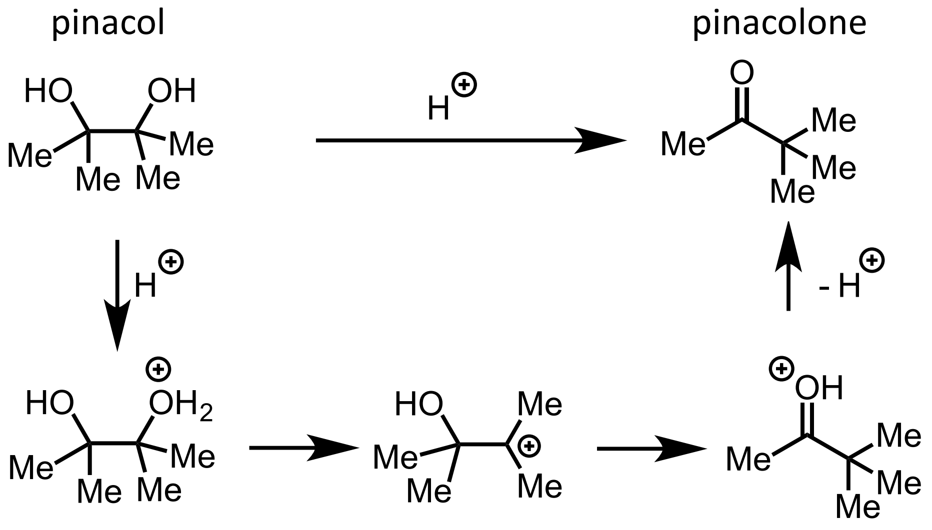
squalene oxide

two 1,2-hydride shifts
two 1,2-methyl shifts

lanosterol

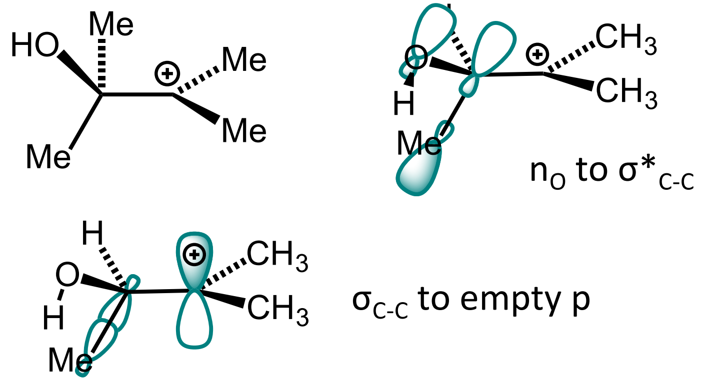
- conformation of squalene oxide controlled by enzyme (lanosterol synthase) – reaction occurs via discrete carbocation intermediates and is not concerted

- Pinacol and semi-pinacol rearrangements

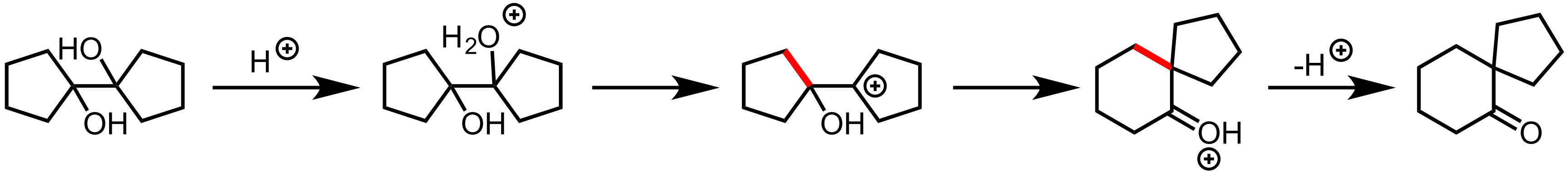


- mechanism in more detail

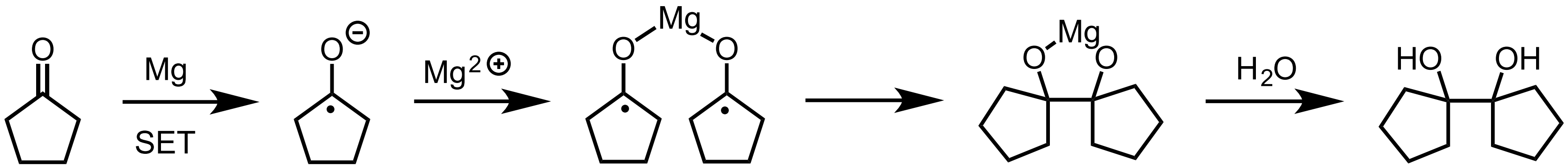
correct orbital overlap required for migration



- useful method for the preparation of spirocyclic ketones.

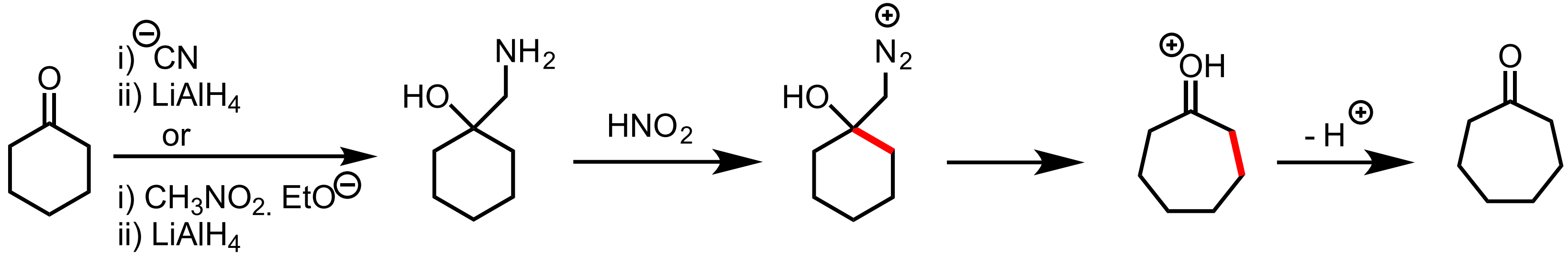


- the starting diols can be readily prepared by the pinacol reaction

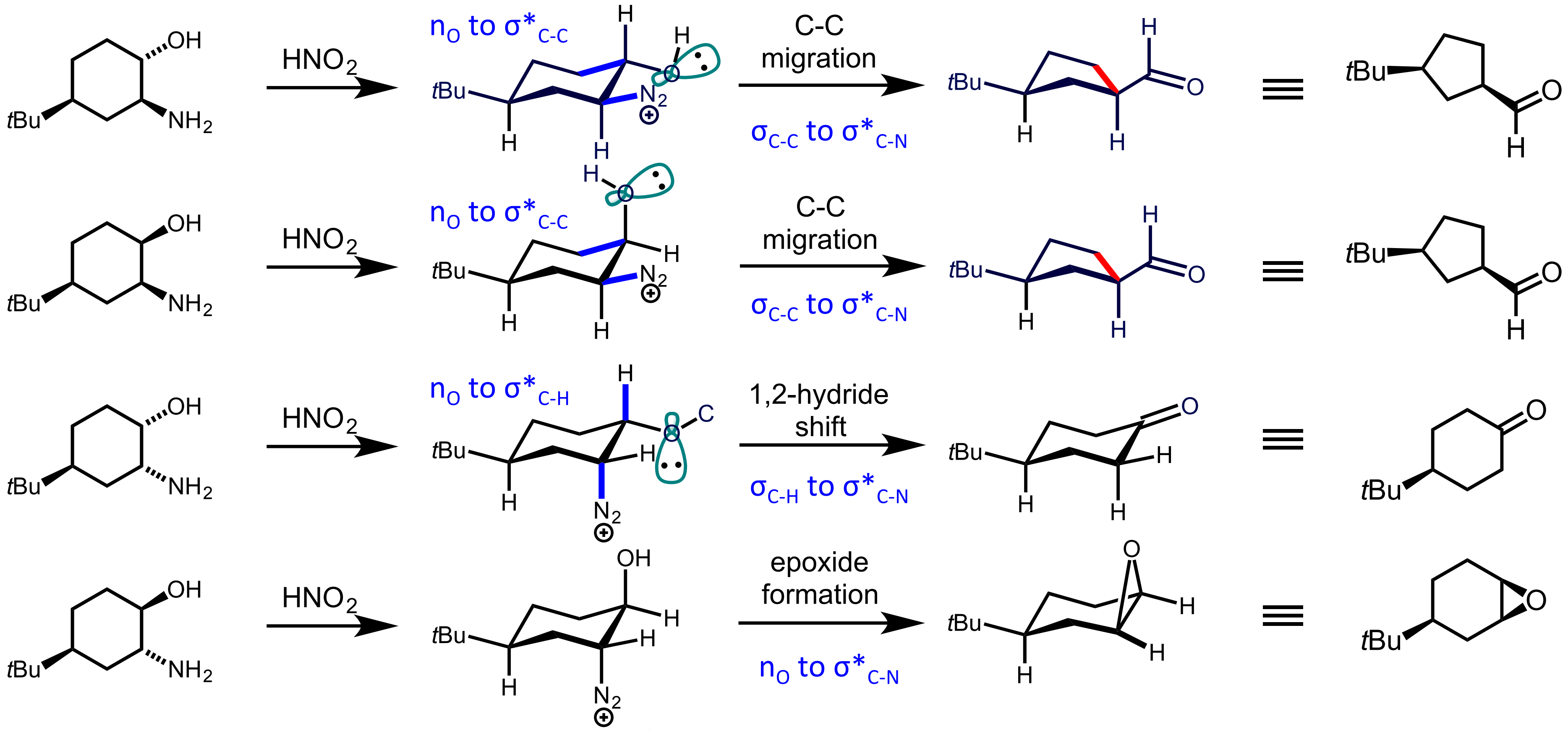


- epoxides and halohydrins can be substrates for the pinacol rearrangement

- semi-pinacol rearrangements – the Tiffeneau-Demayanov reaction

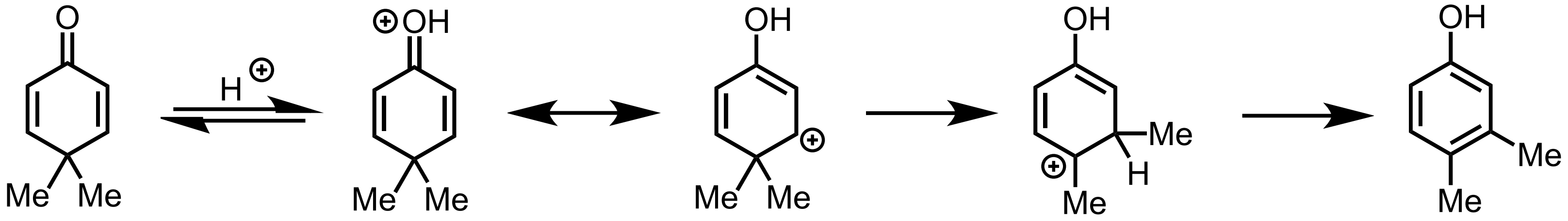


- semi-pinacol rearrangements - stereochemistry

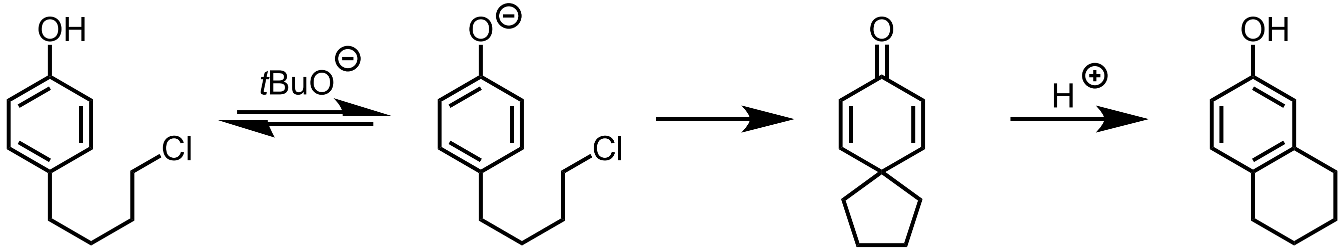


- anti-periplanar bonds means best overlap of σ and σ* orbitals

- the dienone-phenol rearrangement – formally the reverse of the pinacol rearrangement
- the dienone-phenol rearrangement can be mechanistically complex but can also just involve a simple 1,2-shift of an alkyl group

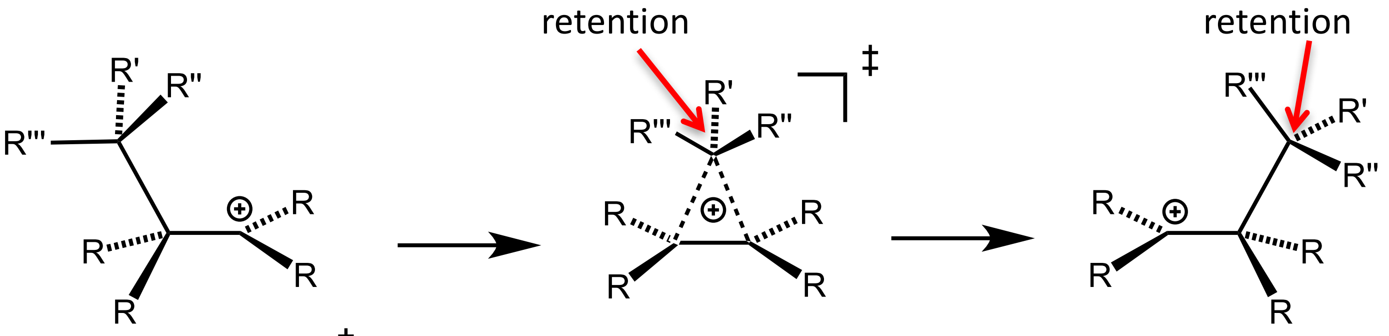


- the pinacol rearrangement is driven by formation of a strong C=O bond
- the dienone-phenol rearrangement involves loss of a C=O bond and gain of an aromatic ring
- the dienone-phenol rearrangement provides a method for ring annulation

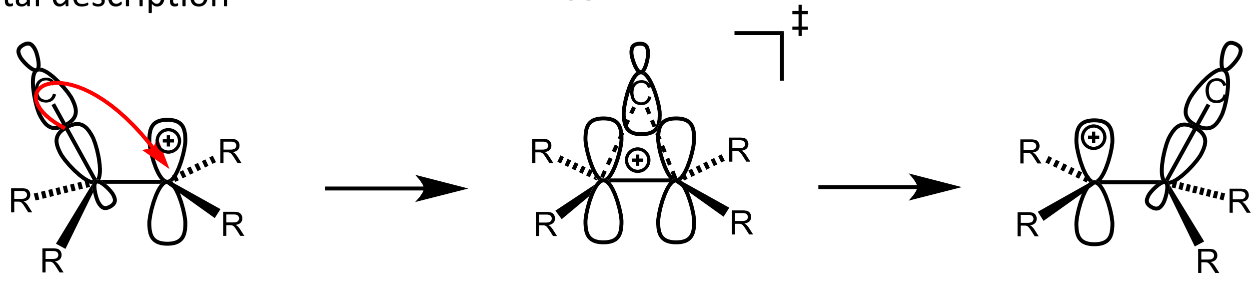


Theory of 1,2-shifts

- curly arrow mechanism

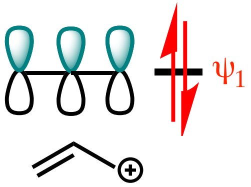


- orbital description

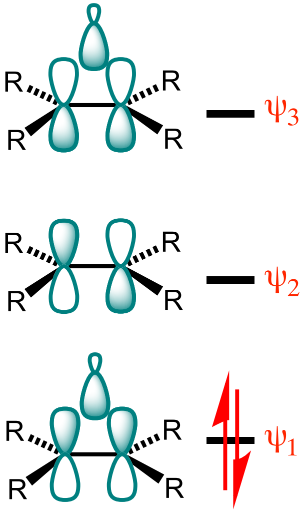


- 3-centre-2-electron system at the transition state

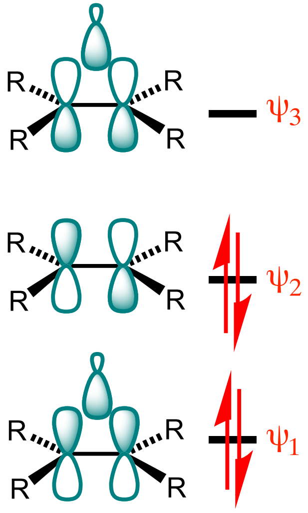
- in the transition state we have three orbitals and two electrons to distribute c.f. the allyl cation



allyl cation

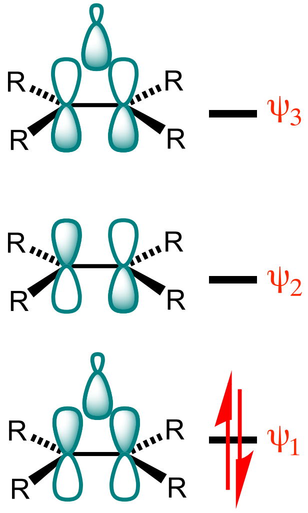


1,2-shift transition state
(carbocation)



1,2-shift transition state
(carbanion)

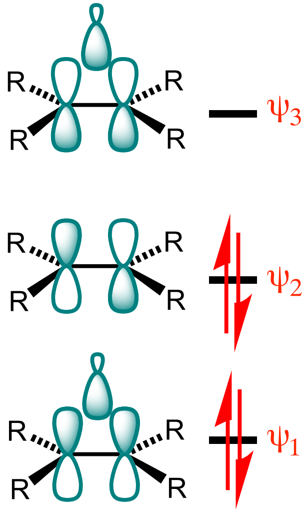
- 1,2-cation and 1,2-anion shifts



1,2-shift transition state carbocation

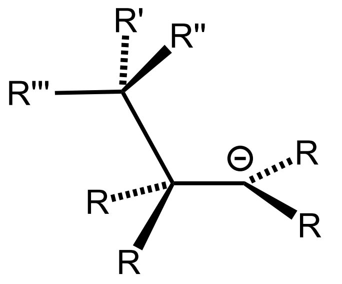
- overall for carbocation 1,2-shift, transition state has net bonding
- the transition state has 2 electrons cyclically conjugated in a ring and is therefore aromatic – more of this next year
- 1,2-shifts occur with retention of configuration in the migrating group
- the 3-centre-2-electron structure may be a transition state or a high energy intermediate
- as we have seen, concerted migration with loss of the leaving group is another mechanistic possibility

- *take home message* – 1,2-shifts easy for carbocations, difficult for carbanions and radicals



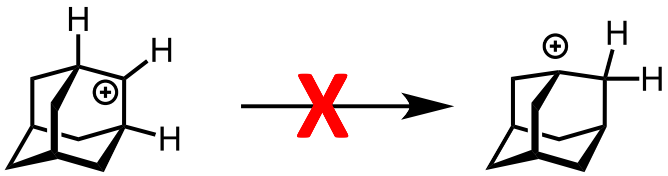
1,2-shift transition state carbanion

- both ψ_2 and ψ_3 are antibonding
- therefore 1,2-shifts of carbanions and radicals would be expected to be far less favourable (ψ_2 is occupied)
- transition state for 1,2-shift of carbanions has 4 electrons cyclically conjugated ($\psi_1^2\psi_2^2$) in a ring and is anti-aromatic
- one can also view the difficulty of 1,2-carbanion shifts arising from the geometrical impossibility of the carbanion performing an intramolecular S_N2 reaction with inversion of configuration

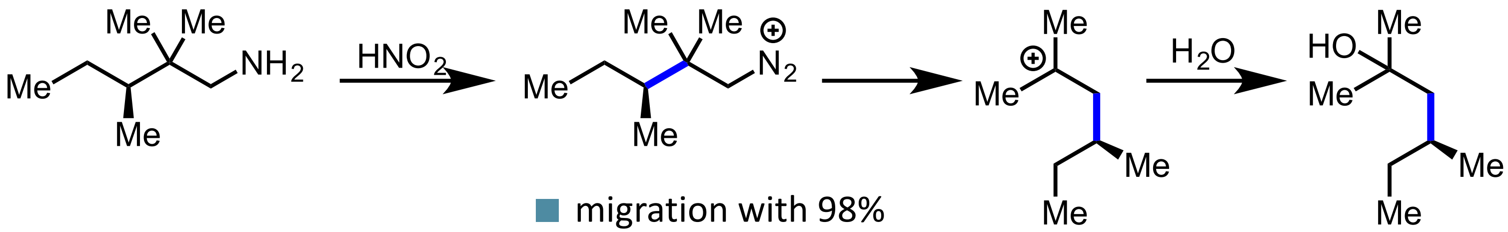


- as we have seen, for efficient rearrangement orbital alignment is critical

- all three indicated hydrogen atoms are in the same plane - rearrangement to the more stable 3° carbocation does not occur

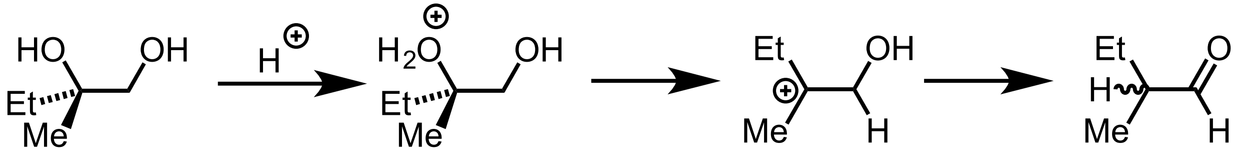


- retention of configuration at the migrating centre is observed



- migration with 98% retention of configuration

- at the migrating terminus inversion or racemisation can occur
- racemisation will occur if the mechanism is S$_N$1-like i.e. *via* a full carbocation



enantiopure

racemic

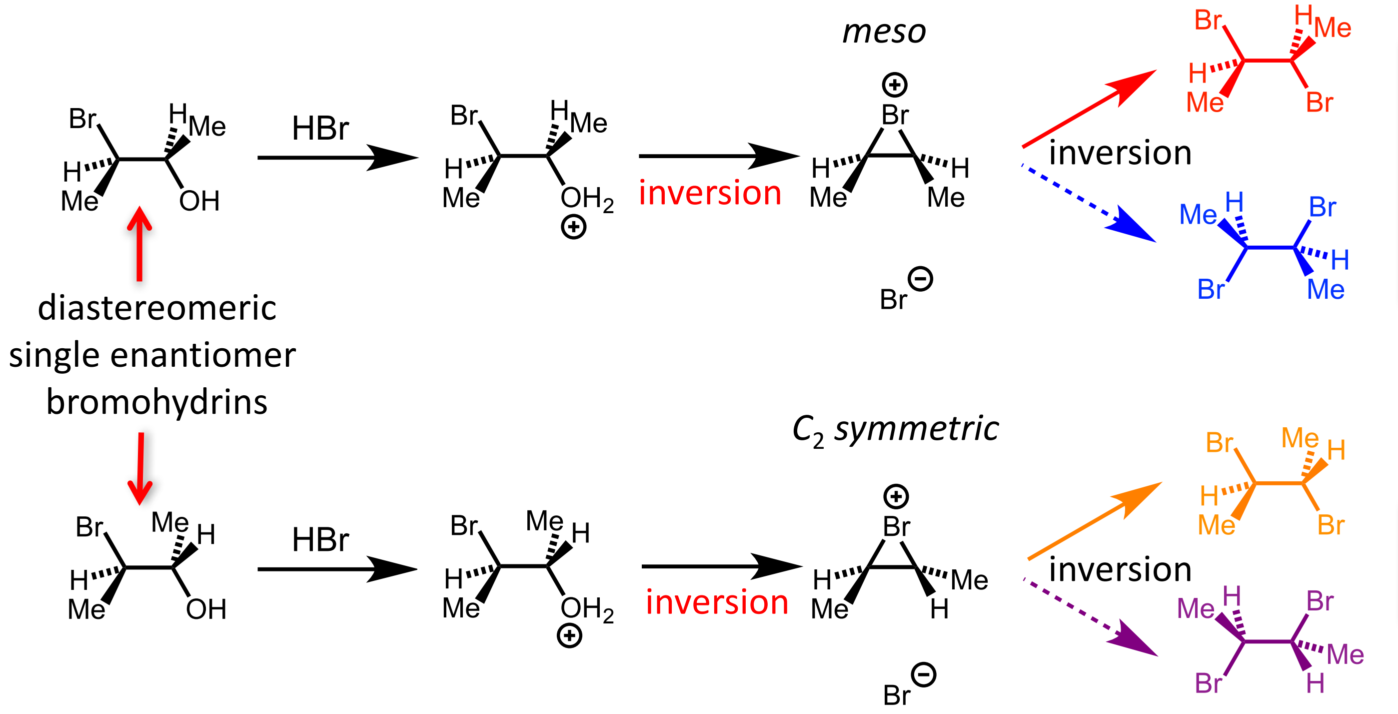
- inversion at the migrating terminus will occur if the mechanism is concerted

Concerted Rearrangements

- Neighbouring group participation (**NGP**)

Definition (IUPAC): the direct interaction of the reaction centre (usually, but not necessarily, an incipient carbenium centre) with electrons contained within the parent molecule *but not conjugated* with the reaction centre – could be lone pair, π-bond, or σ-bond

A rate increase due to neighbouring group participation is known as 'anchimeric assistance'
neighbouring group participation and anchimeric assistance are often used interchangeably



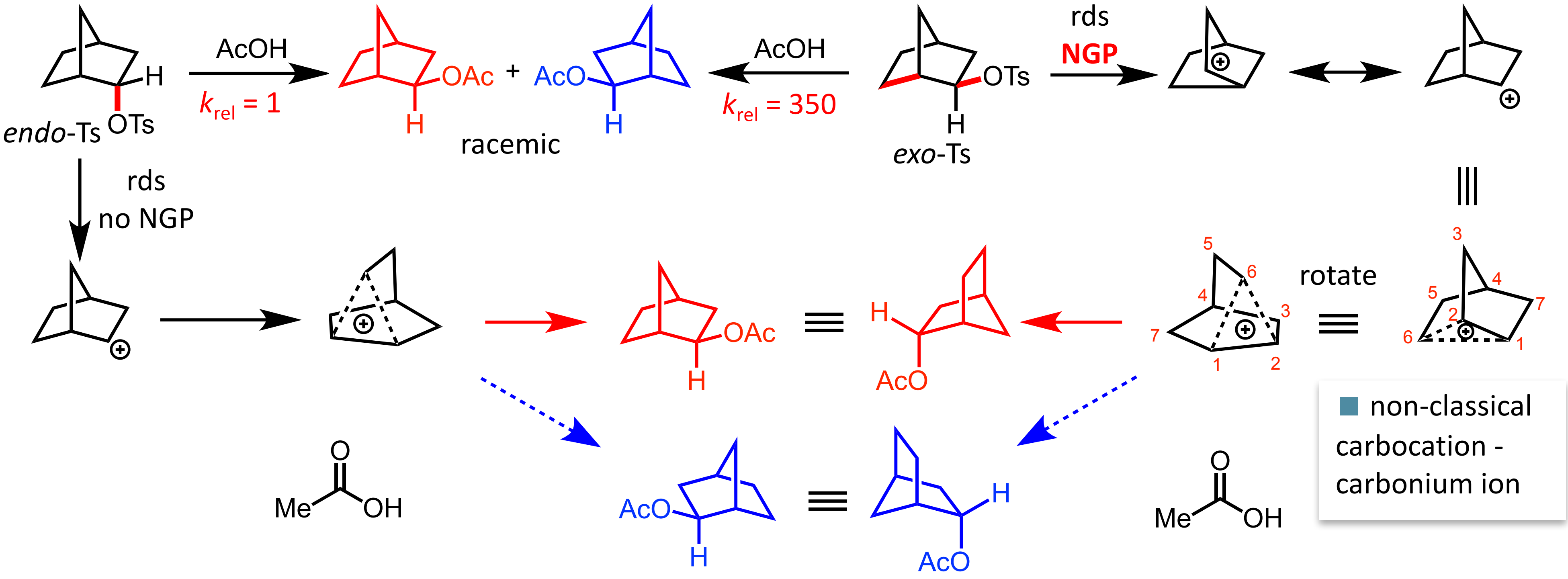
diastereomeric
single enantiomer
bromohydrins

- enantiomers
same relative
configuration as
starting material
racemic product

- same structure
meso - achiral

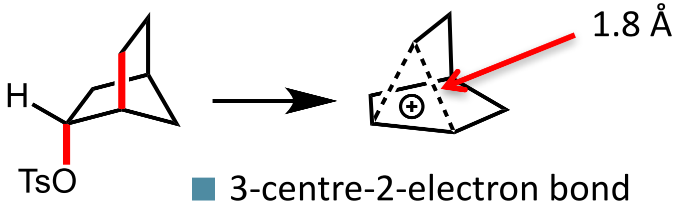
- outcome of above reactions is excellent evidence for symmetrical intermediates and hence neighbouring group participation

- why do these single enantiomer tosylates undergo solvolysis at significantly different rates to give the same racemic product?
- non-classical carbocations, A.K.A. carbonium ions



- non-classical carbocation - carbonium ion

- alternative perspective of **NGP**



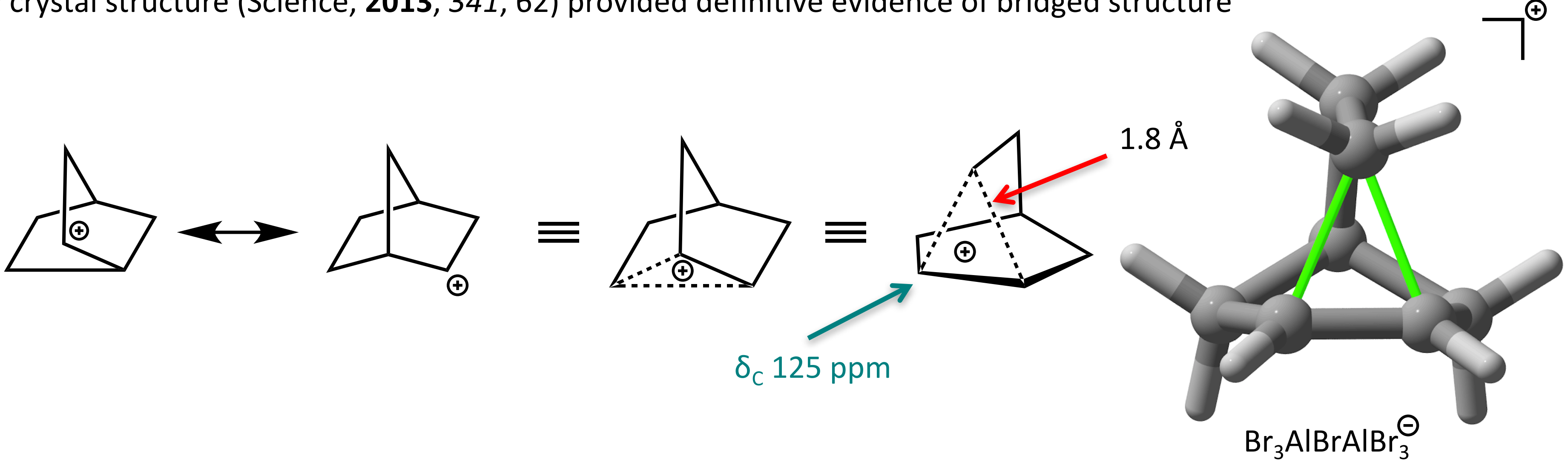
- 3-centre-2-electron bond

- *exo*-Ts reacts faster due to NGP of antiperiplanar C-C sigma bond
- *endo*-Ts ionises slower to give classical carbocation followed by non-classical carbocation formation
- non-classical cation has plane of symmetry leading to racemic products

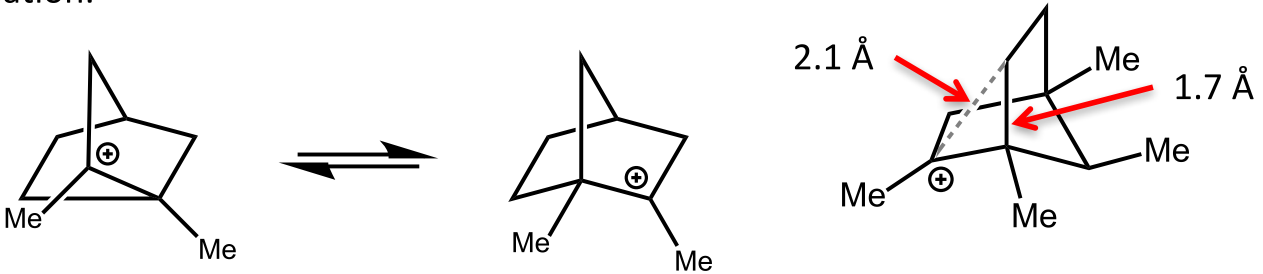
- evidence for non-classical carbocation (carbonium ion) over equilibrating carbenium ions for the 2-norbornyl cation i.e. is the non-classical cation an intermediate or TS?

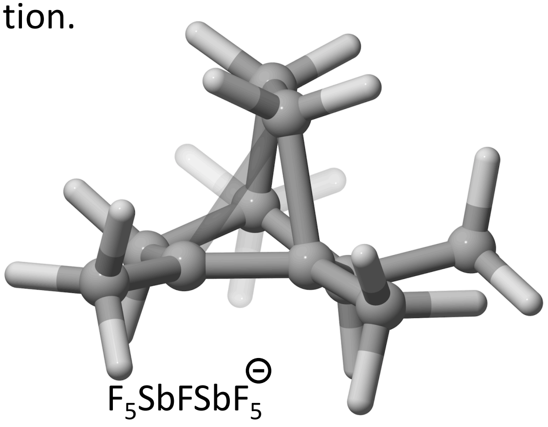
- low temperature ^{13}C NMR (5 K) shows a symmetrical ion

- X-ray crystal structure (Science, **2013**, *341*, 62) provided definitive evidence of bridged structure

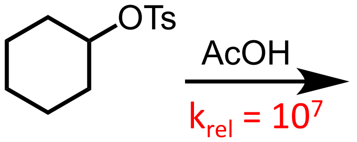


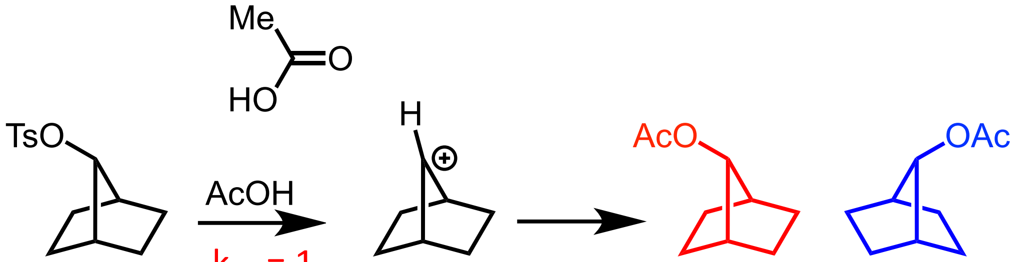
- *Note:* non-classical carbocations are only formed if they are ***more*** stable than their classical counterparts
- The 1,2-dimethylnorbornyl cation is a rapidly equilibrating species with partial σ-delocalisation.
- X-ray structure of the analogous tetramethylnorbornyl cation also demonstrates partial σ-delocalisation.





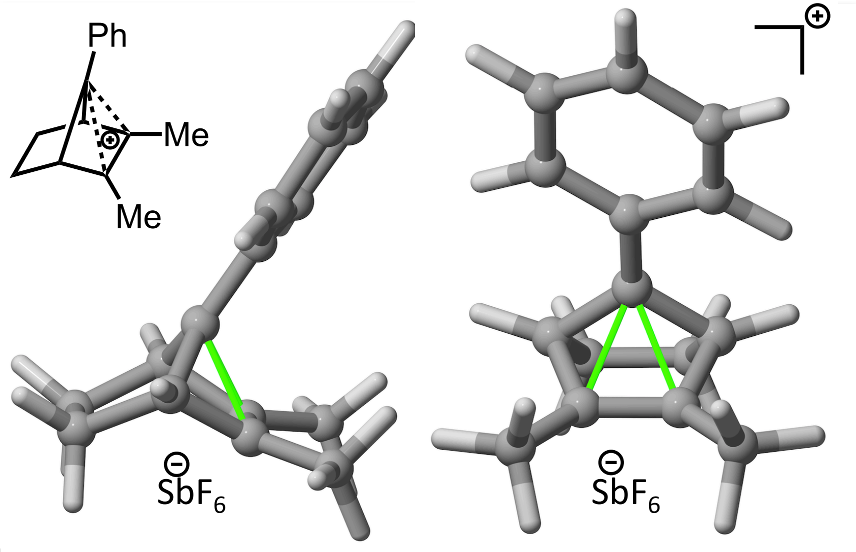
- π-bonds are better donors than σ-bonds



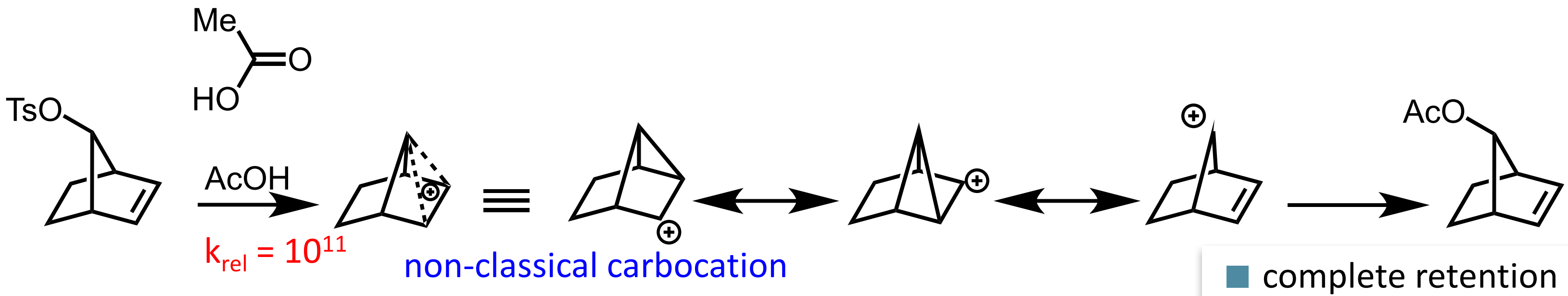


classical carbocation
(carbenium ion)

- same structure

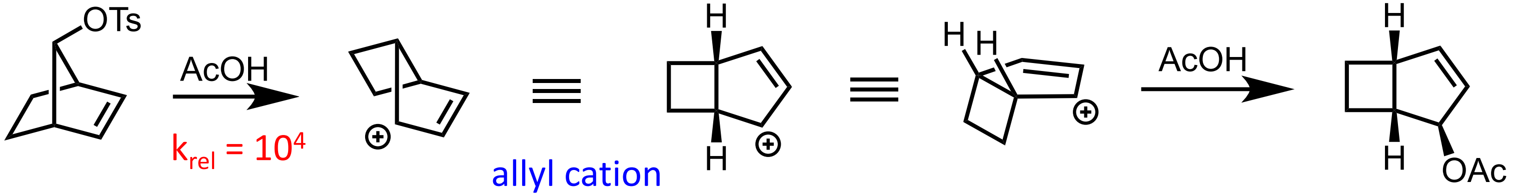


J. Am. Chem. Soc., **1989**, 111, 9224



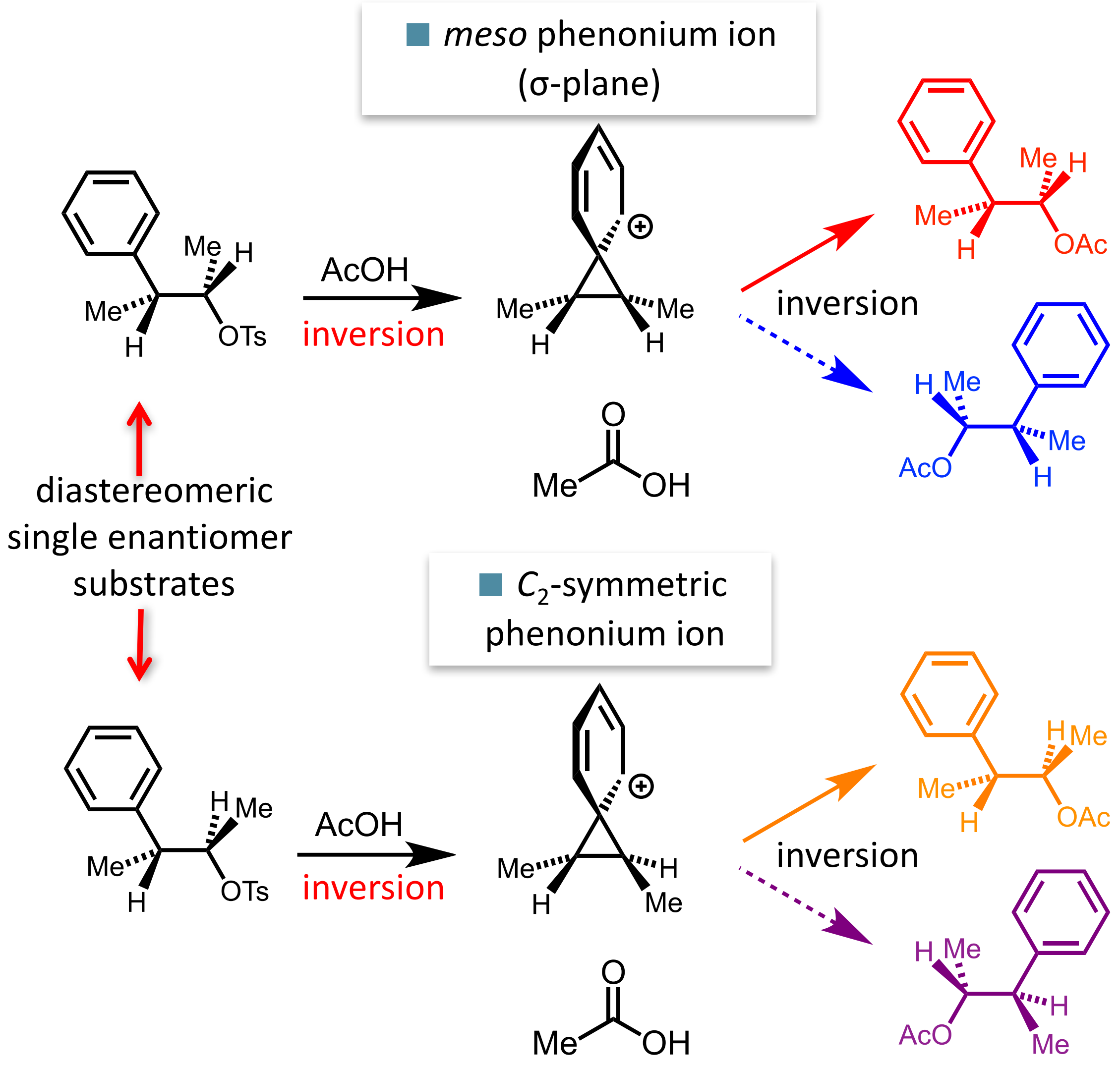
non-classical carbocation
(carbonium ion)

- complete retention of configuration (double inversion)



allyl cation

- More neighbouring group participation with π-bonds – phenonium ions

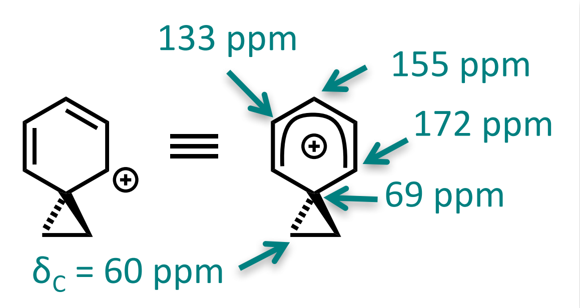


- *meso* phenonium ion (σ-plane)

diastereomeric single enantiomer substrates

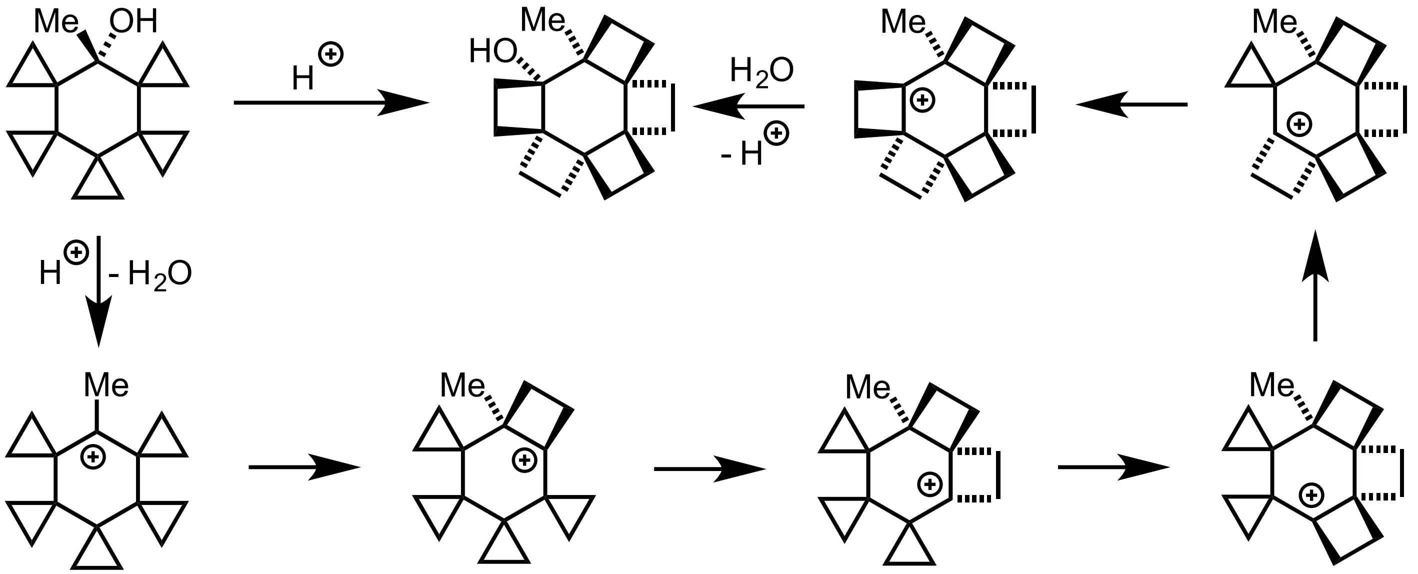
- C_2-symmetric phenonium ion

- enantiomers *racemic product*

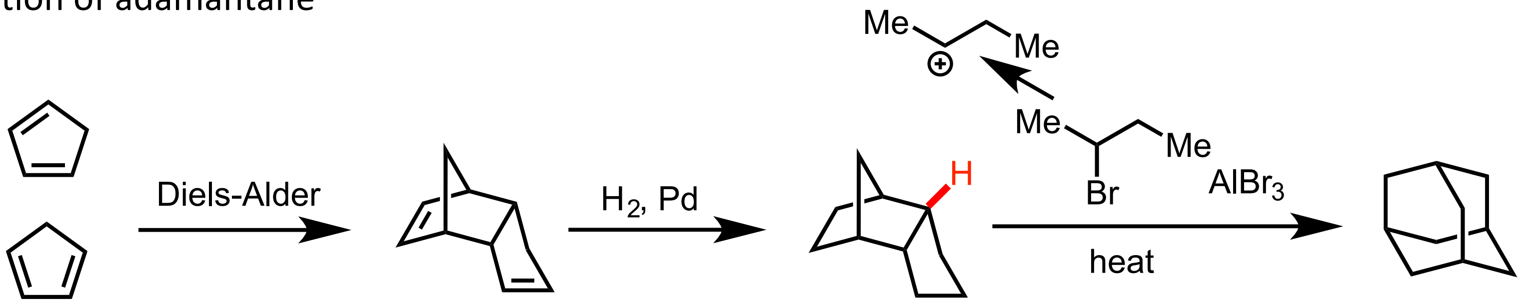


- same single enantiomer product

- multiple 1,2-shifts



- formation of adamantane

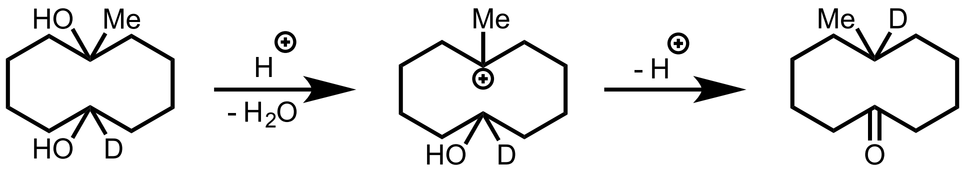


$C_{10}H_{16}$

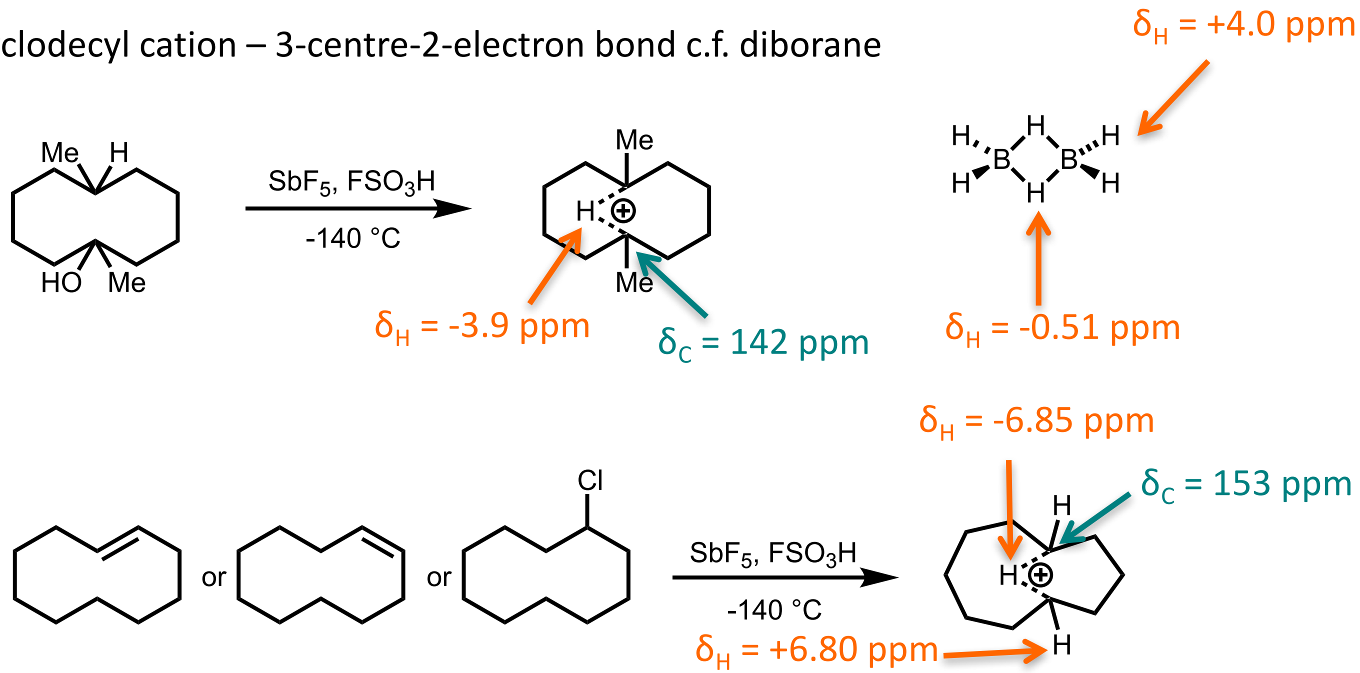
adamantane $C_{10}H_{16}$

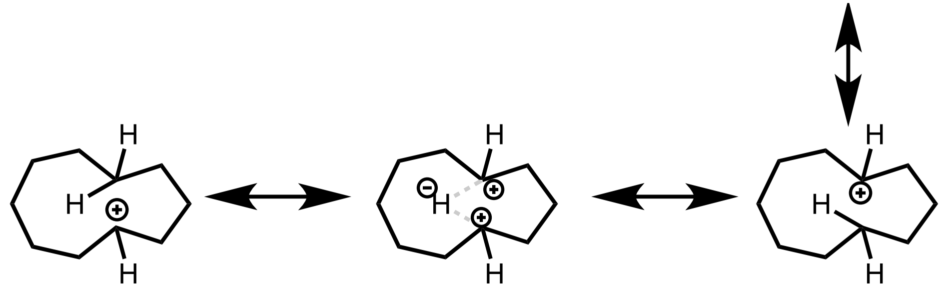
- all $C_{10}H_{16}$ hydrocarbons rearrange to adamantane on treatment with Lewis acid
- adamantane is the thermodynamically most stable $C_{10}H_{16}$ isomer – it possess repeating units of the diamond lattice

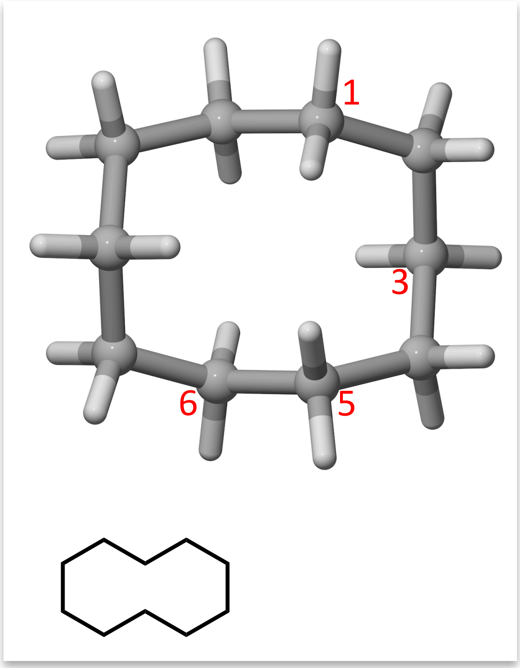
- transannular hydride shifts

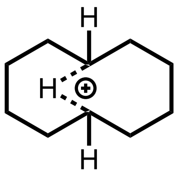


- cyclodecyl cation – 3-centre-2-electron bond c.f. diborane



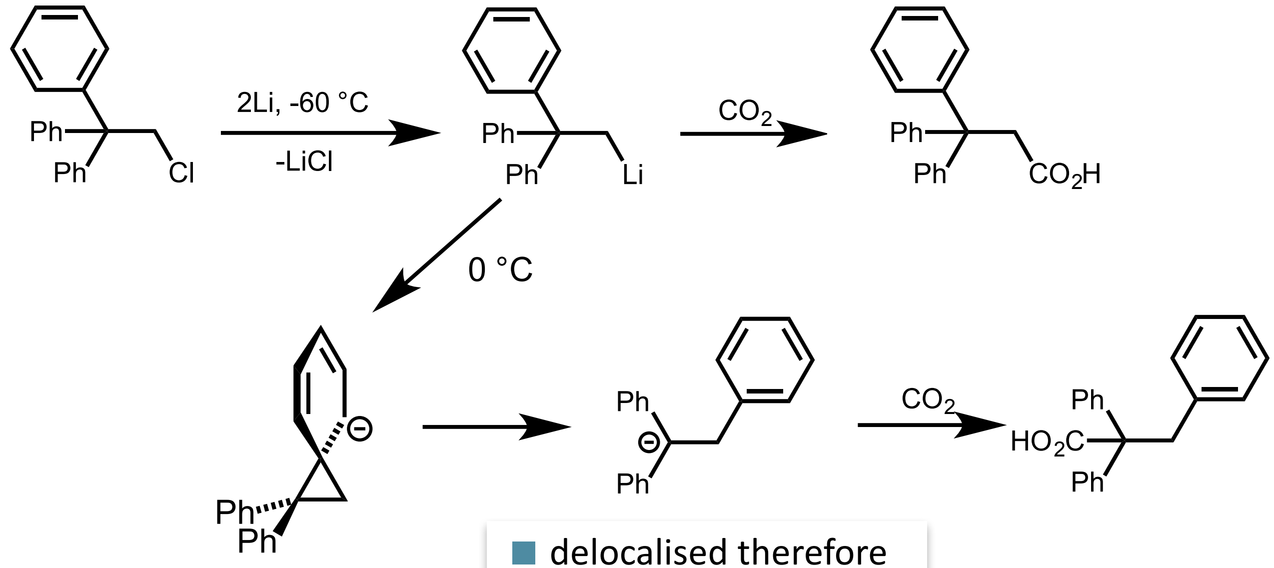




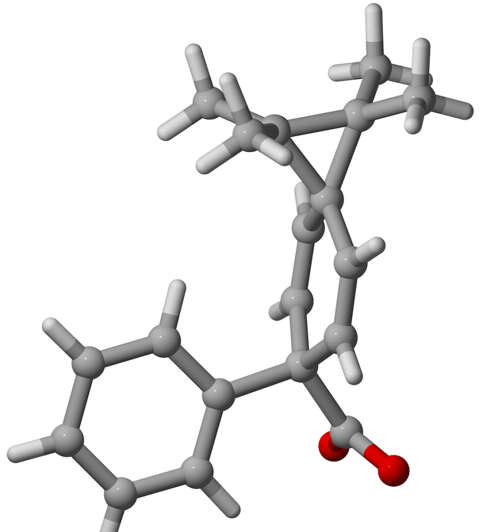


- 1,6-cation slightly higher in energy than 1,5-cation

- Carbanion rearrangements – carbanions are much less prone to rearrangement than carbocations
- 1,2-aryl shifts

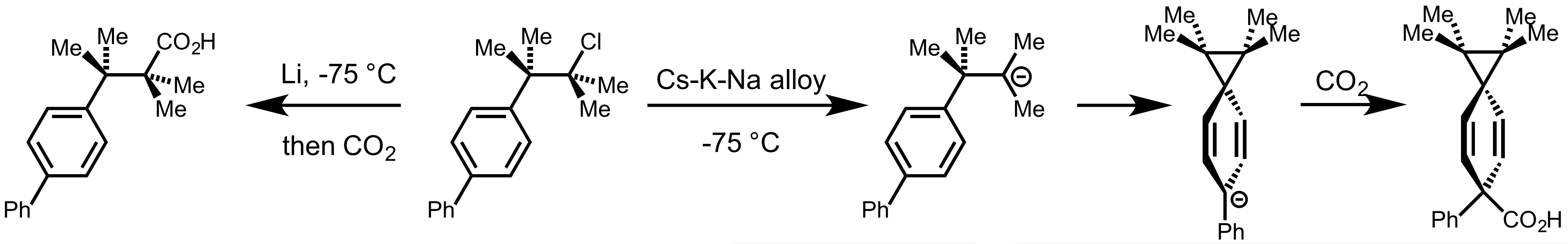


- delocalised therefore more stable carbanion



- X-ray structure

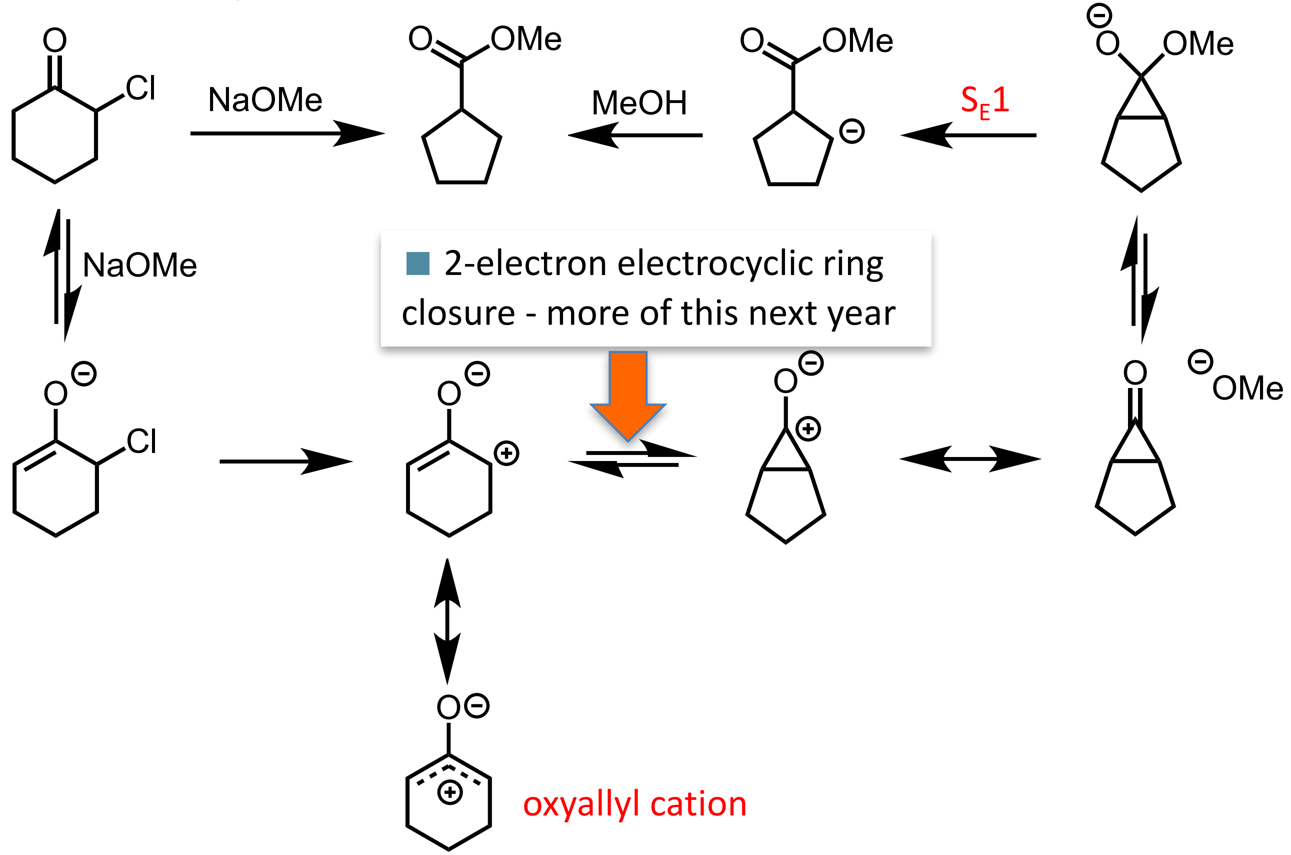
- evidence for spirocyclic intermediate



- 3° carbanion

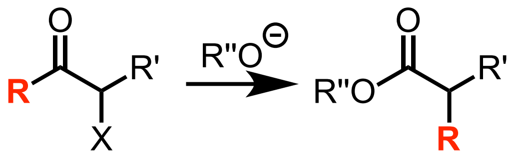
- delocalised, dearomatised carbanion more stable than 3° carbanion

■ Favorskii rearrangement

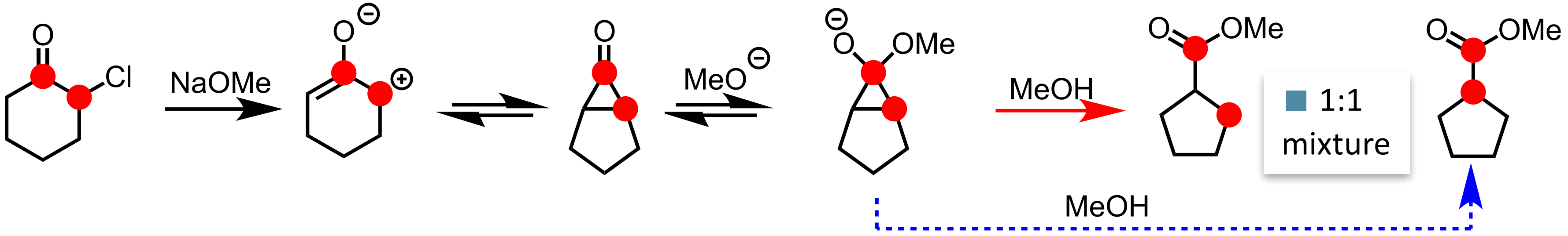


■ 2-electron electrocyclic ring closure - more of this next year

■ overall in the Favorskii rearrangement an alkyl group (**R**) moves from one side of the carbonyl group to the other

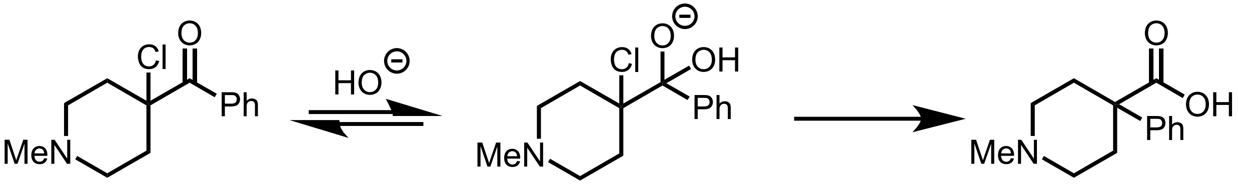


■ symmetrical intermediate established by Loftfield with doubly labelled substrate ● = ^{14}C label



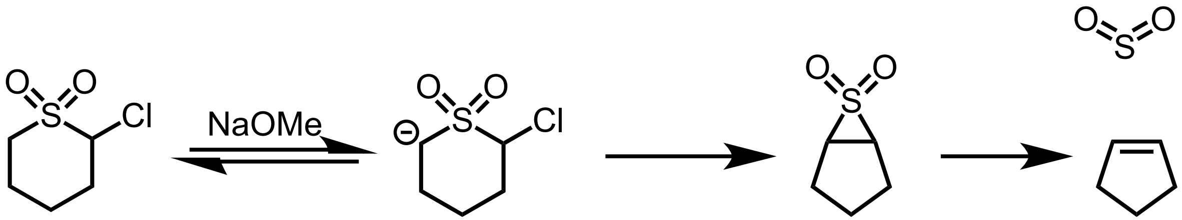
■ 1:1 mixture

- quasi-Favorskii rearrangement – Favorskii rearrangement on substrates with no enolisable hydrogen atoms



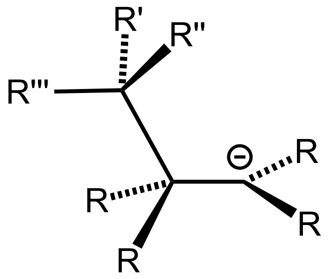
- the mechanism is a base catalysed semi-pinacol rearrangement and is closely related to the mechanism of the benzil-benzillic acid rearrangement

- Ramberg-Bäcklund reaction

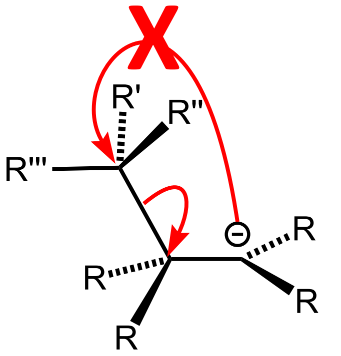


- cheletropic extrusion of SO_2 – more next year

- concerted 1,2-shifts of carbanions are geometrically impossible - as the carbanion cannot reach to perform an intramolecular S_N2 reaction with inversion of configuration

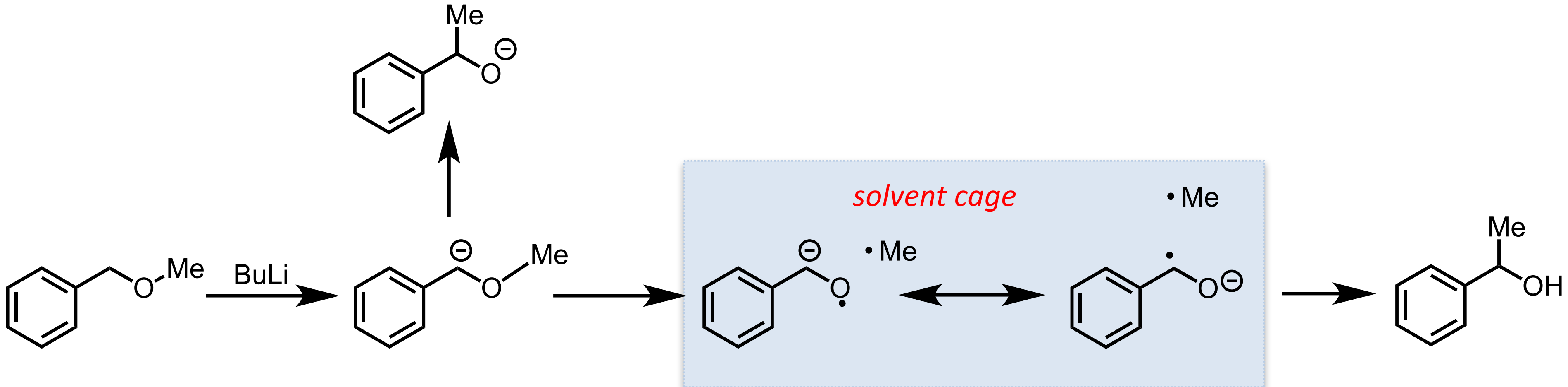


- Concerted 1,2-shifts of carbanions are geometrically impossible - as the carbanion cannot reach to perform an intramolecular S_N2 reaction with inversion of configuration

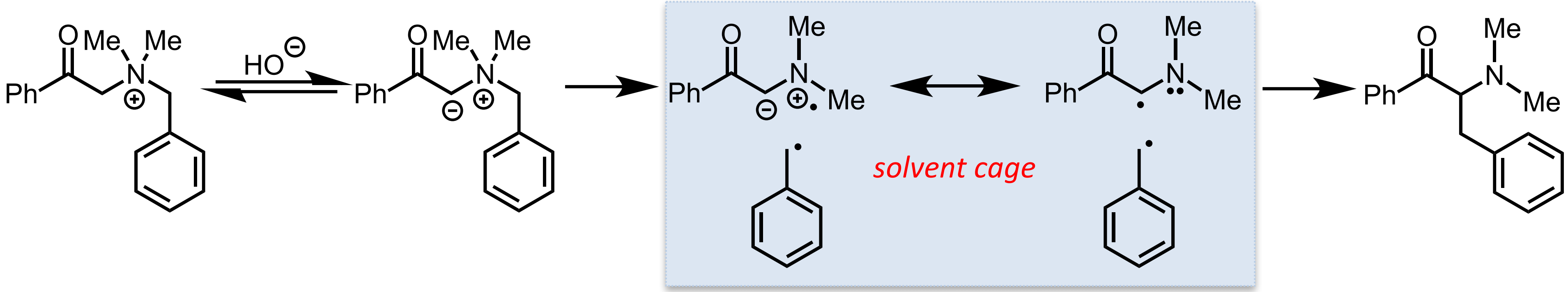


- 1,2-Shifts of carbanions occur by a radical mechanism – 1,2-Wittig, 1,2-Stevens and related rearrangements

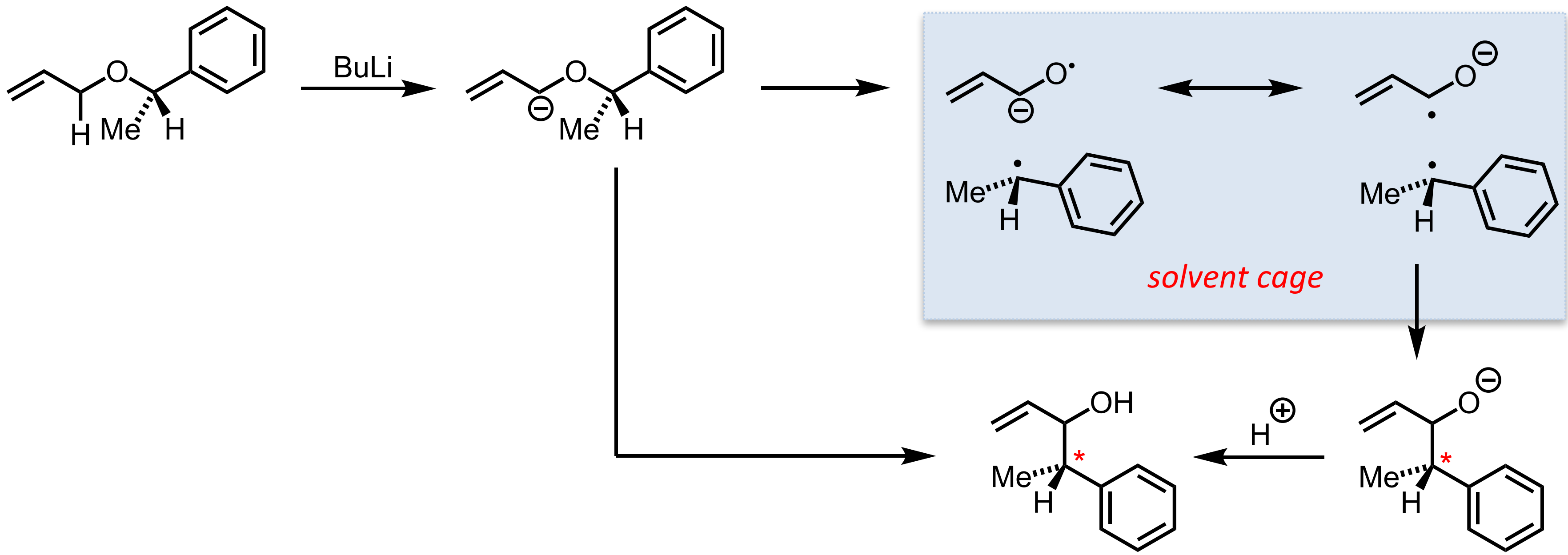
- 1,2-Wittig rearrangement



- Stevens rearrangement



- the 1,2-Wittig rearrangement occurs predominantly with retention of configuration in the migrating group

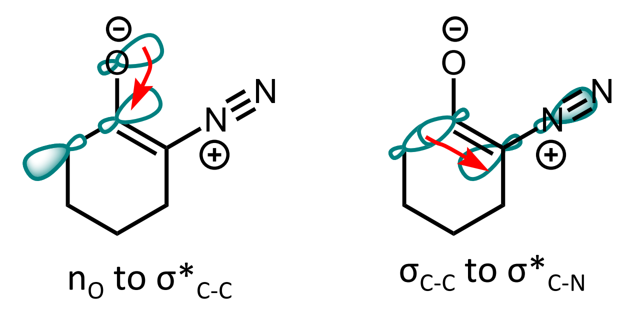


- predominant retention of configuration at the migrating centre *

Rearrangements and Reactive Intermediates

1A Organic Chemistry

Handout 2 - Carbenes and Nitrenes



Carbenes

- neutral divalent carbon species – 6 electrons around central carbon atom – highly reactive, generally electrophilic

- structure – singlet carbenes

- singlet carbenes have three electron pairs and an empty orbital to place around the central atom - a similar case to carbocations (carbenium ions)

- singlet carbenes are bent with the bond pairs and lone pairs in sp^2 hybridised orbitals, along with a vacant p-orbital

- typical bond angle range for singlet carbenes are 100° - 110°

- structure – triplet carbenes

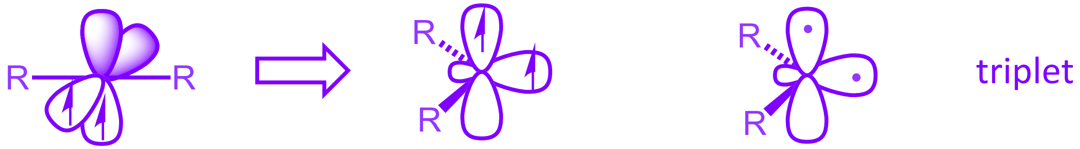
- triplet carbenes are bent with a typical bond angle range of 130° - 150°

- carbene structures from spectroscopy, in low pressure gas, and in low temperature matrix (<77 K)
  - electronic spectra with rotational structure
  - infra red analysis
  - electron spin resonance (for triplets)

- Why are triplet carbenes bent?

- imagine a linear geometry for the triplet carbene
  - there will be a central sp hybridised carbon atom with the two bonding pairs of electrons are in sp-hybrid orbitals (50% s-character)
  - the unpaired electrons are in the two orthogonal 2p orbitals

- this linear arrangement means that the unpaired electrons have no s-character – the more s-character the more stable the electron



- bending the linear state leads to one of the unpaired electrons gaining some s-character and being lowered in energy – here one of the p-orbitals becomes an sp^n hybrid orbital (a σ-orbtial)

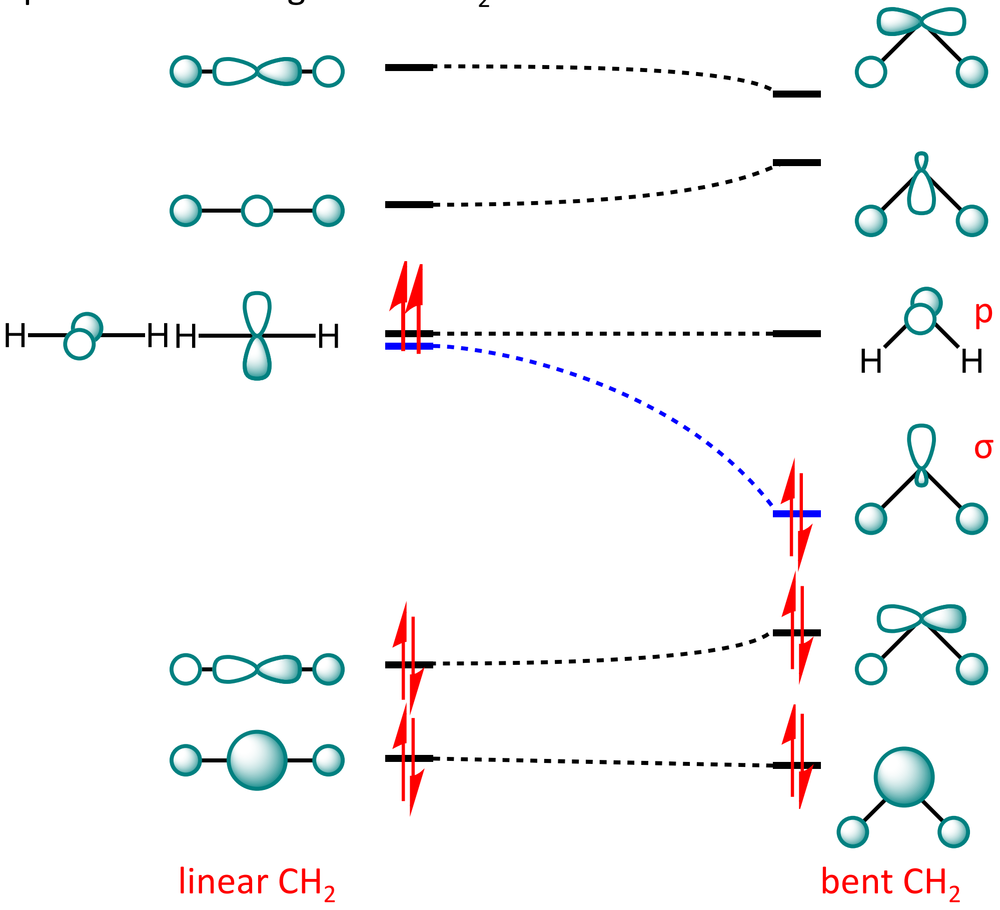
- the more bent the carbene is the greater the difference in energy between the p and σ-orbitals

- due to electron electron repulsion there is an energy cost in pairing electrons (Hund’s rule)

- if there is a small energy gap between σ and p-orbitals the electrons will remain unpaired i.e. triplet

- Walsh diagram for CH_2 gives a more sophisticated analysis and accounts for electronic structure of CH_2 – see Prof McGrady “Bonding in Molecules” course 2nd year

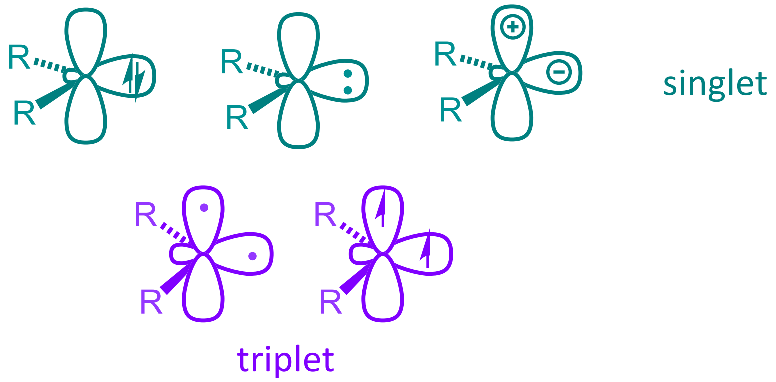
- simplified Walsh diagram for CH_2



- beginning with linear CH_2, MO diagram predicts a triplet ground state

- slight bending should be stabilising as one of the electrons is now in a bonding MO

- with further bending, the lower energy of the bonding MO overcomes electron-electron repulsion and the singlet carbene becomes more stable

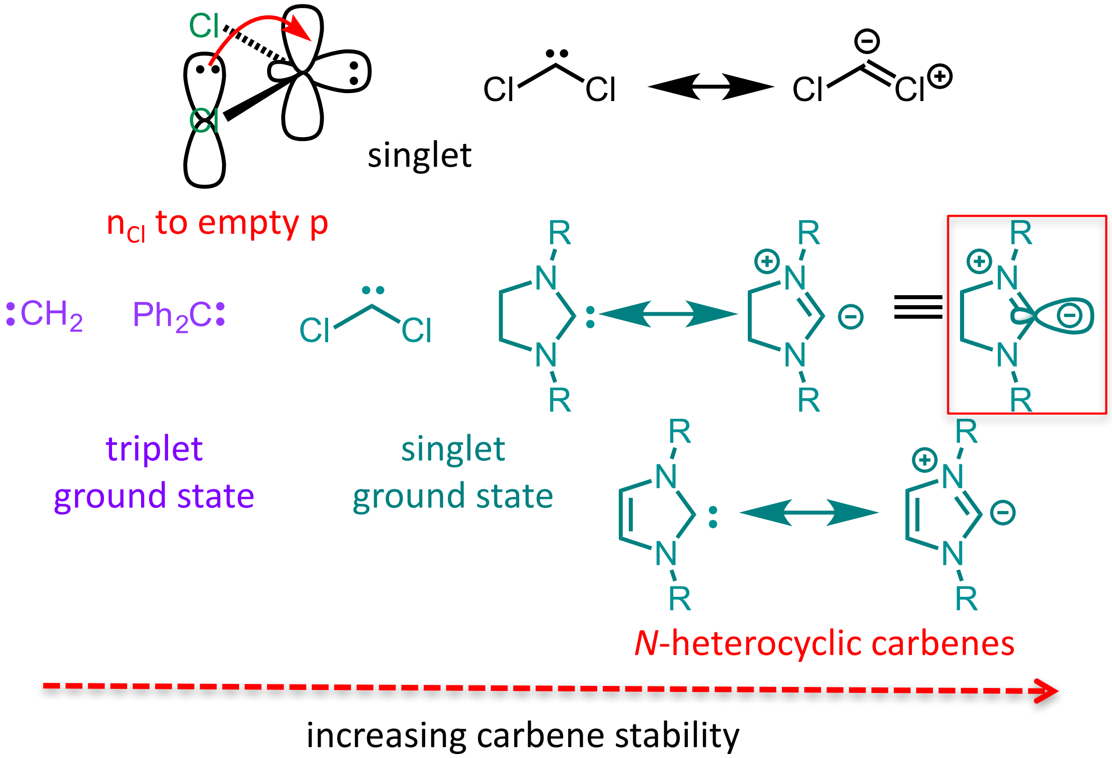


- *take home message* – triplet carbenes and singlet carbenes are bent – we will consider them both to be sp^2 hybridised
- triplet carbenes have a larger bond angle than singlet carbenes
- the above representations are adequate for our purposes
- neither Walsh diagram nor hybridisation allows us to predict the ground state for any particular carbene

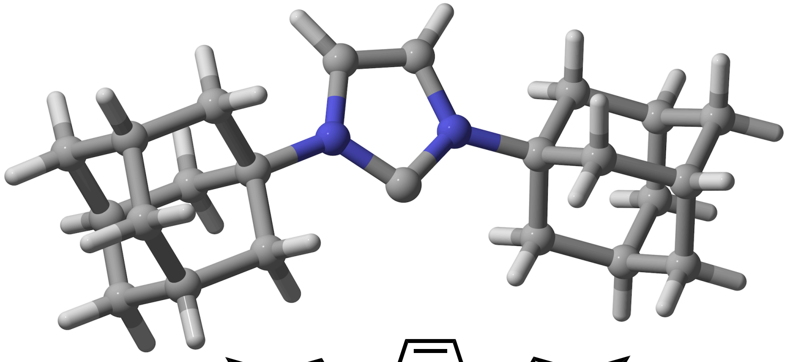
- methylene (CH_2) has a triplet ground state – the singlet state is ca. 38 $kJmol^{-1}$ higher in energy

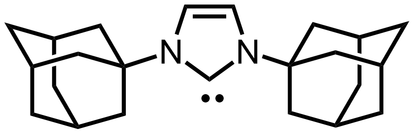
- dialkylcarbenes, arylalkylcarbenes and some diarylcarbenes have triplet ground states

- heteroatom substituted carbenes have singlet ground states due to delocalisation

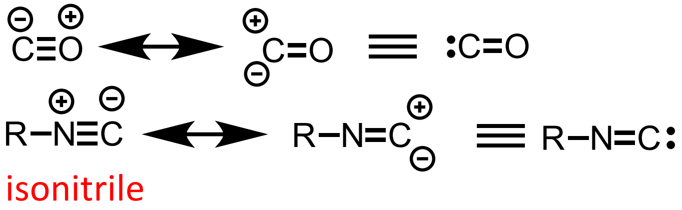


- first X-ray structure of a carbene (*J. Am. Chem. Soc.*, **1991**, *113*, 361).



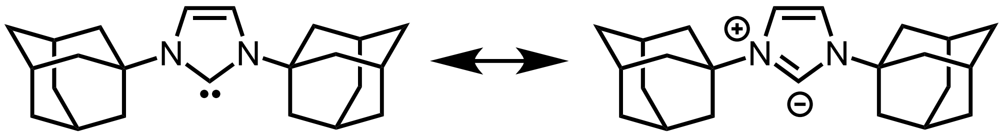


- carbene or ylid? c.f.

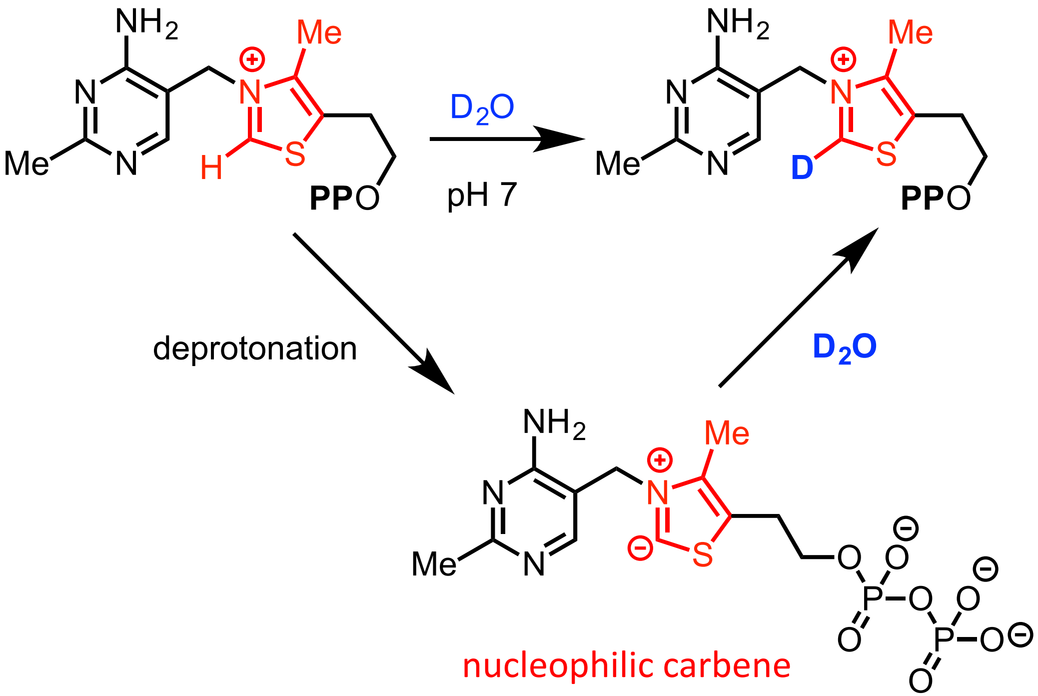


- the majority of carbenes are electrophilic – there are six electrons around the central carbon and hence they are electron deficient

- *N*-heterocyclic carbenes (and related carbenes) are nucleophilic - they are widely used as ligands for transition metals

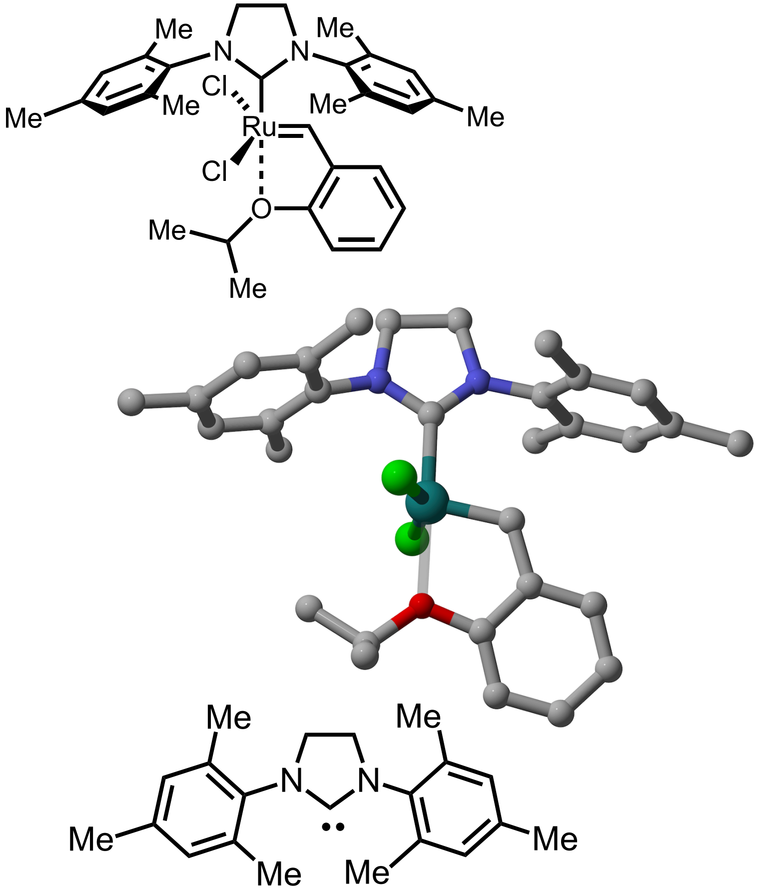


- Nature was here before us with nucleophilic carbenes – thiamine pyrophosphate (vitamin B1) – more next year

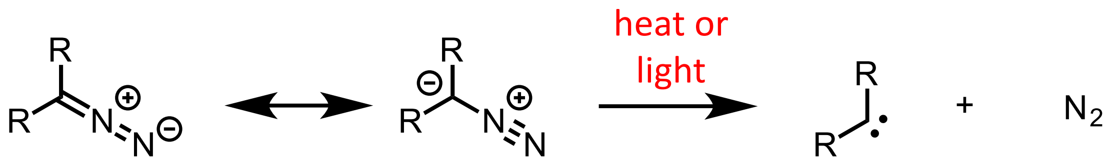


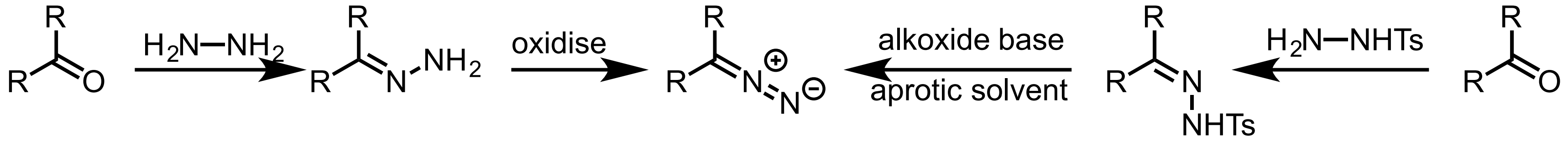
nucleophilic carbene

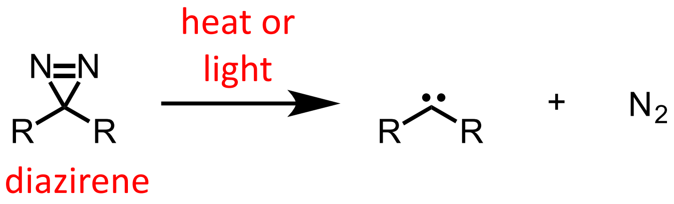
- Grubbs-Hoveyda 2nd generation metathesis catalyst (*J. Am. Chem. Soc.*, **2000**, *122*, 8168) – more next year

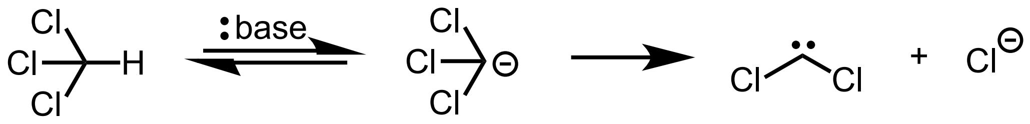


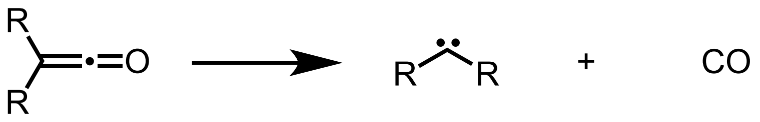
- some methods for carbene formation

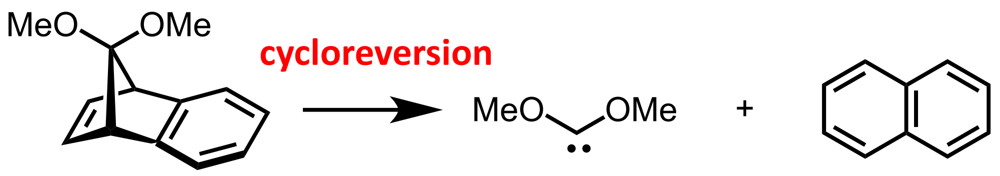












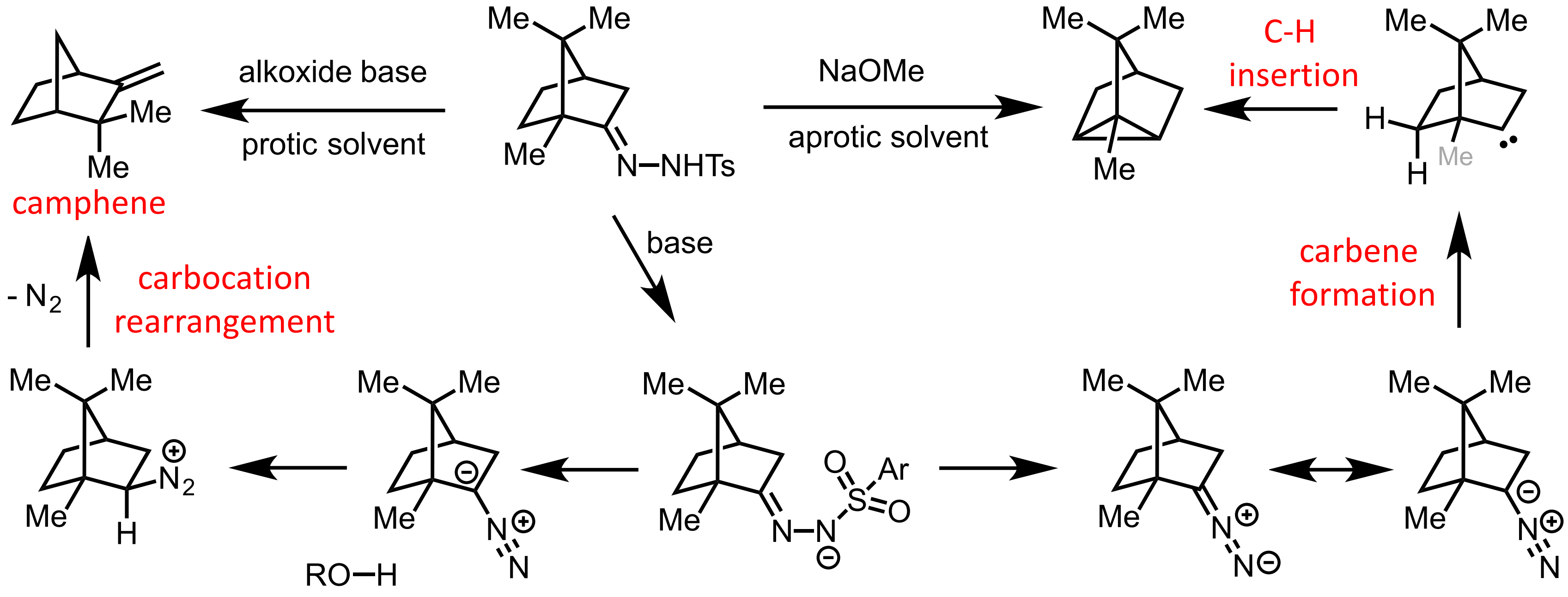
- direct irradiation normally produces a carbene in the singlet excited state

- irradiation or heating diazo or diazirine compounds forms singlet carbenes

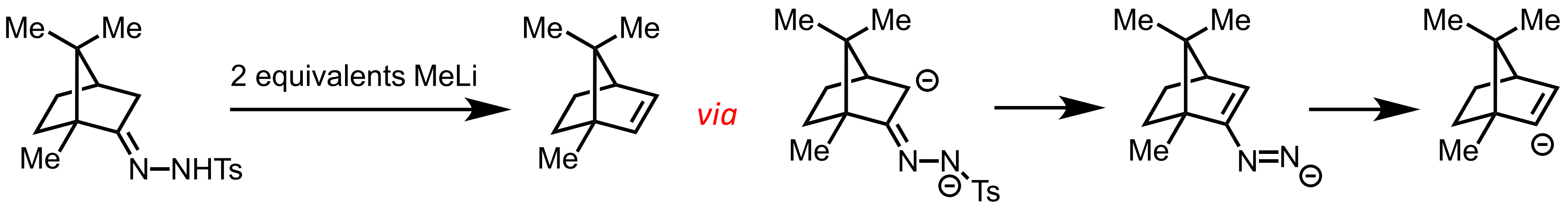
- relaxation of the singlet state to the triplet state (if it is lower in energy) can occur but requires collision with other molecules

- direct formation of the triplet state can occur by irradiation in the presence of a triplet sensitiser

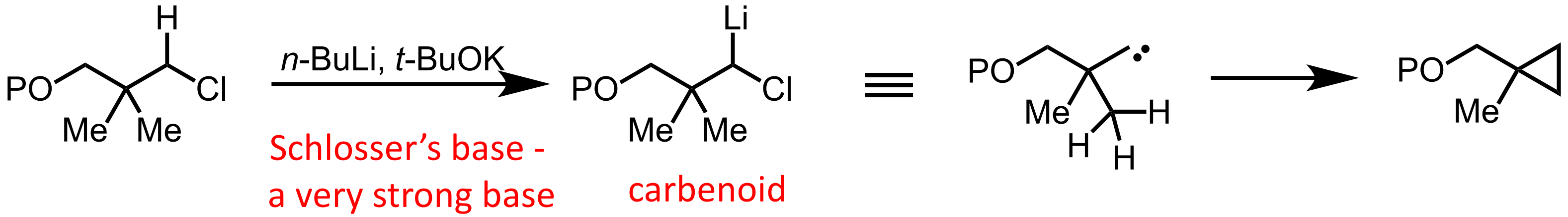
- reactions of carbenes
- insertion into C-H bonds – generally unselective, occurs with very **reactive** carbenes, not Cl_2C**:**
- for singlet carbenes reaction occurs with retention of configuration – with triplet carbenes stereochemistry is lost
- example – the Bamford Stevens reactions – solvent dependent product formation



- remember on treatment with 2 equivalents of an alkyllithium, tosylhydrazones undergo the Shapiro reaction



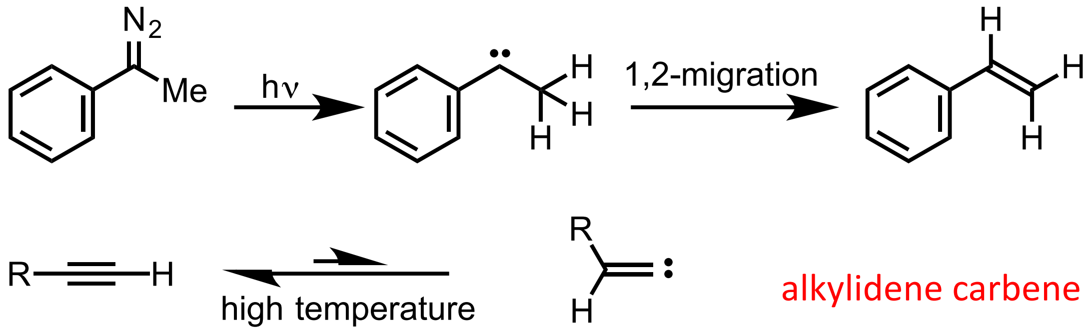
- insertion reactions



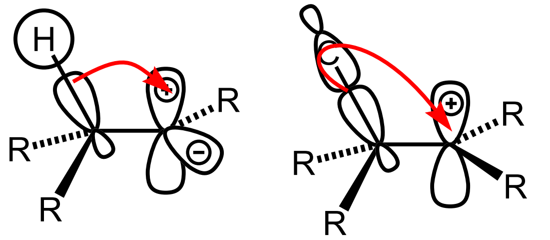
Schlosser’s base - a very strong base

carbenoid

- insertion reactions into adjacent C-H bonds are the equivalent of a 1,2-shift

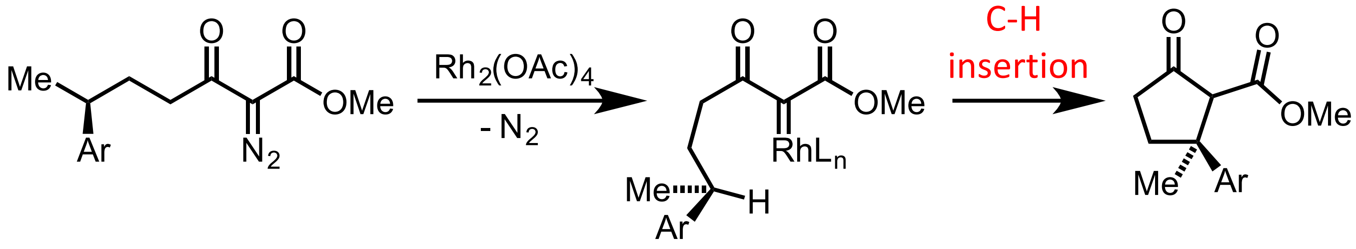


alkylidene carbene

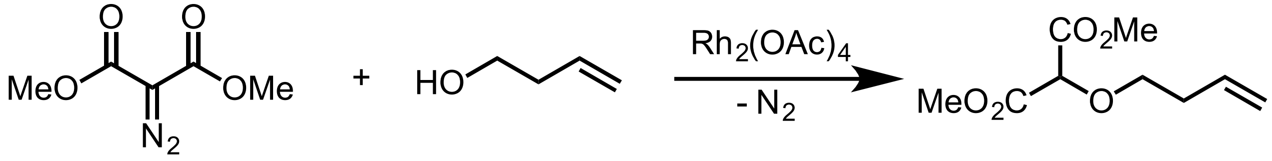


- carbene 1,2-shift
- cation 1,2-shift

- insertion into XH bonds is common using transition metal catalysis

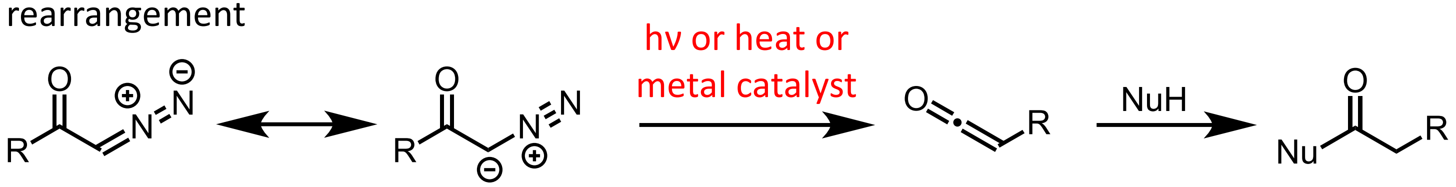


- rhodium carbenoid is equivalent to a carbene

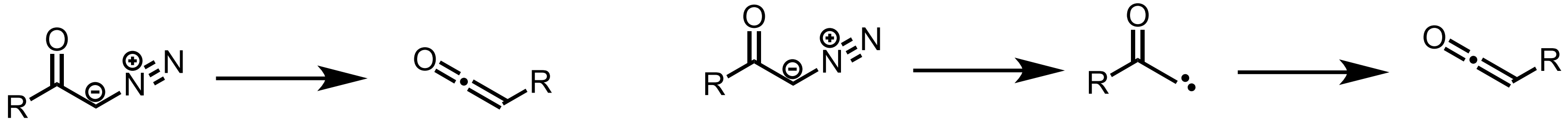


- here the (rhodium) carbene is attacked by the nucleophilic alcohol followed by proton transfer

- Wolff rearrangement

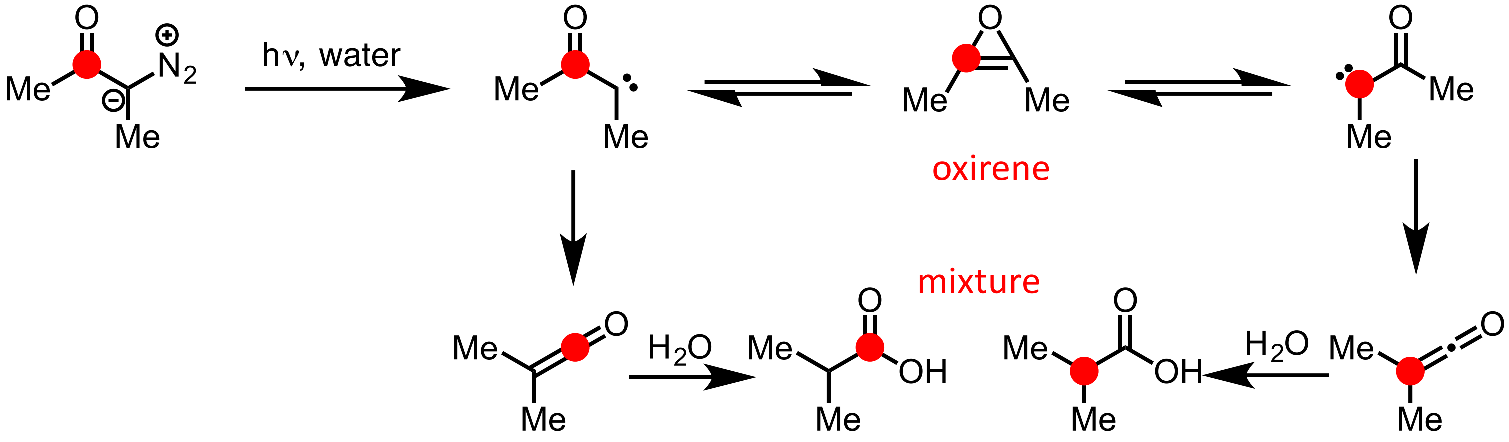


- concerted or stepwise mechanism – depends on substrate and reaction conditions
- as a rule of thumb, the thermal reactions are concerted and the photochemical reactions proceed *via* carbenes

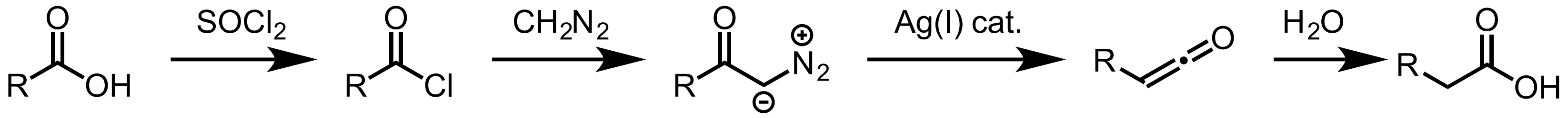

concerted

stepwise via carbene

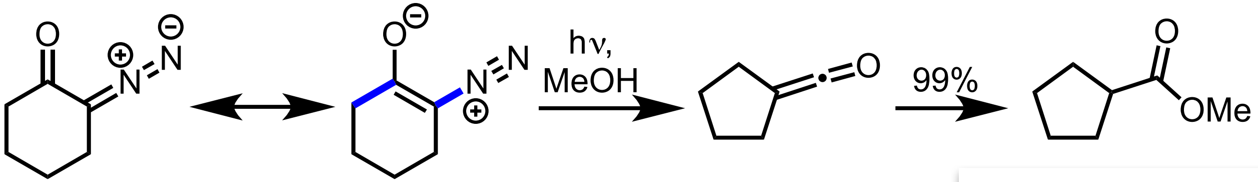
- the acyl carbenes are also in equilibrium with an oxirene in some cases (● = ^{13}C)



- Arndt-Eistert homologation

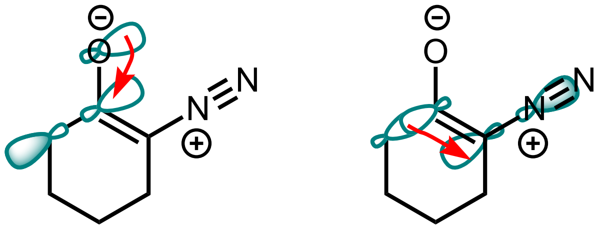


- Wolff rearrangement – a look at the orbitals
- with cyclic ketones the reaction is likely to be concerted under most conditions



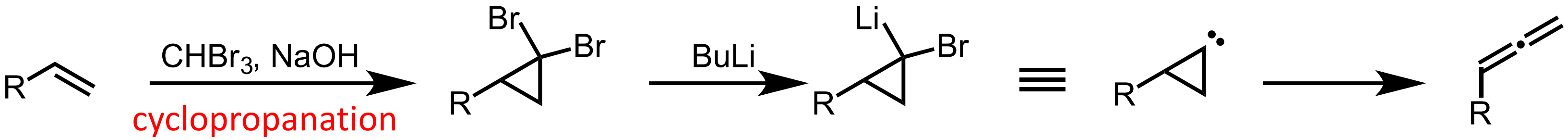
antiperiplanar bonds

- mechanism in more detail correct orbital overlap required for migration



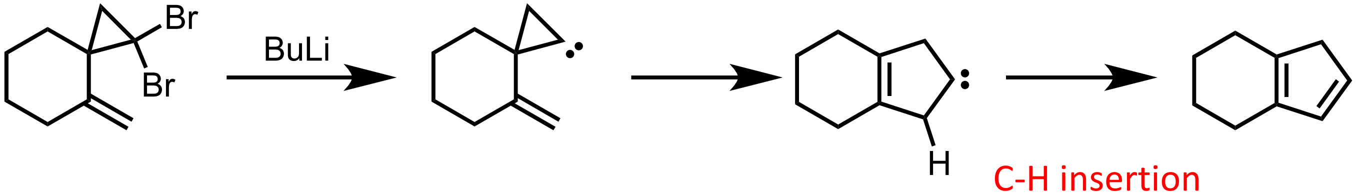
n_O to $\sigma^*_{C\text{-}C}$ $\sigma_{C\text{-}C}$ to $\sigma^*_{C\text{-}N}$

- migration with retention of configuration
- some other rearrangements
- Doering-LaFlamme allene synthesis



cyclopropanation via carbene

- Skattebol rearrangement

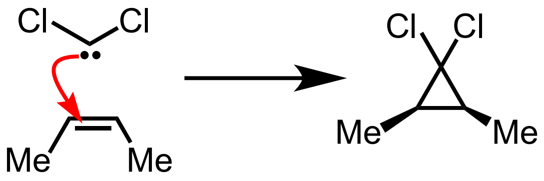


C-H insertion

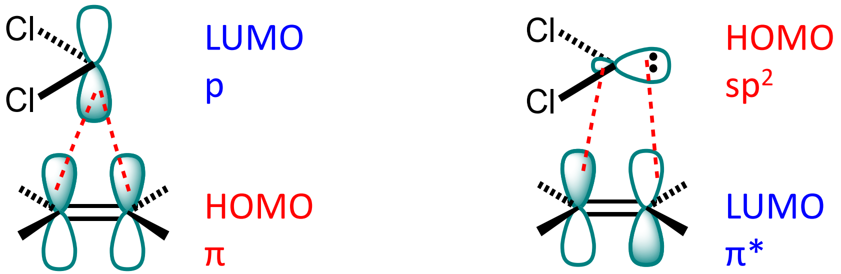
- carbene addition reactions

- addition to C=C bonds: i) stereospecific for singlet carbenes; ii) non-stereospecific for triplet carbenes; iii) distinguishes between triplet and singlet carbenes

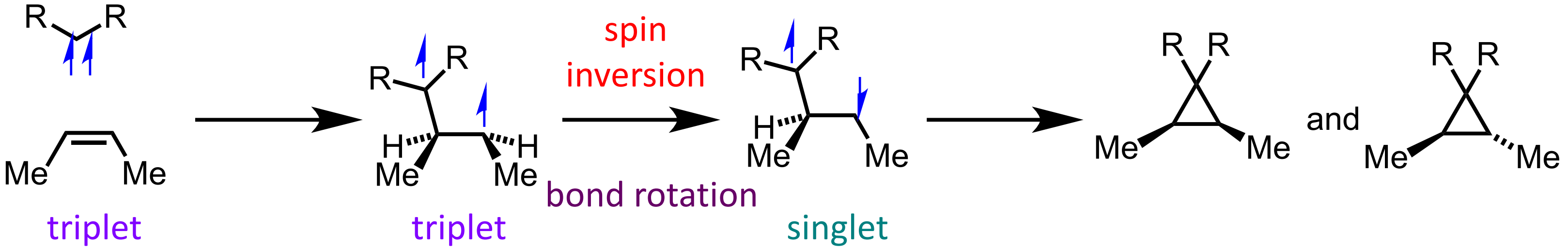
- singlet carbene – concerted reaction



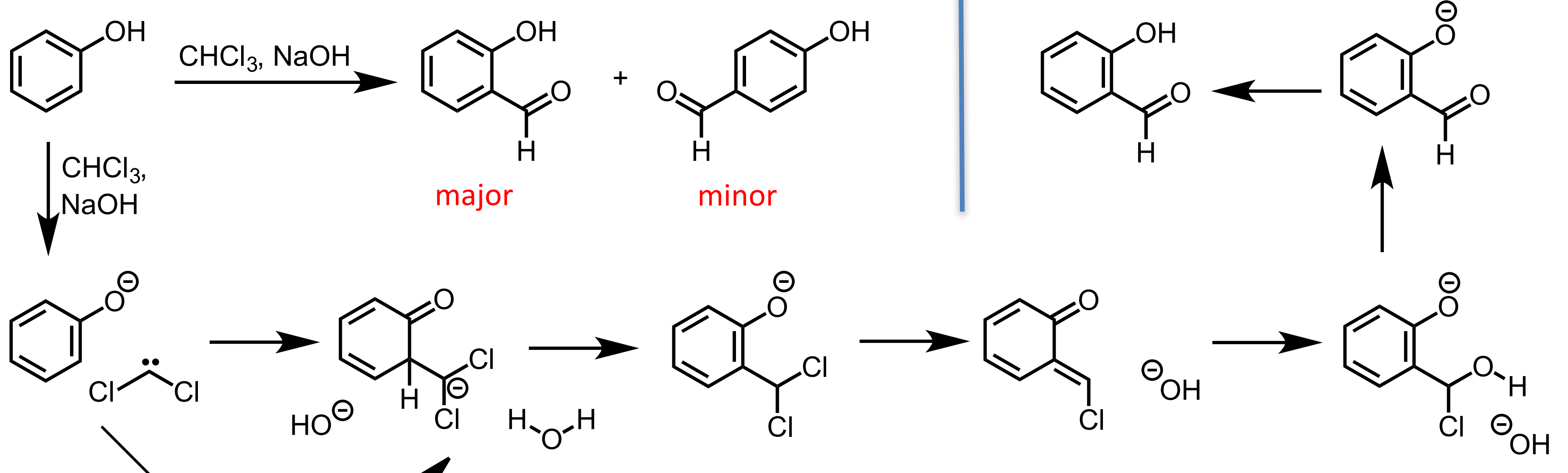
- orbital picture

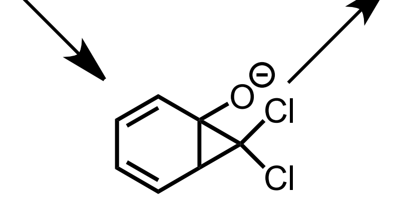


- triplet carbene – non-concerted radical reaction – spin inversion (requires molecular collision) may be slower than bond rotation leading to stereochemical scrambling

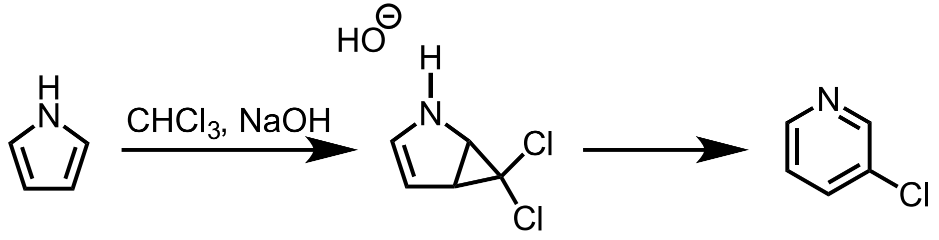


- Reimer – Tiemann reaction

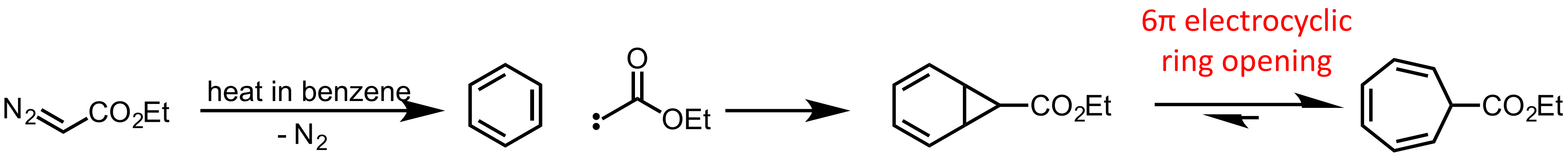




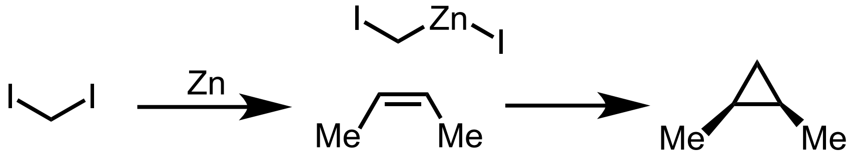
- dichlorocarbene adds to pyrrole followed by rearrangement

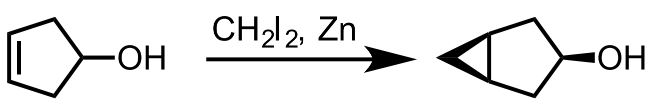


- very electrophilic carbenes will add to benzene

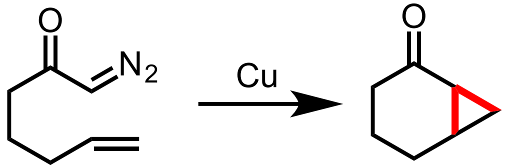


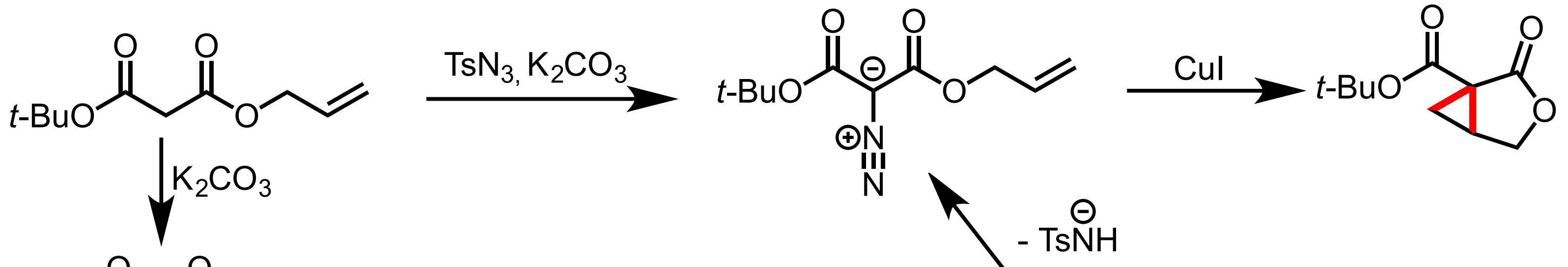
Simmons Smith cyclopropanation

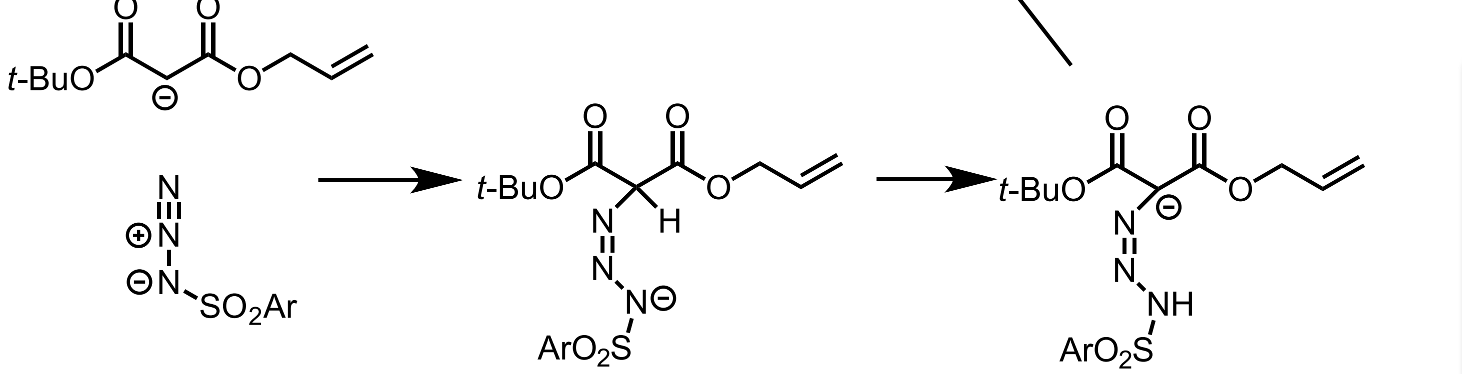

zinc carbenoid


zinc carbenoid coordinated by OH group

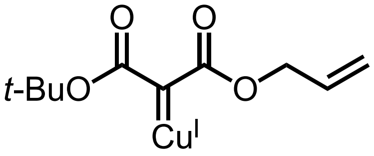
metal catalysed addition reactions of diazocompounds - common catalysts include: Cu, CuI, $Rh_2(OAc)_4$, $Cu(OAc)_2$



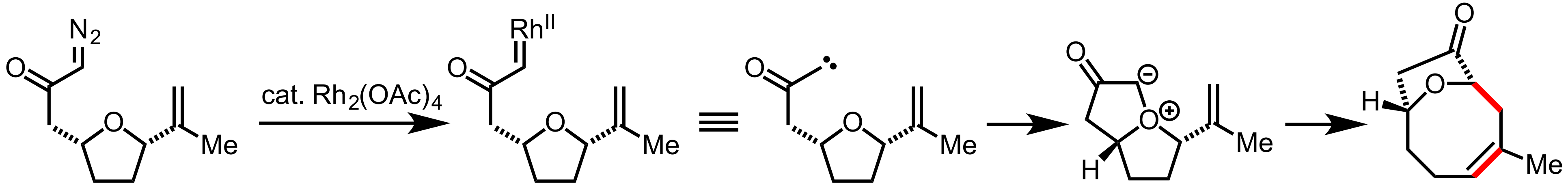




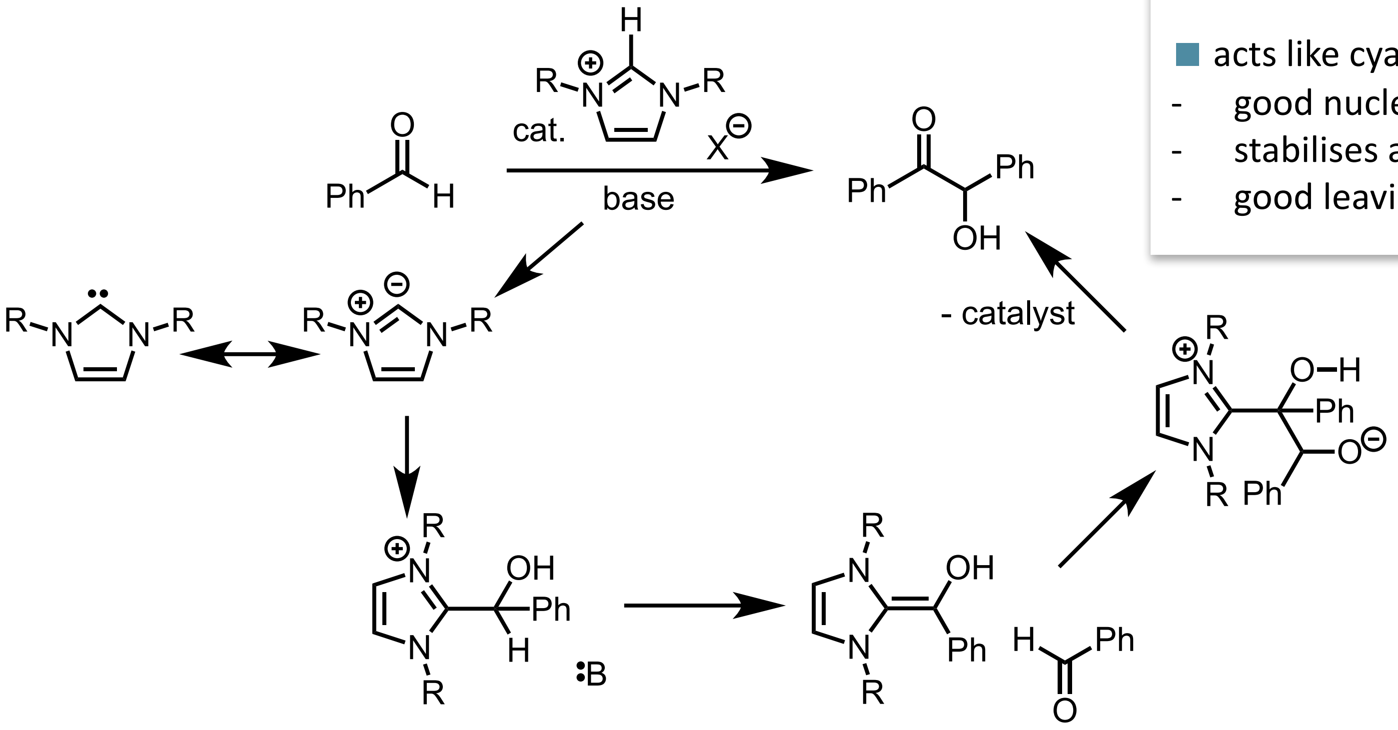
- cyclopropanation most likely proceeds by Cu(I) carbene intermediate



- carbenes readily react with nucleophiles



- nucleophilic carbenes are useful catalysts



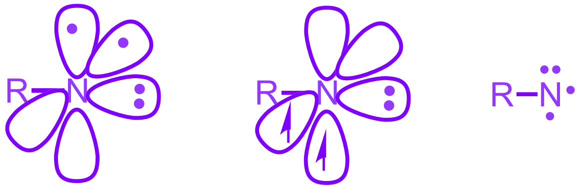
- *N*-heterocyclic carbene catalyses the benzoin reaction

- acts like cyanide:
  - good nucleophile
  - stabilises adjacent negative charge
  - good leaving group

Nitrenes

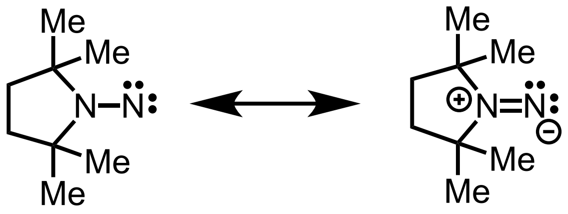
- neutral monovalent nitrogen species – 6 electrons around nitrogen atom, isoelectronic with carbenes
- similar chemistry to carbenes, some differences and nitrenes are generally more reactive

singlet sp^2

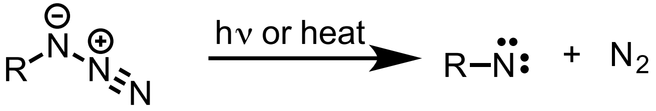


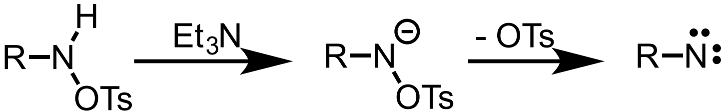
triplet sp

- nitrenes are by definition linear, as with carbenes they have singlet and triplet states
- nitrenes have a larger energy separation between the triplet and singlet states – triplet is usual ground state
- as with carbenes, good π donor substituents can give singlet ground sates



- most common method for generation is thermolysis or photolysis of azides

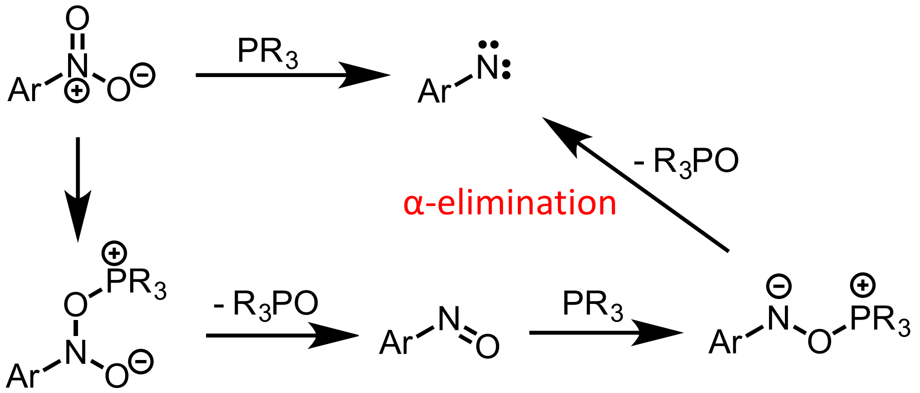




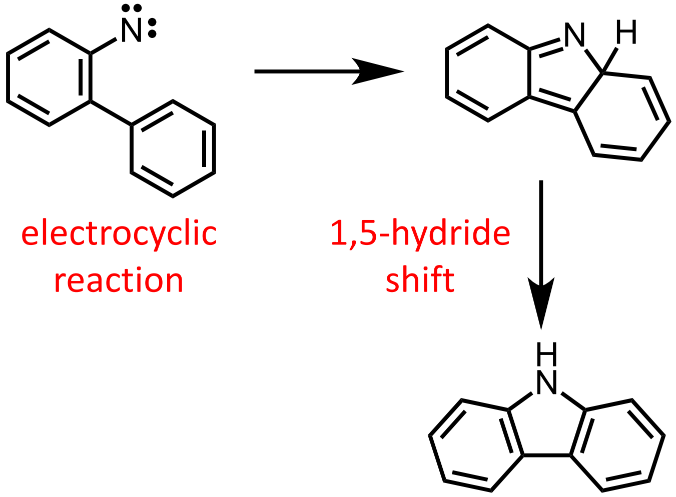
α-elimination

- a number of methods for nitrene generation, analogous to the methods for carbene generation, are known
- free nitrenes are not always formed under these conditions

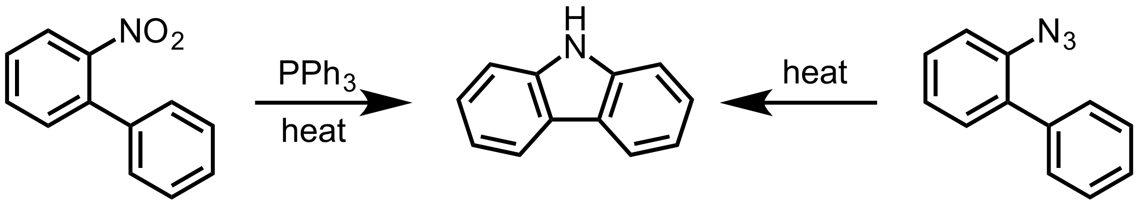
generation by reduction of nitro compounds



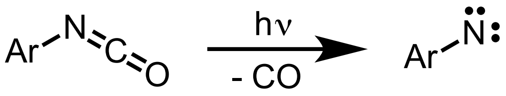
plausible mechanism



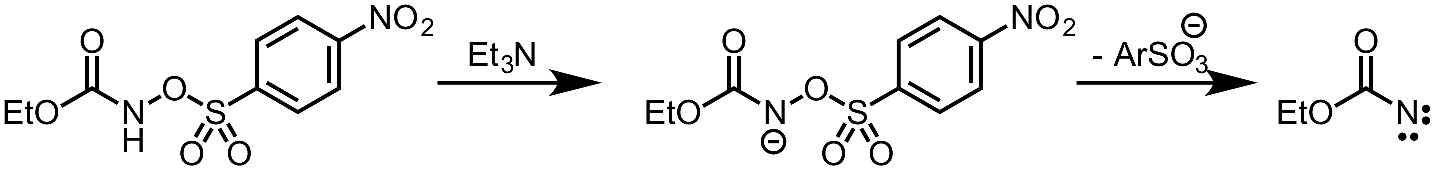
carbazole synthesis



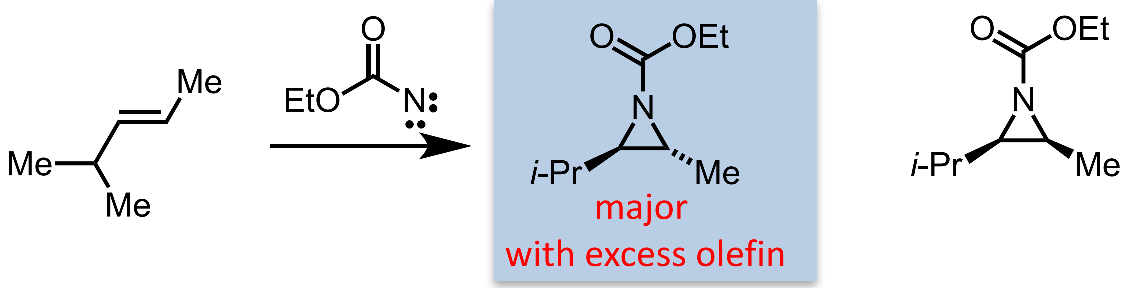
generation from isocyanates



- addition to C=C bonds
- as with carbenes, addition of nitrenes to alkenes is stereospecific with singlet nitrenes, and non-stereospecific with triplet nitrenes



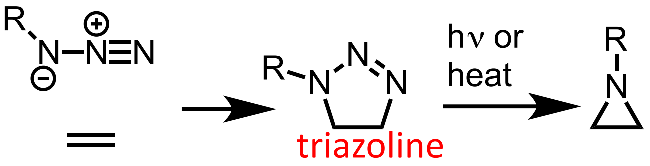
singlet nitrene



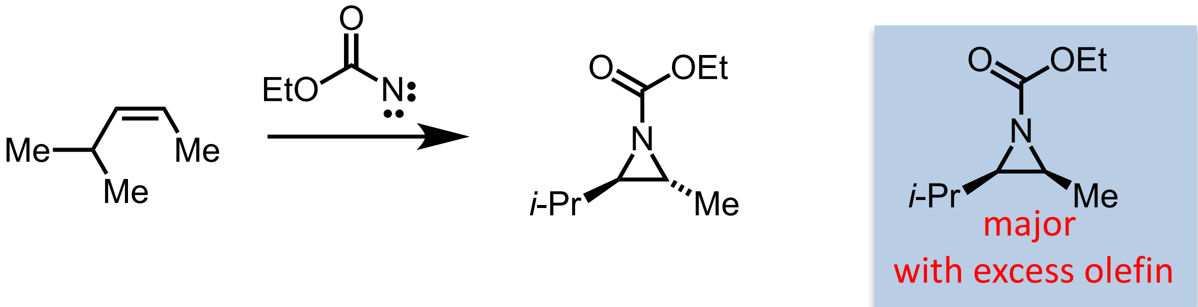
major
with excess olefin

mixture of cis and trans aziridines
with 1 equivalent olefin

- competing reaction – 1,3-dipolar cycloaddition



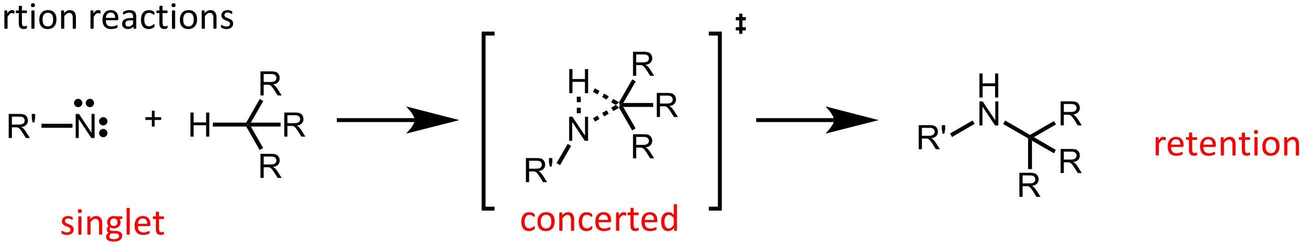
triazoline

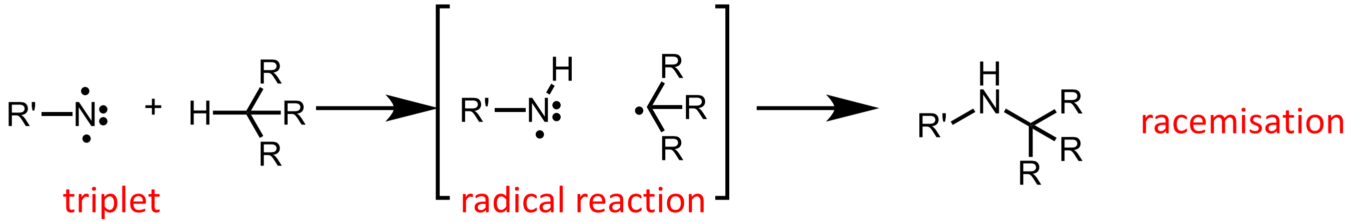


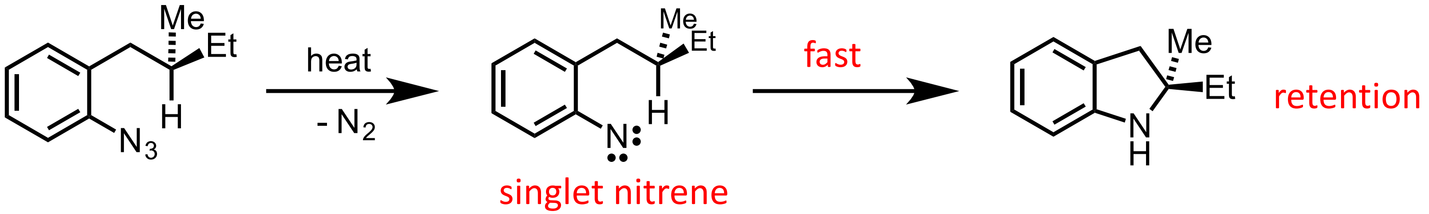
major
with excess olefin

- with high concentration of olefin singlet nitrene reacts stereospecifically to give aziridine products – trans-olefin gives trans-aziridine; cis-olefin gives cis-aziridine
- with low concentraion of olefin singlet nitrene undergoes intersystem crossing to ground state triplet and reacts non-stereospecifically with each alkene (diradical mechanism) to give mixtures of aziridine products
- photochemical generation of nitrene gives analogous results

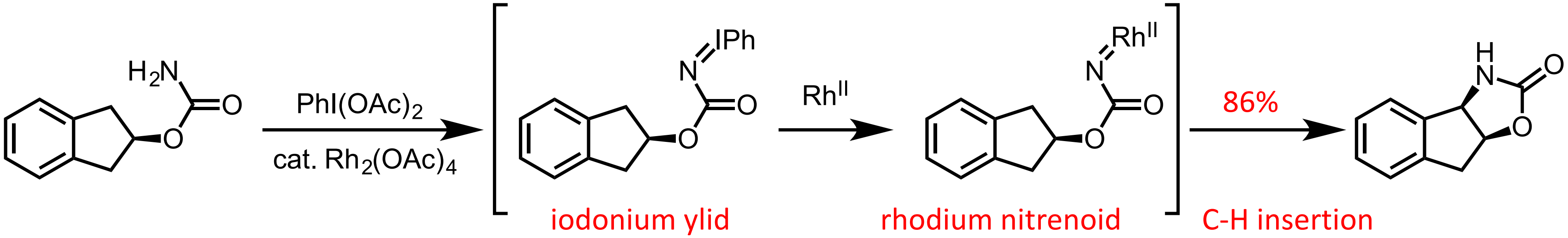
- insertion reactions





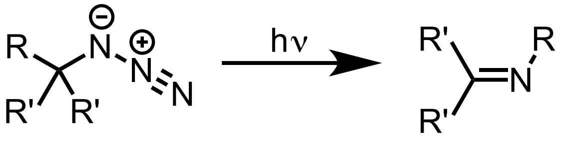


- nitrenoids frequently give better yields of C-H insertion reactions under milder conditions



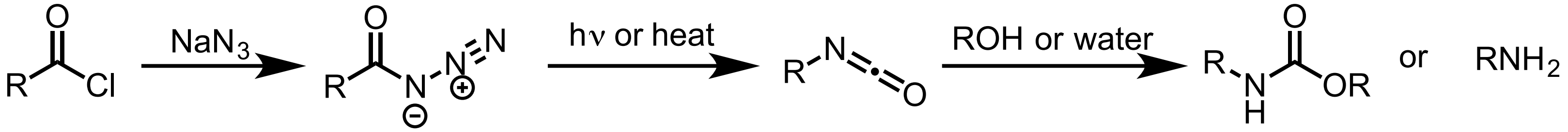
- in a similar manner transition metal nitrenoids react with alkenes to give good yields of aziridines

- rearrangement of nitrenes
- photolysis of alkyl azides yields imines – nitrenes are most likely not intermediates in such reactions

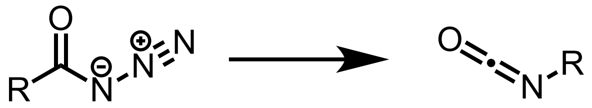


concerted 1,2 shift

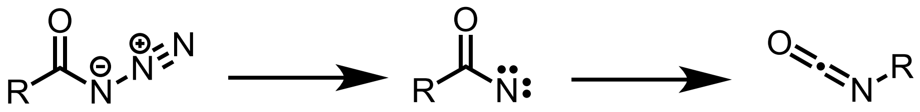
- Curtius rearrangement or acyl azides



- there are two plausible mechanisms



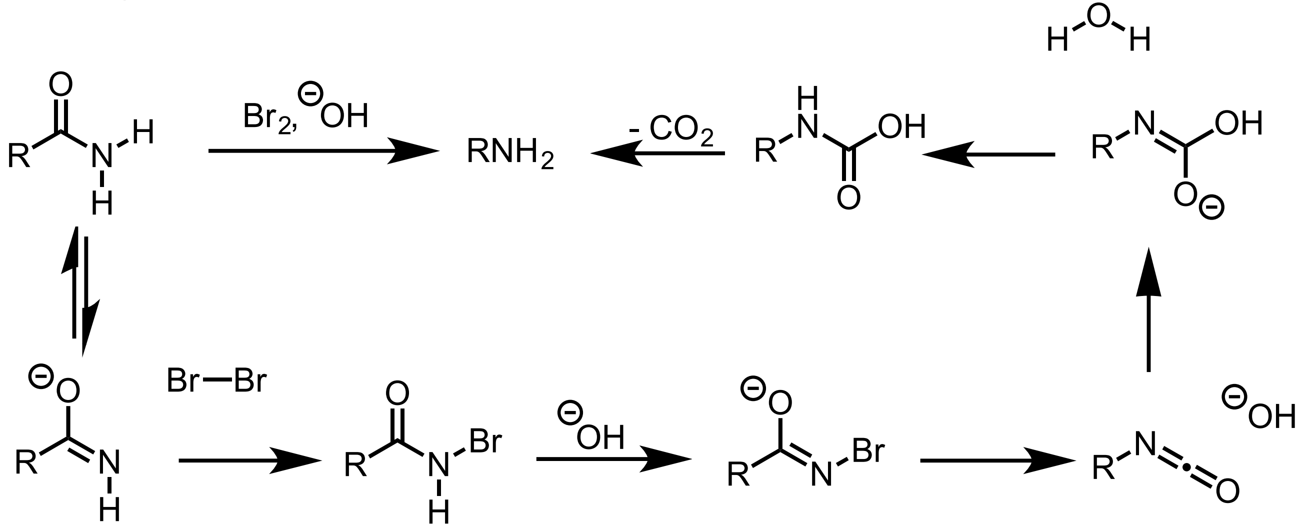
concerted



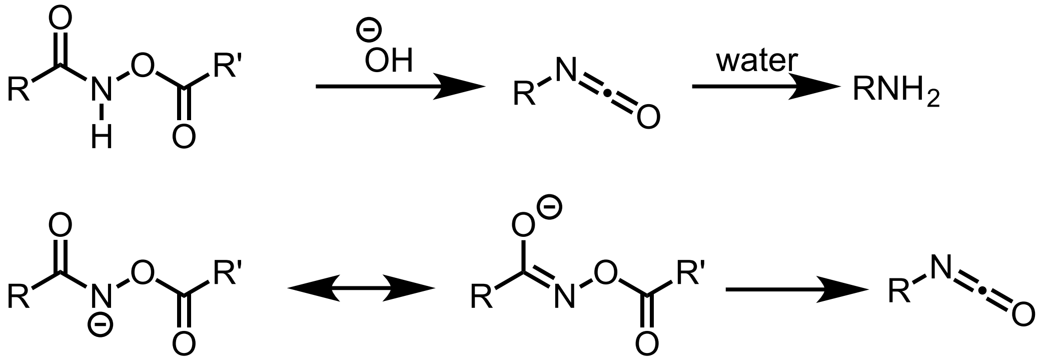
stepwise via nitrene

- the thermal reaction is concerted; the photochemical reaction may proceed *via* a nitrene, but may be concerted
- the Curtius rearrangement proceeds with retention of configuration in the migrating group

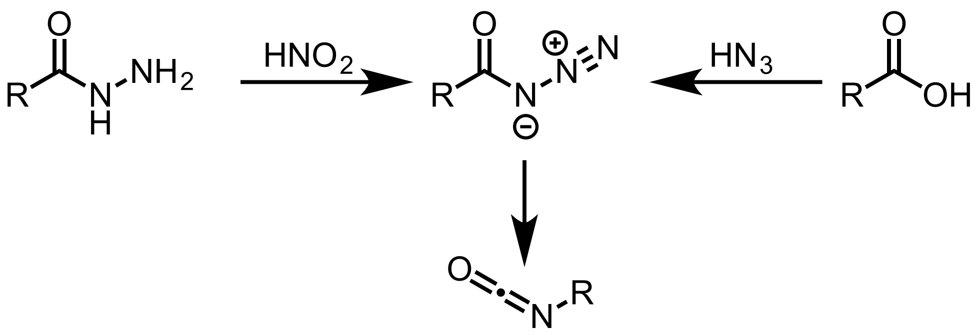
- other rearrangements to electron deficient nitrogen – these rearrangements are unlikely to involve nitrenes
- Hoffman rearrangement



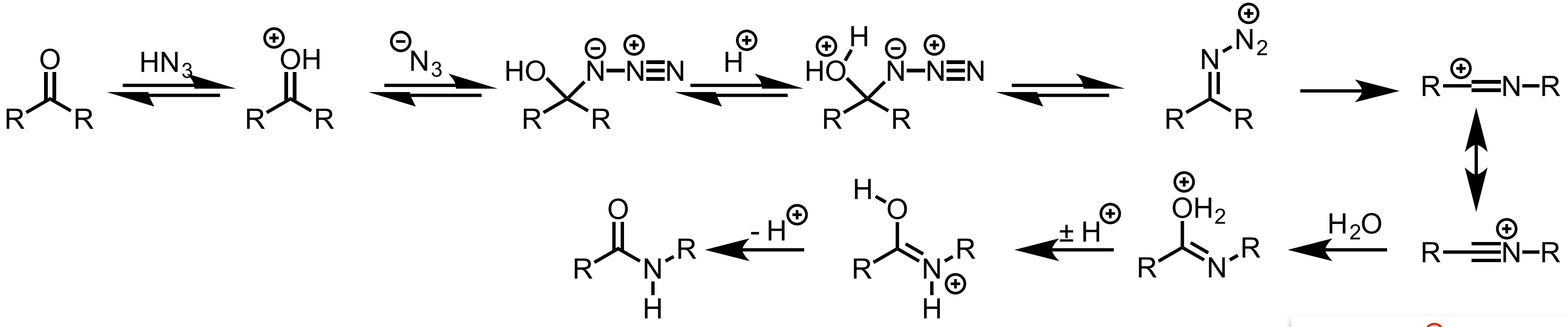
- Lossen rearrangement



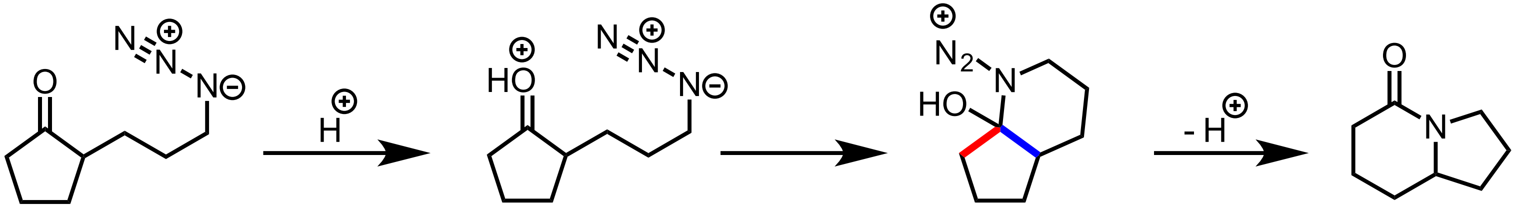
Schmidt rearrangement

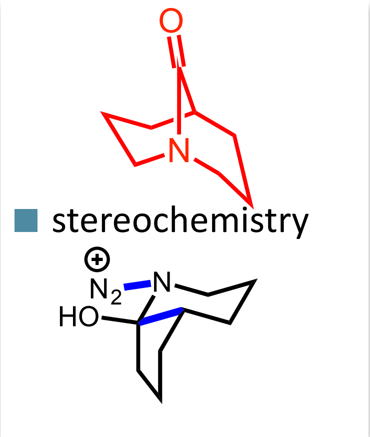


Schmidt rearrangement with ketones (aldehydes give nitriles)



Intramolecular Schmidt rearrangement with alkyl azides

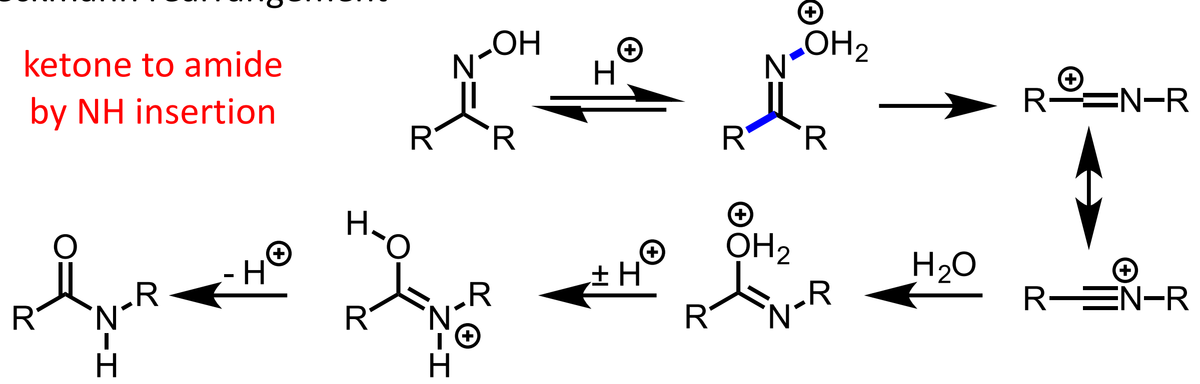




stereochemistry

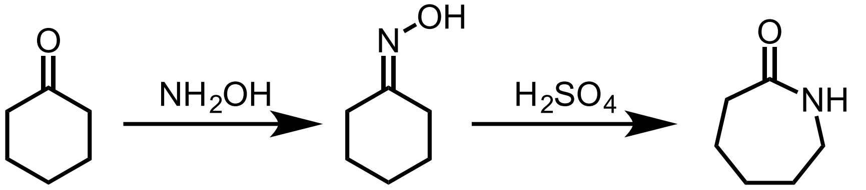
Beckmann rearrangement

ketone to amide
by NH insertion

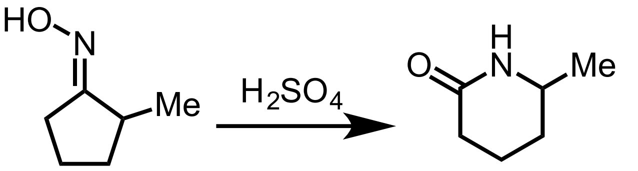


- the group anti to the leaving group migrates (σ_{C-C} to σ^*_{N-O})
- oximes can undergo *E*/*Z* isomerisation under the acidic reactions conditions
- migration with retention of configuration

Beckmann rearrangement – synthesis of caprolactam, precursor to nylon 6

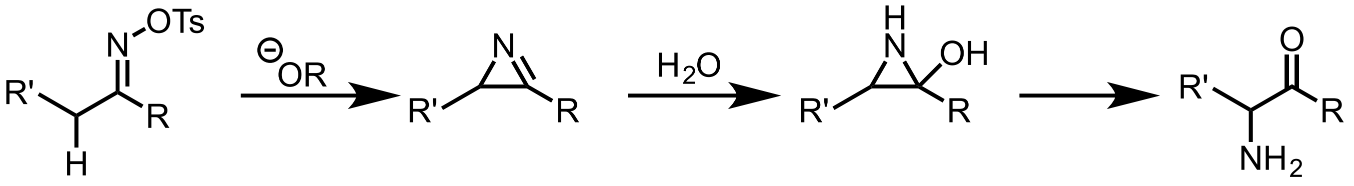


carpolactam

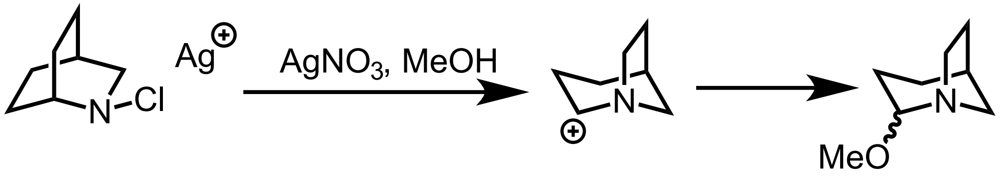


most stable oxime with bulky groups trans

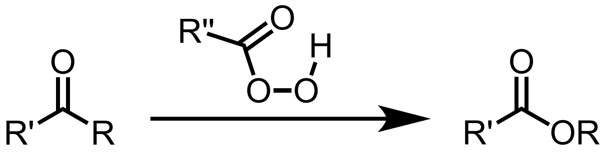
Neber rearrangement – substituent possessing most acidic hydrogen migrates



Stieglitz rearrangement



- Baeyer-Villiger



conversion of a ketone into an ester by oxygen insertion

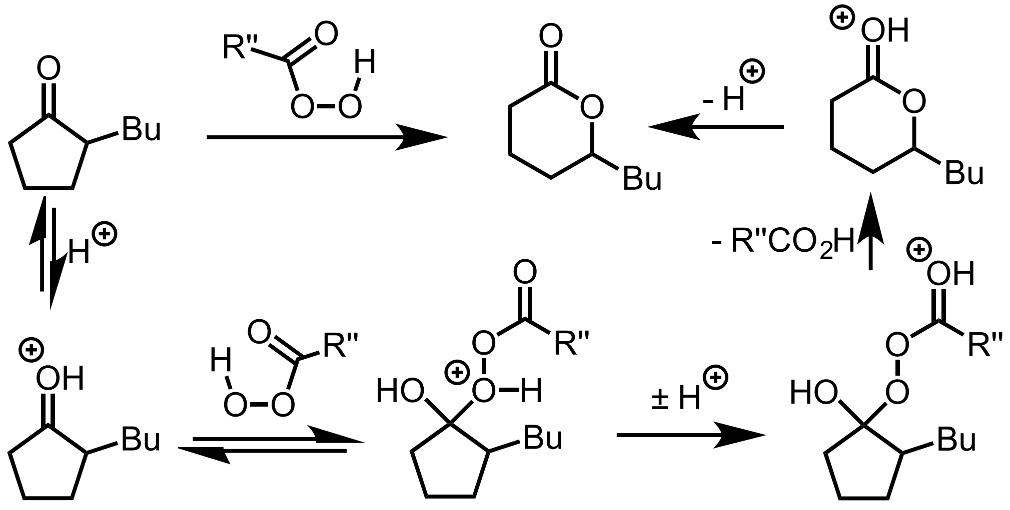
- order of migration A.K.A migratory aptitude

3° alkyl > 2° alkyl > aryl > 1° alkyl > methyl
i.e. the group which best supports a positive charge migrates

- with aromatic groups, electron donating groups increase migratory aptitude

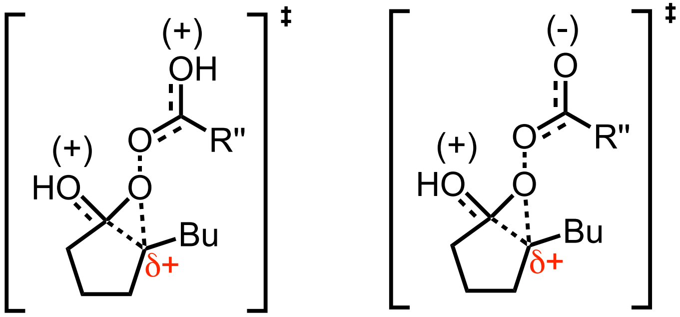
- migration occurs with retention of configuration in the migrating group

- with aldehydes migration of “H” usually occurs to give carboxylic acids



- transition state is electron deficient (electron withdrawing group on oxygen)

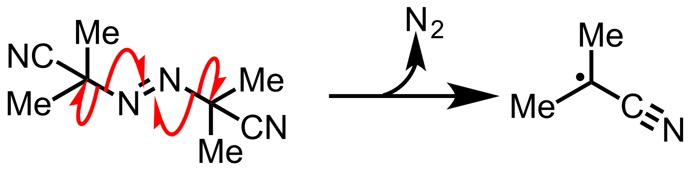
- electron releasing groups stabilise the transition state giving the order of migratory aptitude above



Rearrangements and Reactive Intermediates

1A Organic Chemistry

Handout 3 - Introduction to Radicals



AIBN - azobisisobutyronitrile

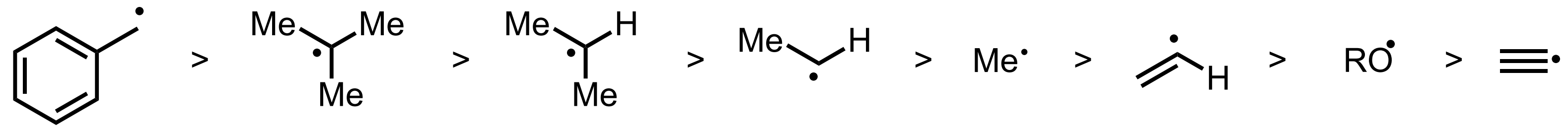
RADICALS

- a radical is “ a molecular entity that contains an unpaired electron” – C-centred radicals are generally very reactive

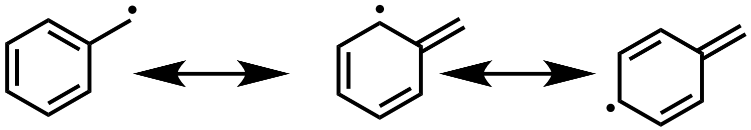
- structure – methyl radical is planar but pyramidal conformer is very close in energy

- C-centred radicals $R_3C^\bullet$ are generally slightly pyramidal (unpaired electron in sp^3 orbital) – we will consider $R_3C^\bullet$ to be pyramidal (sp^3 hybridisation)

- stability – a good guide to radical stability comes from C—H (and X-H in general) bond dissociation energies

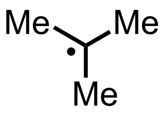


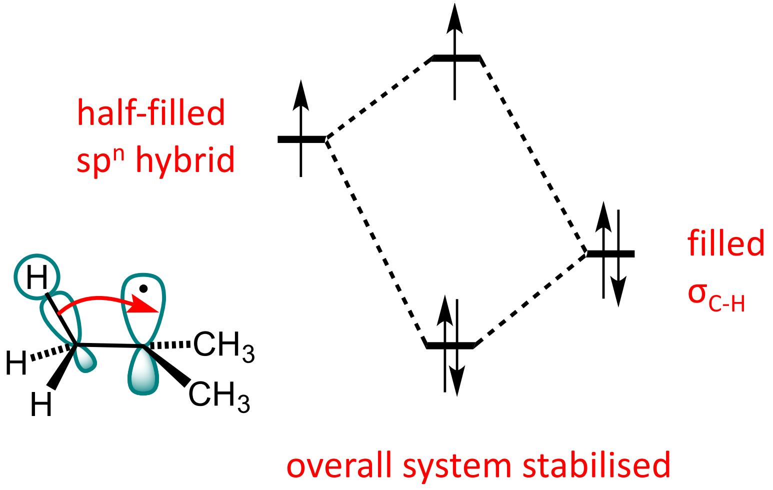
356 381 395 410 430 427 436 523 $kJmol^{-1}$



- stabilised through delocalisation

- C-centred radicals have 7 electrons around carbon and order of stability parallels that of carbocations i.e. 3° > 2° > 1°
- stabilised through hyperconjugation





- some bond dissociation energies – ΔH° for R—R → R• + R•

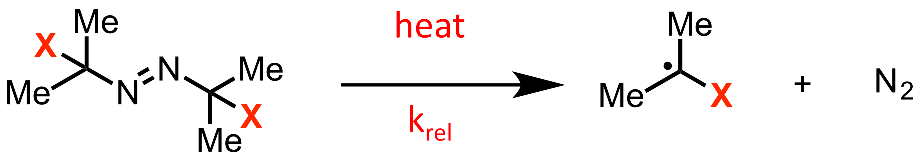
X-H bonds	kJmol^{-1}
O—H	455
C—H	410
N—H	385
S—H	367
Sn—H	290

C-X bonds	kJmol^{-1}		
C—F	425		
C—H	410		
C—O	330	C=O	750
C—C	330	C=C	585
C—Cl	325		
C—Br	270		
C—I	240		

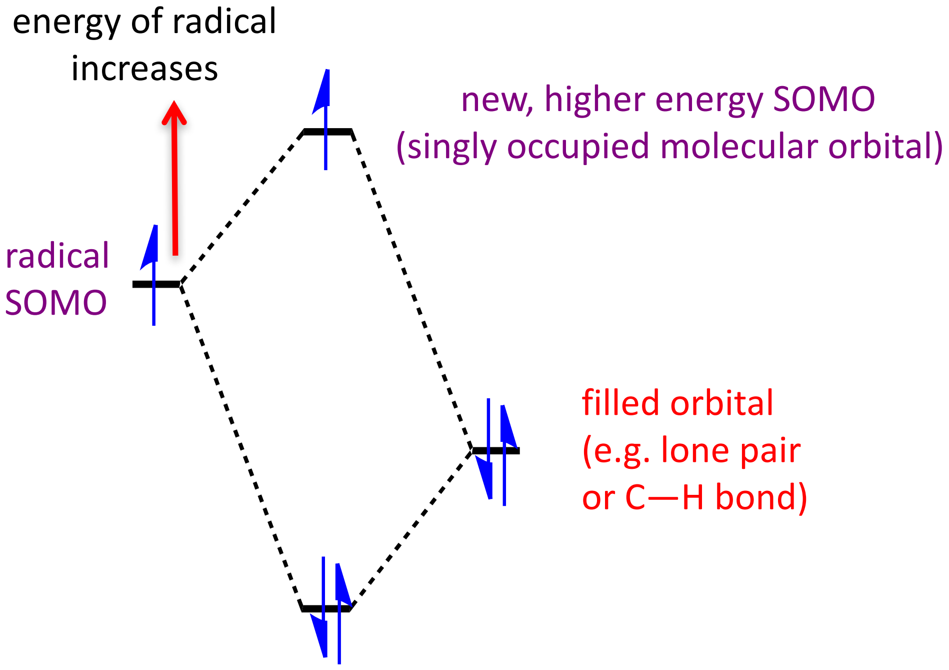
X-X bonds	kJmol^{-1}
H—H	431
C—C	330
Cl—Cl	239
Br—Br	189
N—N	150
I—I	149
O—O	140

C-H bonds	kJmol^{-1}
C≡C—H	523
Ph—H	431
C=C—H	427
CH_3—H	430
Et—H	410
i-Pr—H	395
t-Bu—H	381
$PhCH_2$—H	356
O=C—H	364

- radical stability – radicals are stabilised both by overlap with filled or/and empty adjacent orbitals.
- model reaction: diazoalkane decomposition. How does **X** stabilise radical and hence influence rate?



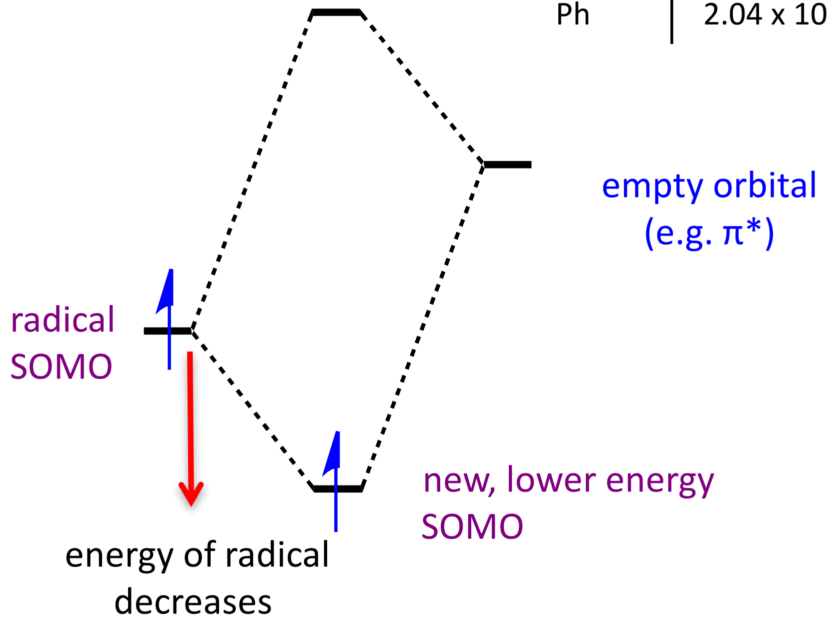
X	k_{rel}
H	1
CH_3	501
OMe	5248
CO_2R	1.25×10^8
CN	1.45×10^8
Ph	2.04×10^8


energy of radical increases

new, higher energy SOMO (singly occupied molecular orbital)

radical SOMO

filled orbital (e.g. lone pair or C—H bond)


empty orbital (e.g. π*)

radical SOMO

new, lower energy SOMO

energy of radical decreases

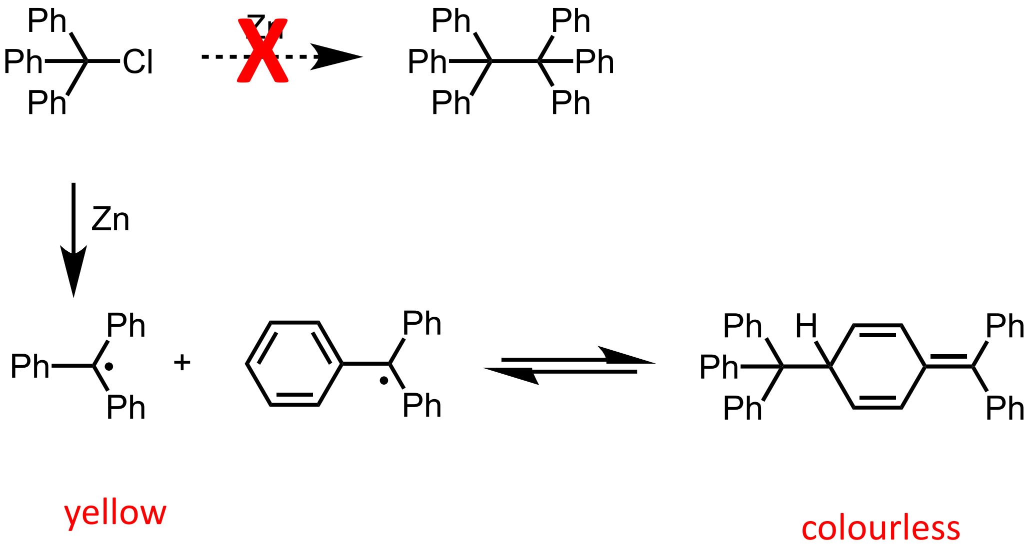
- radical with adjacent filled orbital
SOMO raised, overall system stabilised

- radical with adjacent empty orbital
SOMO lowered, system stabilised

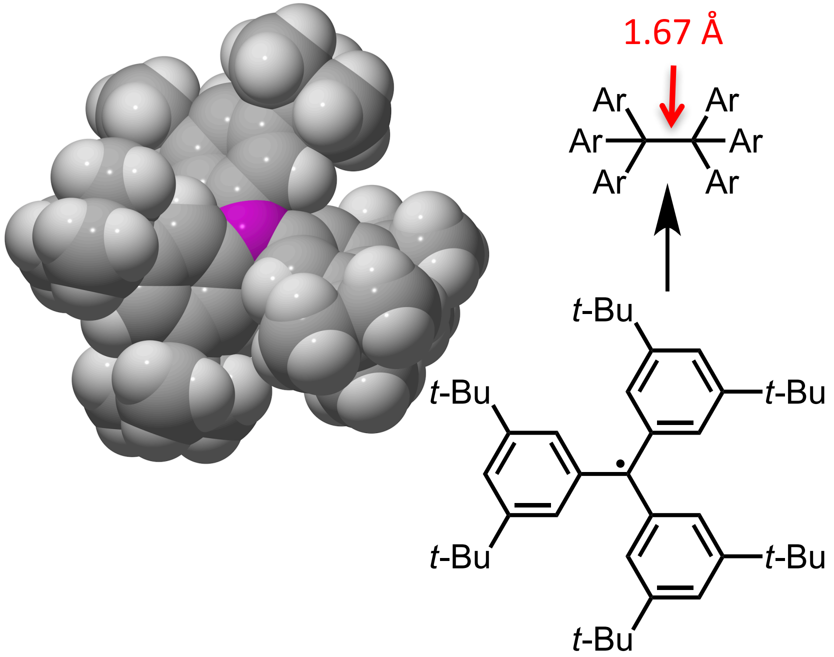
- anything that can stabilise a cation or anion can stabilise a radical: EWG (Z), EDG (X), conjugation.

- Radical stability – radicals are stabilised both by overlap with filled or/and empty adjacent orbitals.

- first synthesis of a stable radical by Moses Gomberg in 1901 while attempting to prepare hexaphenyl ethane



- An X-ray structure of a substituted trityl radical



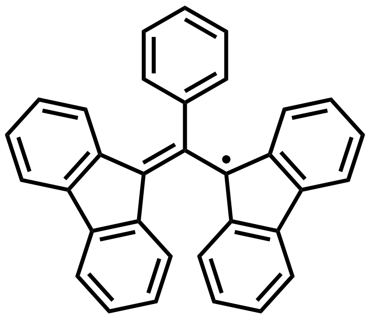
- most organic radicals are transient (very short lifetimes) – radicals without special stabilisation dimerise or disproportionate

- trityl radical is a stabilised radical – stabilised radicals include C-centred radicals $R^\bullet$ for which the R-H bond strength is less than for the corresponding C-H bond (1°, 2° or 3° etc.) in an alkane – they are generally transient

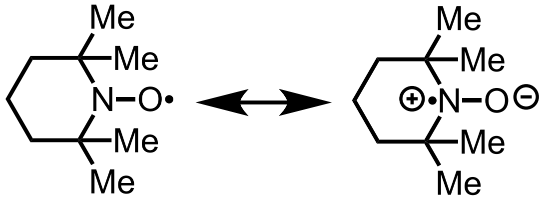
- some stable free radicals have long lifetimes and are resistant to bimolecular decomposition modes – here the stability is generally due to delocalisation – i.e. they are inherently stable

- persistent radicals: these are long lived radicals that are kinetically stable frequently for steric reasons

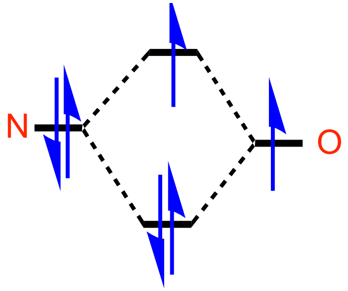
- examples of stable, persistent radicals



mp 210 °C

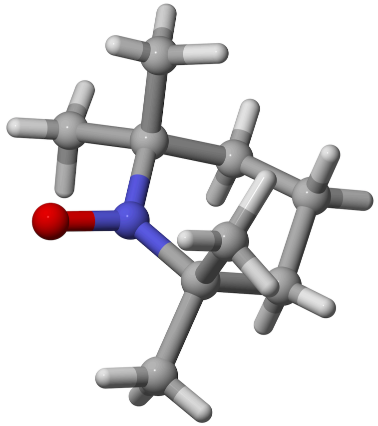


- TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical)



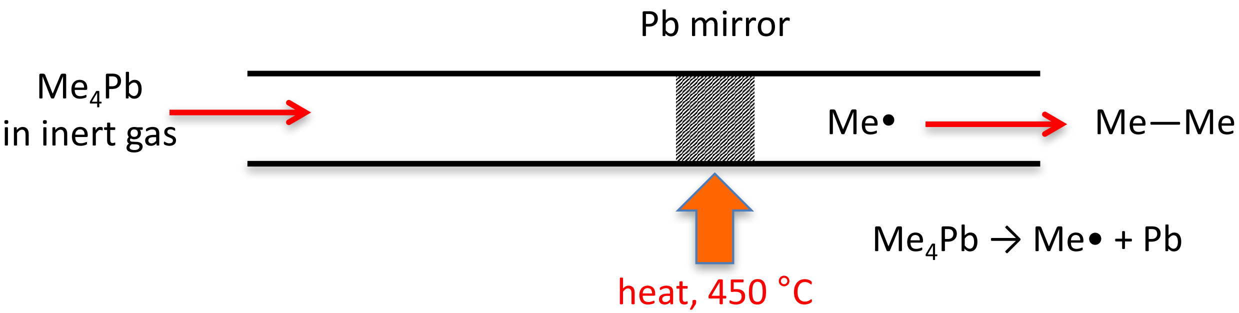
- X-ray structure

N-O bond length 1.295 Å
typical N-O bond length 1.45 Å

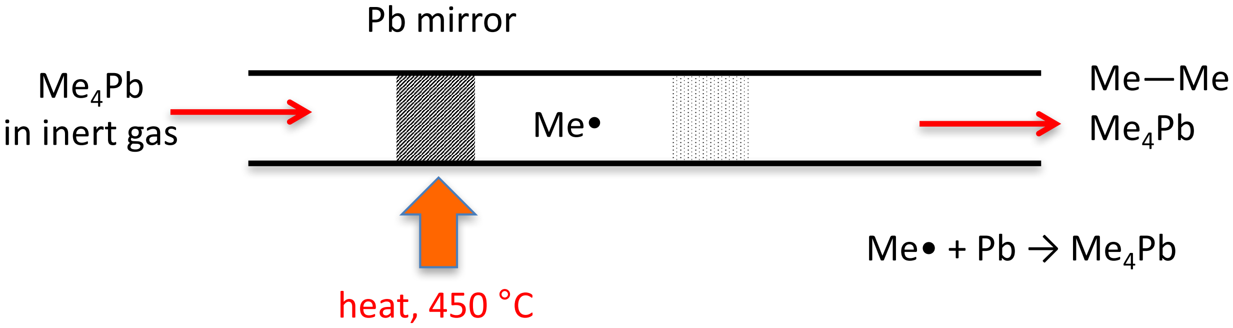


- both commercially available, stable in pure form, react rapidly with simple radicals

- detection of radicals – Paneth lead mirror experiment – historically important, 1929



Me_4Pb → Me• + Pb



Me• + Pb → Me_4Pb

- radical detection

Electron Spin Resonance (ESR)
[R•] > 10^{-6} M therefore require long lived radicals or low temperatures
electron - ^1H coupling yields structural information

Chemically Induced Nuclear Dynamic Polarisation (CIDNP)
indirect method of radical detection
detects reactions involving radical pairing

- elementary reaction steps
- homolysis / recombination
- redox
  - these are initiation and termination steps

- addition / β-scission
- substitution
  - these are propagation steps

- homolysis / recombination

- ease depends on bond dissociation energy

- general guidelines for radical reactions

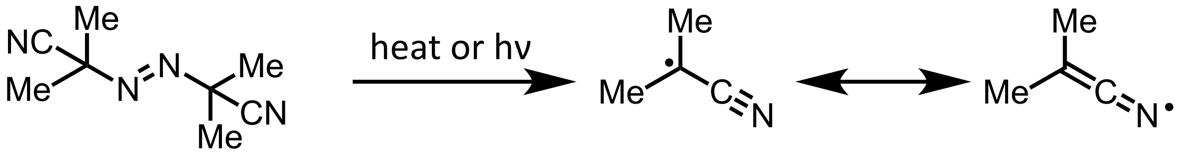
- reactions usually exothermic – favour the formation of more stable products

- good to break weak bonds (e.g. C-I, C-Br, C-S, C-Se) and make strong bonds

- radicals add to π-bonds or abstract atoms

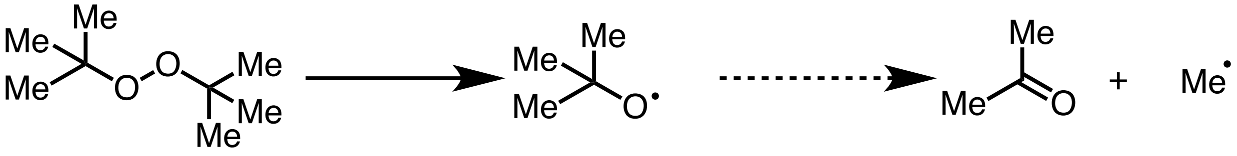
- radicals attack univalent and sometimes divalent atoms – very rarely tri- or tetravalent atoms

$$X{-}Y \xrightarrow{\text{heat or } h\nu} X^{\bullet} + Y^{\bullet}$$

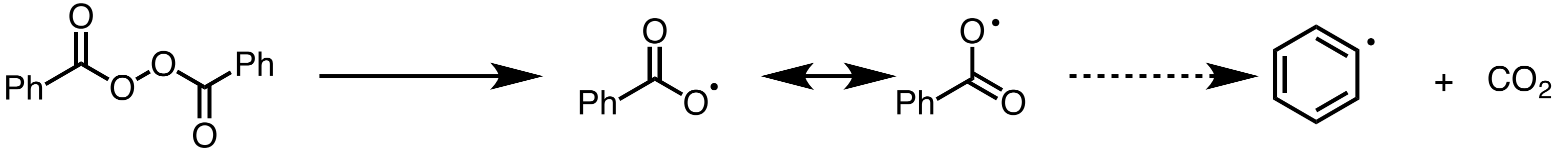


AIBN - azobisisobutyronitrile

$t_{\frac{1}{2}}$ ~ 1 h at 80 °C

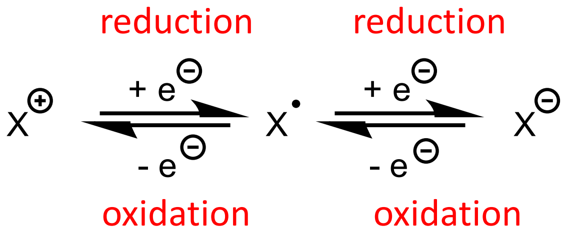


$t_{\frac{1}{2}}$ ~ 1 h at 150 °C

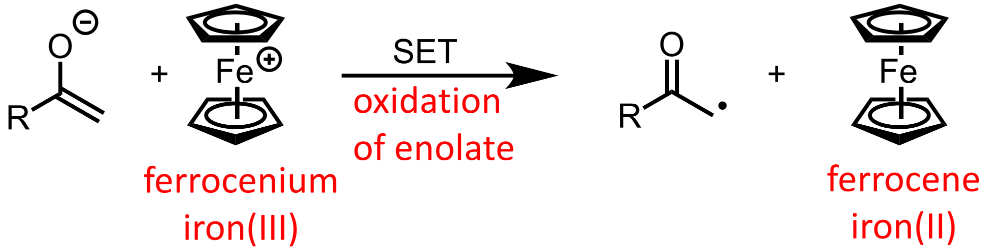


$t_{\frac{1}{2}}$ ~ 1 h at 90 °C

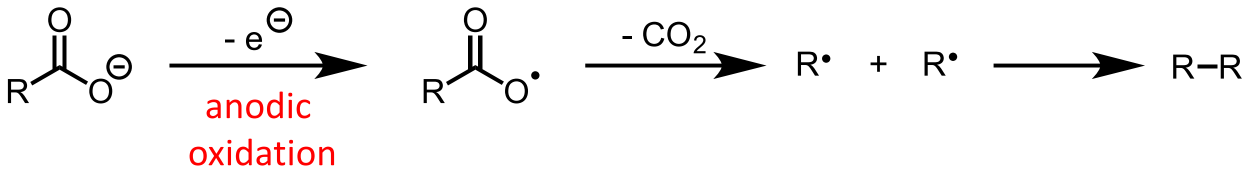
- redox



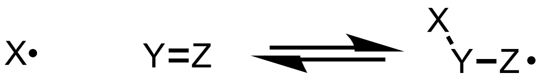
- many (transition) metal salts are good single electron oxidants for enolates and related functional groups



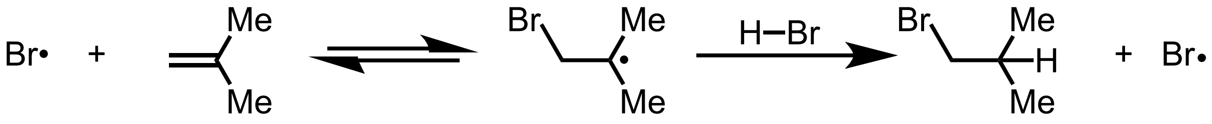
- Kolbe electrolysis



- addition / β-scission



- example – anti-Markovnikov addition of HBr to alkenes



- addition of radicals to alkenes is reversible for: RS•, Br•, I•, Bu$_3$Sn•, but not for Cl•

- addition of R• to C=O is unfavourable (endothermic) and reversible

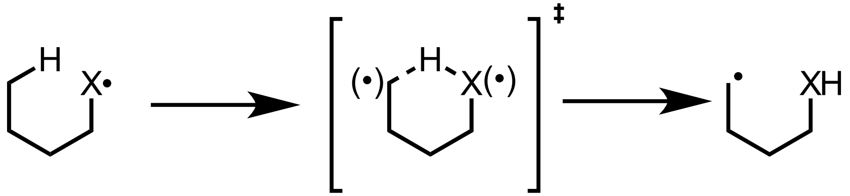
- substitution S_H2 (substitution, homolytic, bimolecular)

$$X\bullet \quad Y{-}Z \longrightarrow X{-}Y \; + \; Z\bullet$$

- Y is univalent atom e.g. H or Br occasionally divalent e.g. SPh, SePh – **almost** never tetravalent carbon

$$Cl\bullet + H{-}CH_3 \longrightarrow Cl{-}H + \dot{C}H_3 \qquad Bu_3Sn\bullet + Br{-}R \longrightarrow Bu_3Sn{-}Br + R\bullet$$

- intramolecular 1,5-hydrogen atom transfer – common for alkoxy radicals with appropriately positioned C—H bond



6-membered transition state

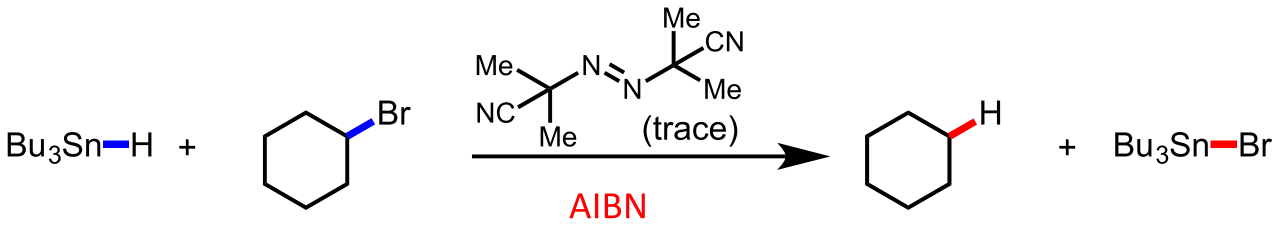
- disproportionation – H-atom abstraction β to radical centre – a type of termination

- the majority of radical reactions we will meet will be chain processes which have three steps:

- initiation i.e. generation of radicals e.g. thermal decomposition of AIBN ($k_i = 10^{-5}\ s^{-1}$)
- propagation steps e.g. addition of Br• to an alkene – typical propagation rate constants are 10^2-$10^5\ M^{-1}s^{-1}$
- termination (destruction of radicals) e.g. R• + R'• → R—R' typical rate constant $10^9\ M^{-1}s^{-1}$ (near diffusion controlled)

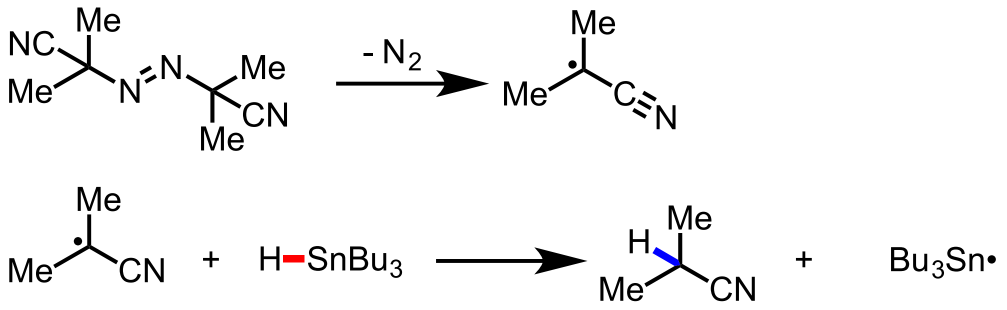
- for an efficient chain process the rate of the propagating steps must out compete the rate of the termination steps - given the vast difference in rate constants for these processes the [R•] must be low – typically 10^{-8} **M**

- a typical radical chain process



Bond	$kJmol^{-1}$
C—Br	270
Sn—H	267
C—H	419
Sn—Br	332

- initiation



- overall exothermic reaction

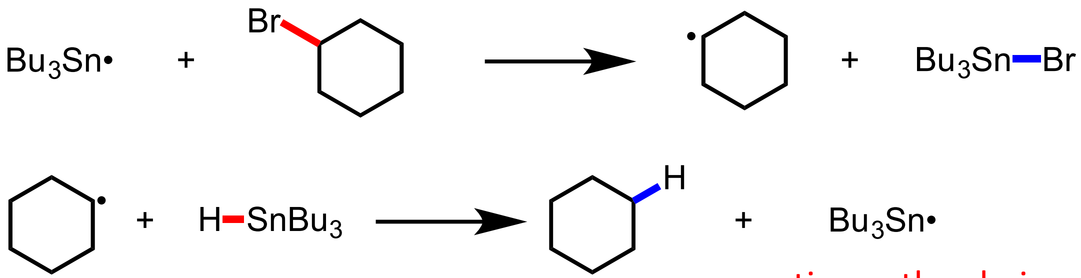
bonds made = **-419 - 332 = -751**

bonds broken = **+270 + 267 = +537**

ΔH = -692 + 537 = -214 $kJmol^{-1}$

very crude analysis due to wide variation in reported bond dissociation energies

- propagation



continues the chain
(chain process)

- kinetics

$$R\bullet + R\bullet \xrightarrow{k_T = 10^9\ M^{-1}s^{-1}} R{-}R$$

$$R\bullet + X{-}Y \xrightarrow{k_P} R{-}X + Y\bullet$$

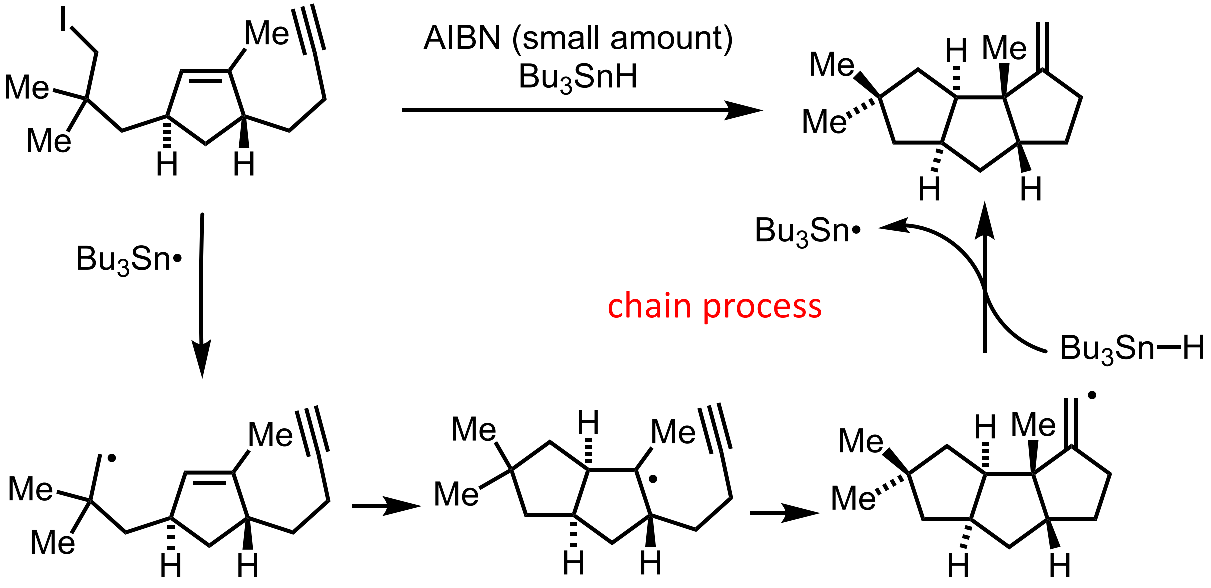
$$\frac{d[R{-}R]}{dt} = k_T[R\bullet]^2 = 10^9x(10^{-8})^2 = \mathbf{10^{-7}\ Ms^{-1}}$$

$$\frac{d[R{-}X]}{dt} = k_P[R\bullet][X\text{-}Y] = 10^{-8}x10^0 = \mathbf{k_P 10^{-8}\ Ms^{-1}}$$

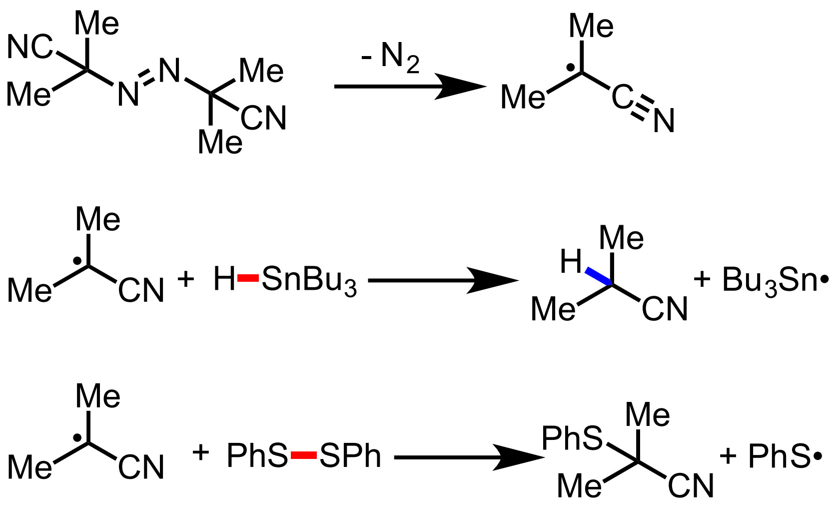
- for efficient propagation $k_p > 10^2\ M^{-1}s^{-1}$ and [R•] should be as low as possible

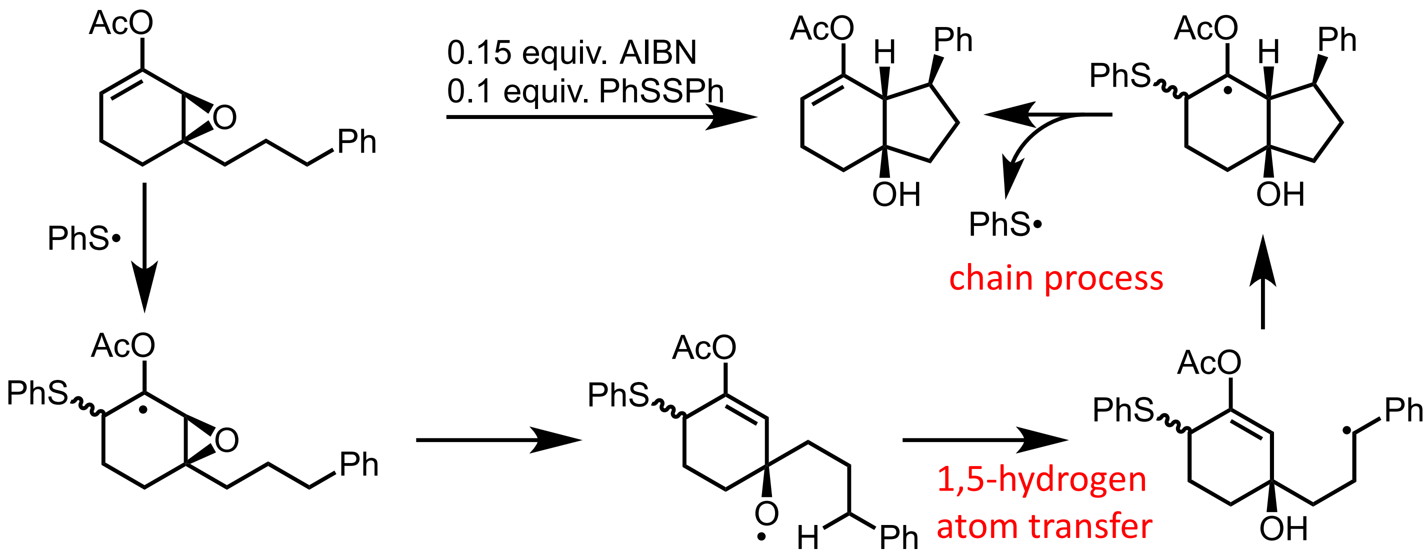
- termination – radical-radical recombination or disproportionation

- examples

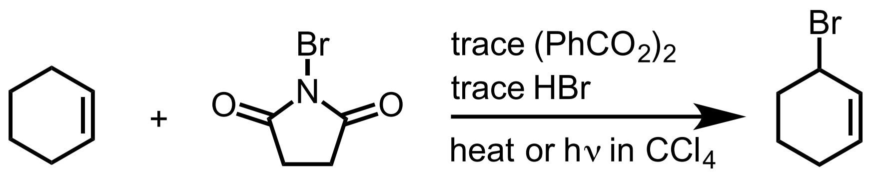


- initiation



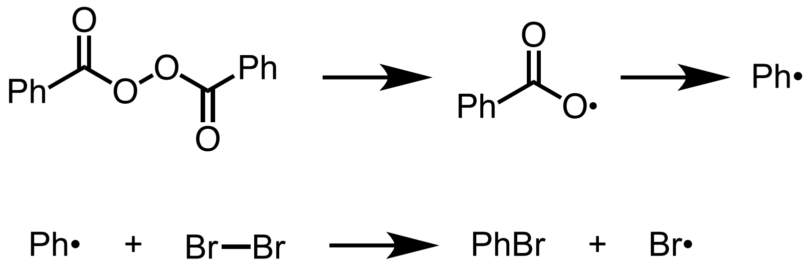


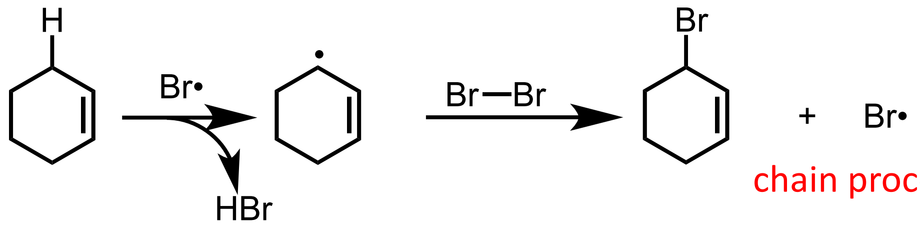
- Wohl–Ziegler bromination – the Goldfinger mechanism



N-bromosuccinimide, NBS

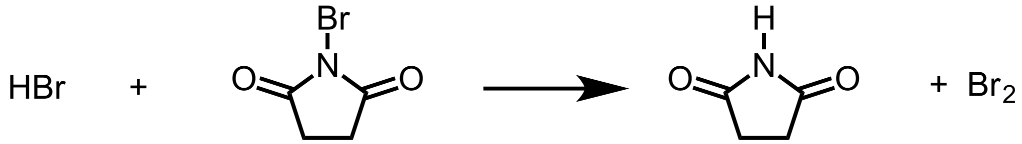
- plausible initiation



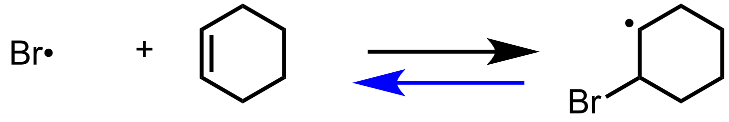


chain process

- NBS provides low steady state concentration of Br_2 by reaction with HBr formed in H-atom abstraction step

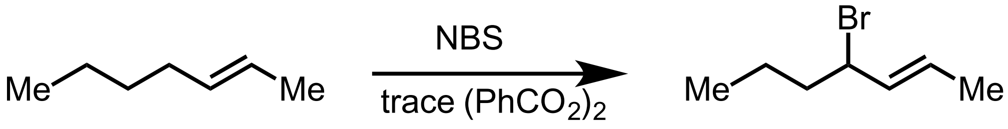


- low $[Br_2]$ and [HBr] prevent unwanted radical and polar reactions



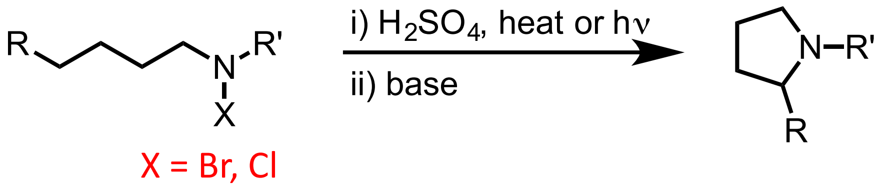
- addition of Br• to alkene is reversible (nothing to trap the adduct radical)

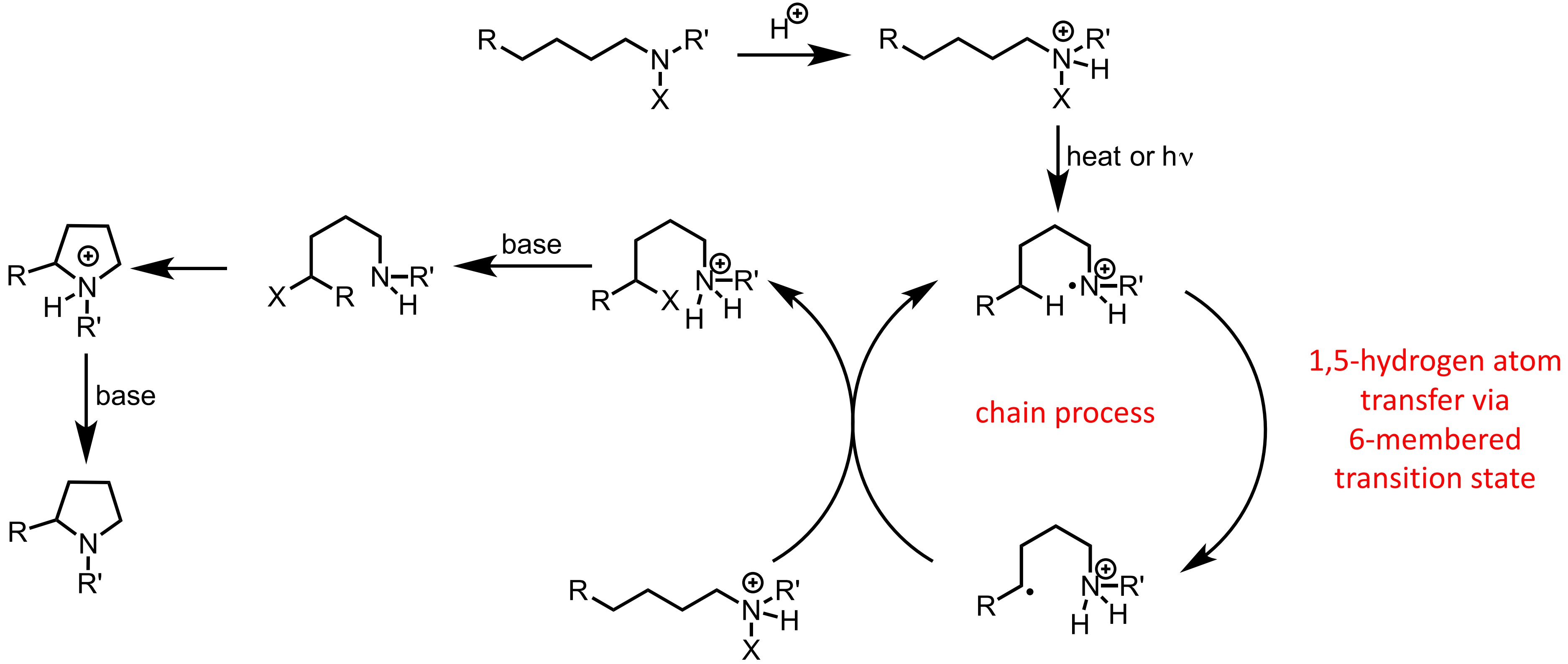
- with unsymmetrical alkenes Br• abstracts the hydrogen atom so as to give the most stable radical



Hofmann-Löffler-Freytag reaction

- both the Wohl-Ziegler bromination and the Hofmann–Löffler–Freytag reaction provide methods for functionalising unactivated C—H bonds





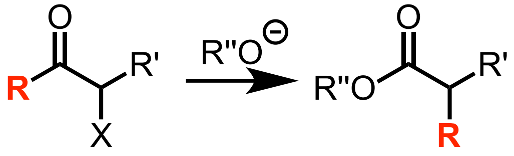
chain process

1,5-hydrogen atom transfer via 6-membered transition state

Rearrangements and Reactive Intermediates

1A Organic Chemistry

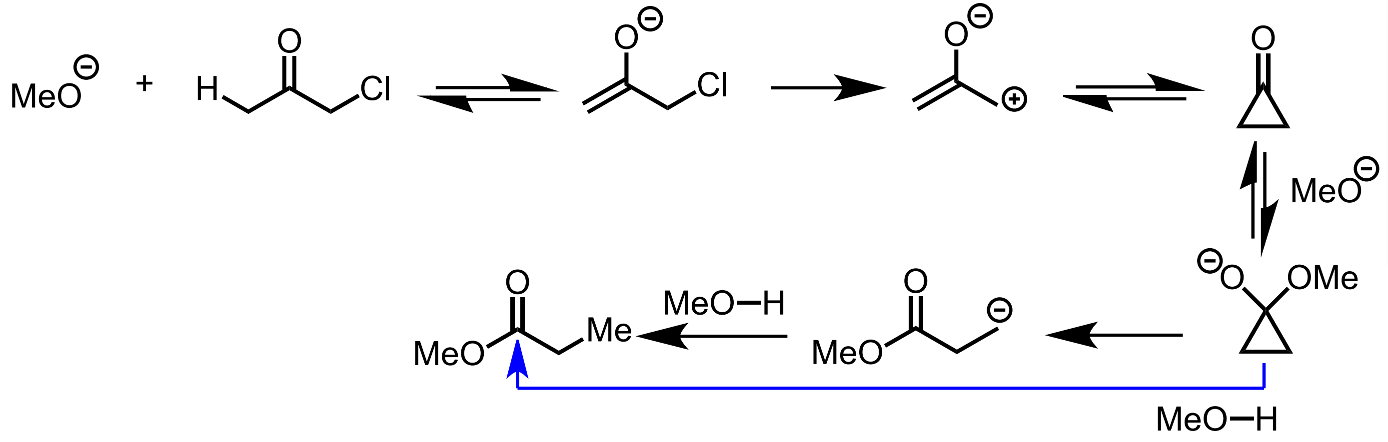
Handout 4 - Elucidating the Mechanisms of Rearrangements



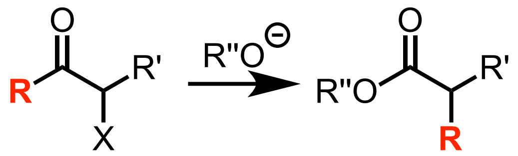
Favorskii rearrangement

Case Studies: Elucidating the Mechanisms of Rearrangements

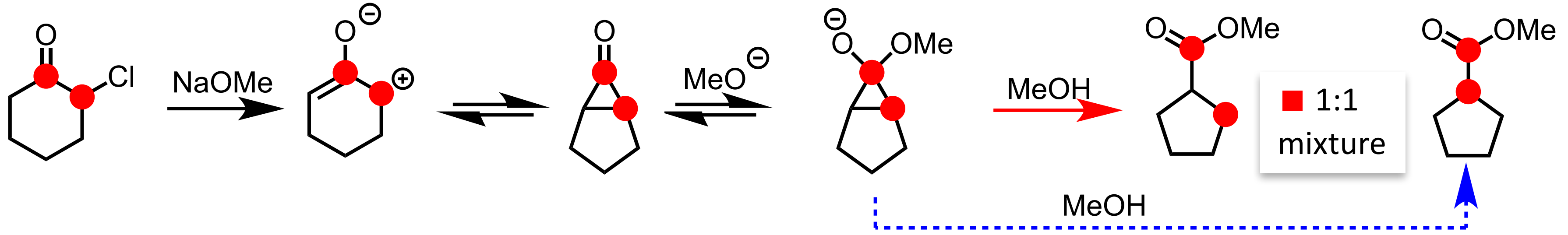
- chemists gather evidence to both support and refute a proposed mechanism
- Favorskii rearrangement – previously discussed mechanism



- overall in the Favorskii rearrangement an alkyl group (**R**) moves from one side of the carbonyl group to the other

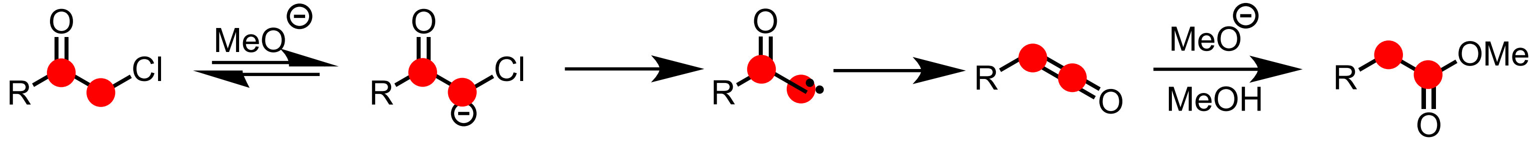


- symmetrical intermediate established by Loftfield with doubly labelled substrate (● = ^{14}C label)



■ 1:1 mixture

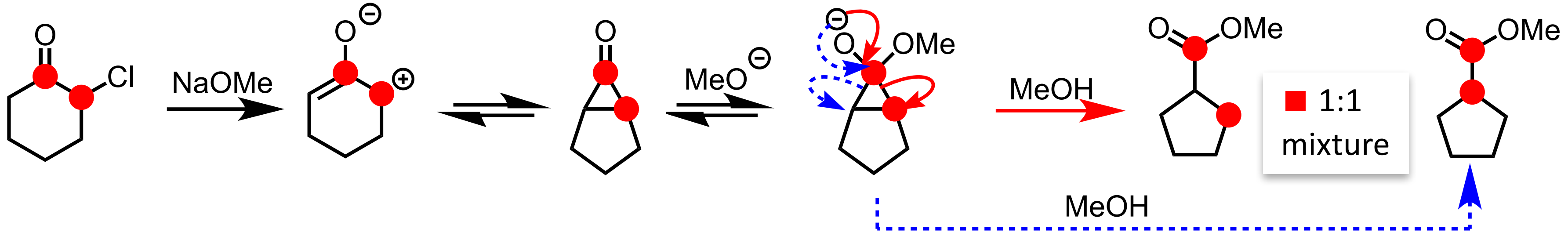
- Loftfield experiment ruled out a number of previously proposed mechanisms such as:



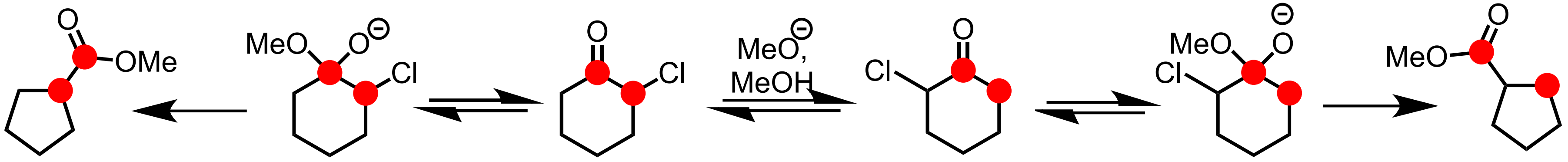
reasonable mechanism ruled out by double labeling experiment

- but does the Loftfield experiment really demonstrate a symmetrical intermediate?

- symmetrical intermediate established by Loftfield with doubly labelled substrate ● = ^{14}C label

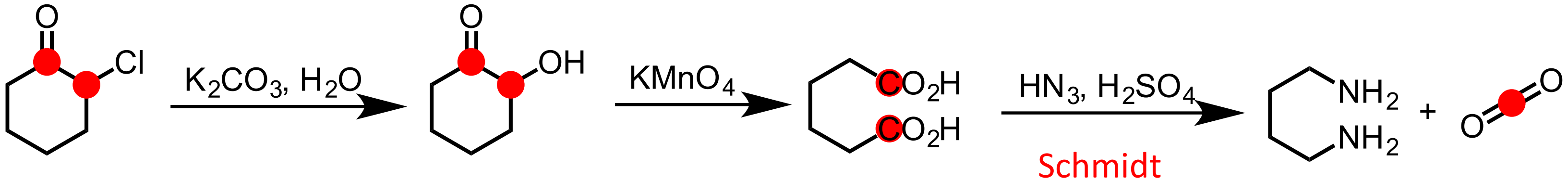


- if the α-chloroketone undergoes isomerisation under basic conditions then the same isotope distribution could be observed by a quasi-Favorskii mechanism



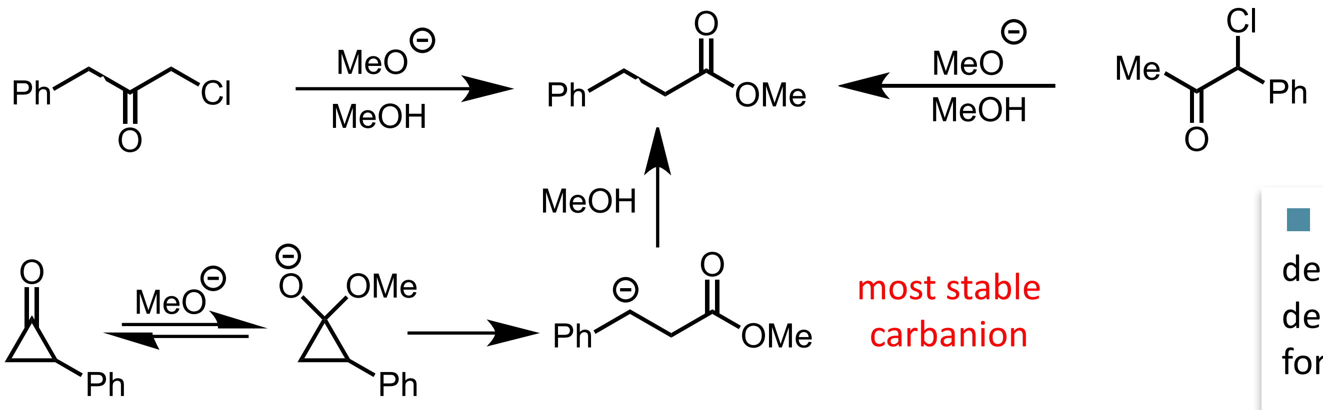
chloride isomerisation does not occur under reaction conditions

- Loftfield demonstrated that the isomerisation proposed above **does not** occur under the reaction conditions by halting the reaction prior to completion and reisolating the starting material which had the labelled carbons at their original positions



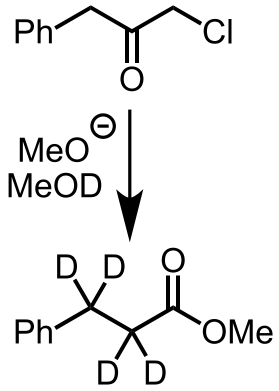
Schmidt reaction

- further evidence for a cyclopropanone intermediate – isomeric substrates give the same product

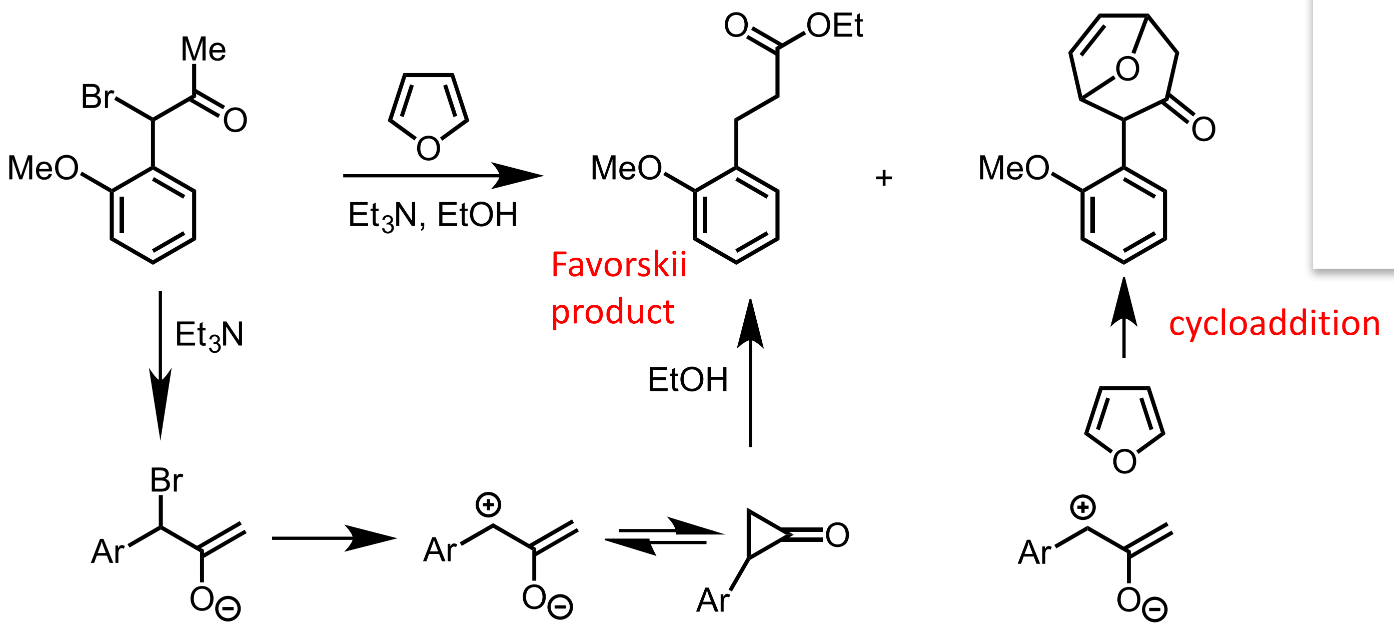


most stable carbanion

- in the Favorskii reaction deuterium exchange occurs demonstrating that enolates are formed reversibly



- evidence for an oxyallyl intermediate

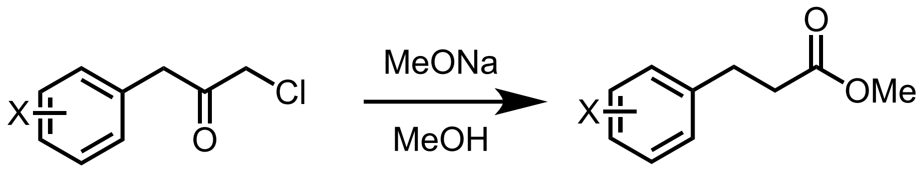


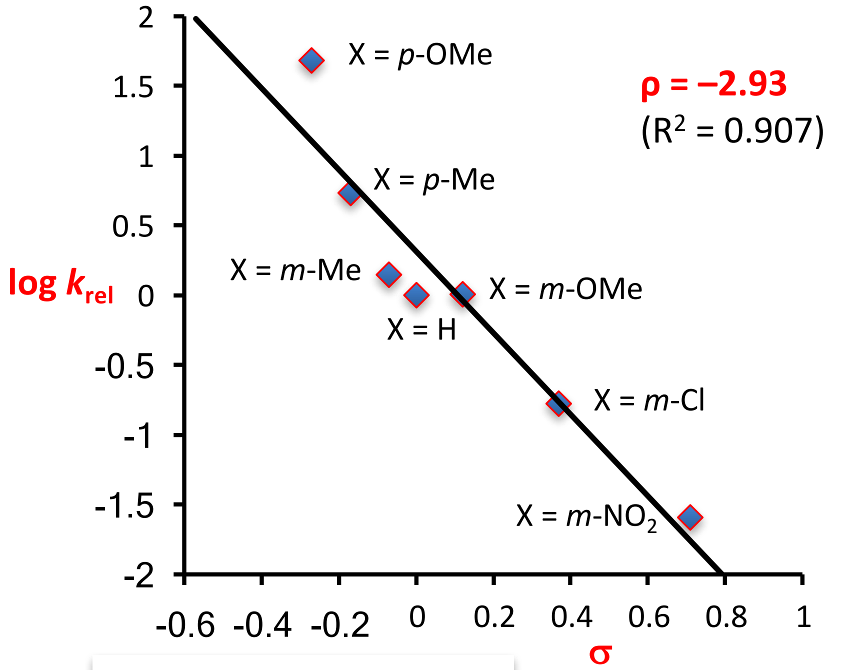
Favorskii product

cycloaddition

- deuterium exchange indicates a rapid equilibrium prior to rearrangement

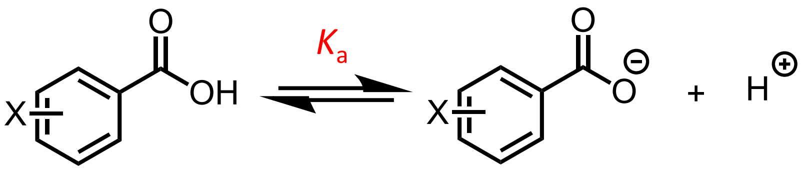
- substituent effects: a Hammett plot showing the effect of substituents on the rate of reaction is given below





🟥 $k_{rel} = k_X/k_H$, $\sigma = \sigma_X$

- Hammett equation - refresher



$\sigma_x = \log_{10}K_{ax} - \log_{10}K_{aH}$

$\therefore\ \sigma_x = pK_a(C_6H_5CO_2H) - pK_a(XC_6H_4CO_2H)$

i.e. **σ_x is positive for EWG and negative for EDG**

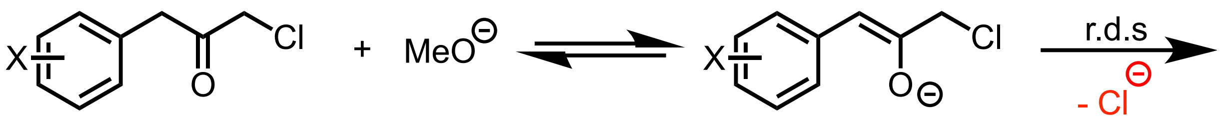
- Hammett equation $\log_{10}(k_x/k_H) = \rho\sigma$

- **a positive ρ means electrons flow into transition state** i.e. electrons flow towards aromatic ring

- **a negative ρ means electrons flow out of transition state** i.e. electrons flow away from aromatic ring

- the above also applies to equilibria - a positive ρ means that the product side of the equilibrium is favoured by EWGs and *vice versa*

- negative ρ value for Favorskii rearrangement needs to be interpreted carefully due to equilibrium prior to rearrangement



$\rho = -2.93$

- Hammett ρ value is a combined value for all the steps up to and including the rate determining step

- ρ value for enolisation of arylmethyl phenyl ketones = **+1.73**

$\rho = +1.73$

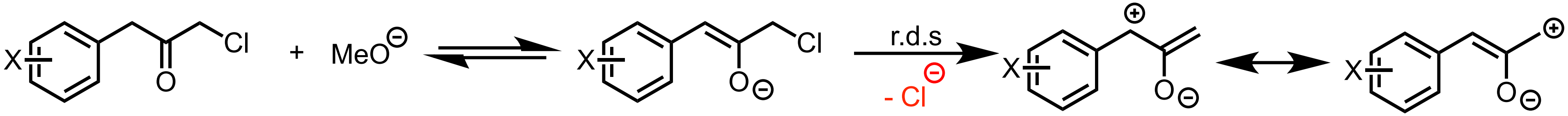
- enolisation in base should be favoured by EWG on aromatic ring ∴ ρ = **+1.73** makes sense

- for Favorskii reaction ρ_{reaction} = **–2.93** which is made up of the enolisation step and the subsequent loss of chloride

- $\rho_{\text{reaction}} = \rho_{\text{enolistion}} + \rho_{\text{chloride loss}}$

- ∴ $\rho_{\text{chloride loss}} = -2.93 - 1.73 = -4.66$ i.e. moderate-to-large and negative - electrons flow out of transition state

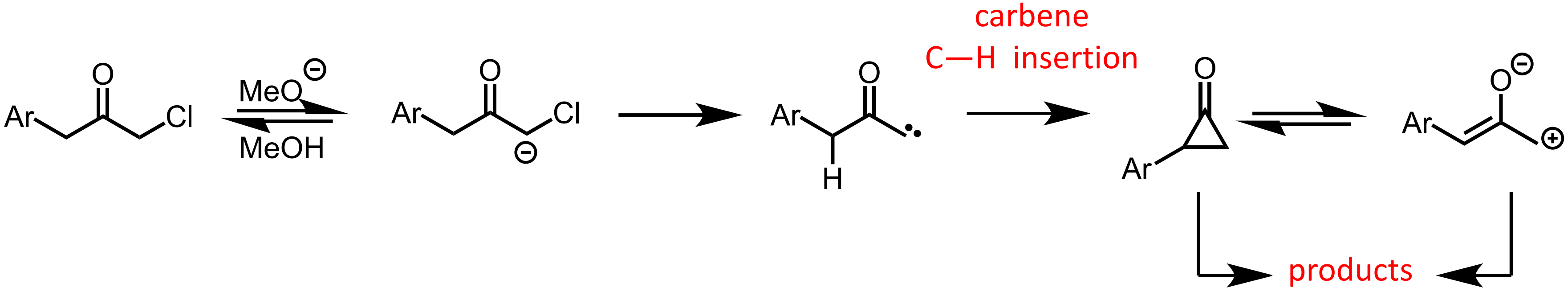
- magnitude of negative ρ implies positive charge near the ring and is consistent with loss of chloride to give an oxyallyl cation



$\rho = +1.73$ **$\rho = -4.66$**

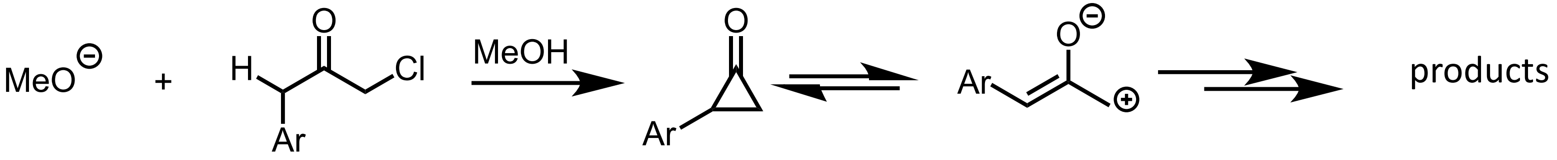
- proposed mechanisms which **do not** fit the data

- carbene mechanism

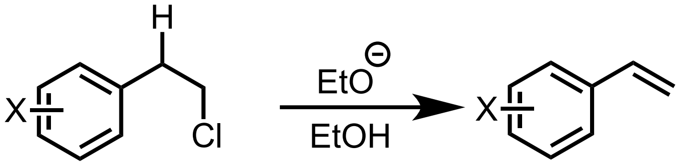


- deprotonation followed by loss of chloride should be relatively insensitive to substituents on the aryl group as there is no conjugation – the inductive effect of the aryl group will be small ∴ **ρ = –2.93** inconsistent with carbene mechanism

- concerted mechanism



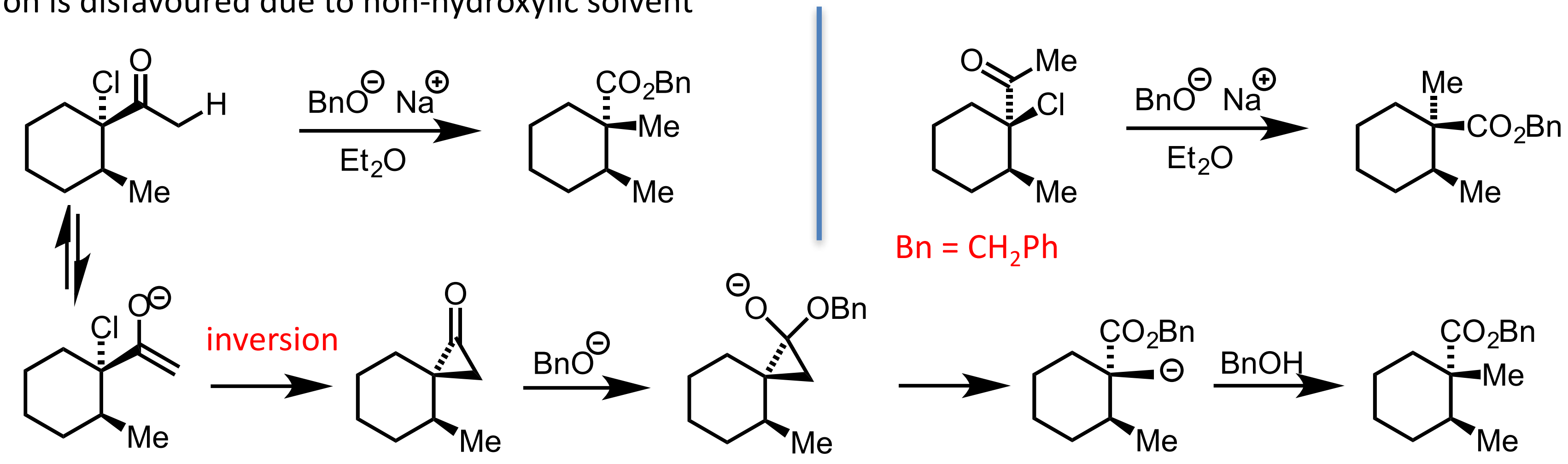
- for E2 elimination (1,2-elimination) from arylethyl chlorides **ρ = +2.61** i.e. reaction is accelerated by EWG



ρ = +2.61

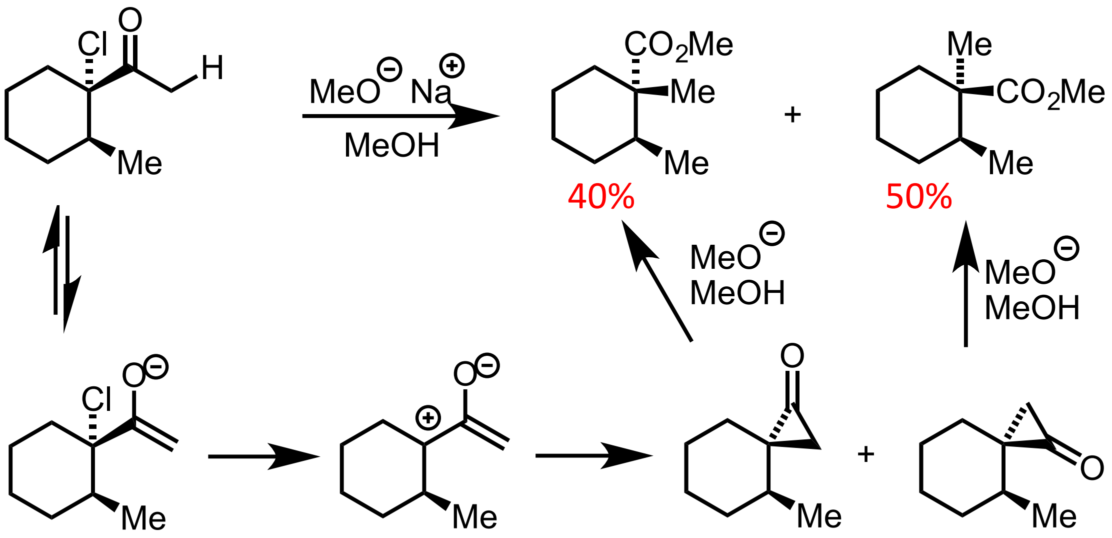
- the concerted 1,3-elimination should have a simliar **ρ** value but as **ρ = –2.93** for the Favorskii rearrangement this allows the concerted mechanism to be discounted in this system

- stereochemistry of the Favorskii rearrangement
- in non-hydroxylic solvents, stereospecific reactions can be observed – here S_N1 loss of chloride to form an oxyallyl cation is disfavoured due to non-hydroxylic solvent

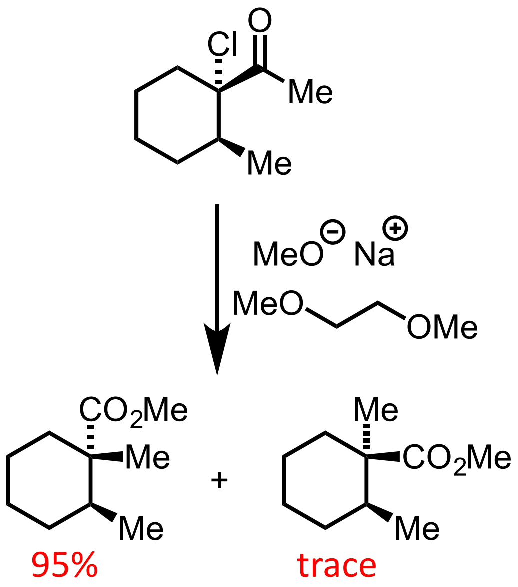


Bn = CH_2Ph

- in more polar, alcoholic solvent, reaction is no-longer stereospecific

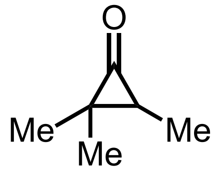


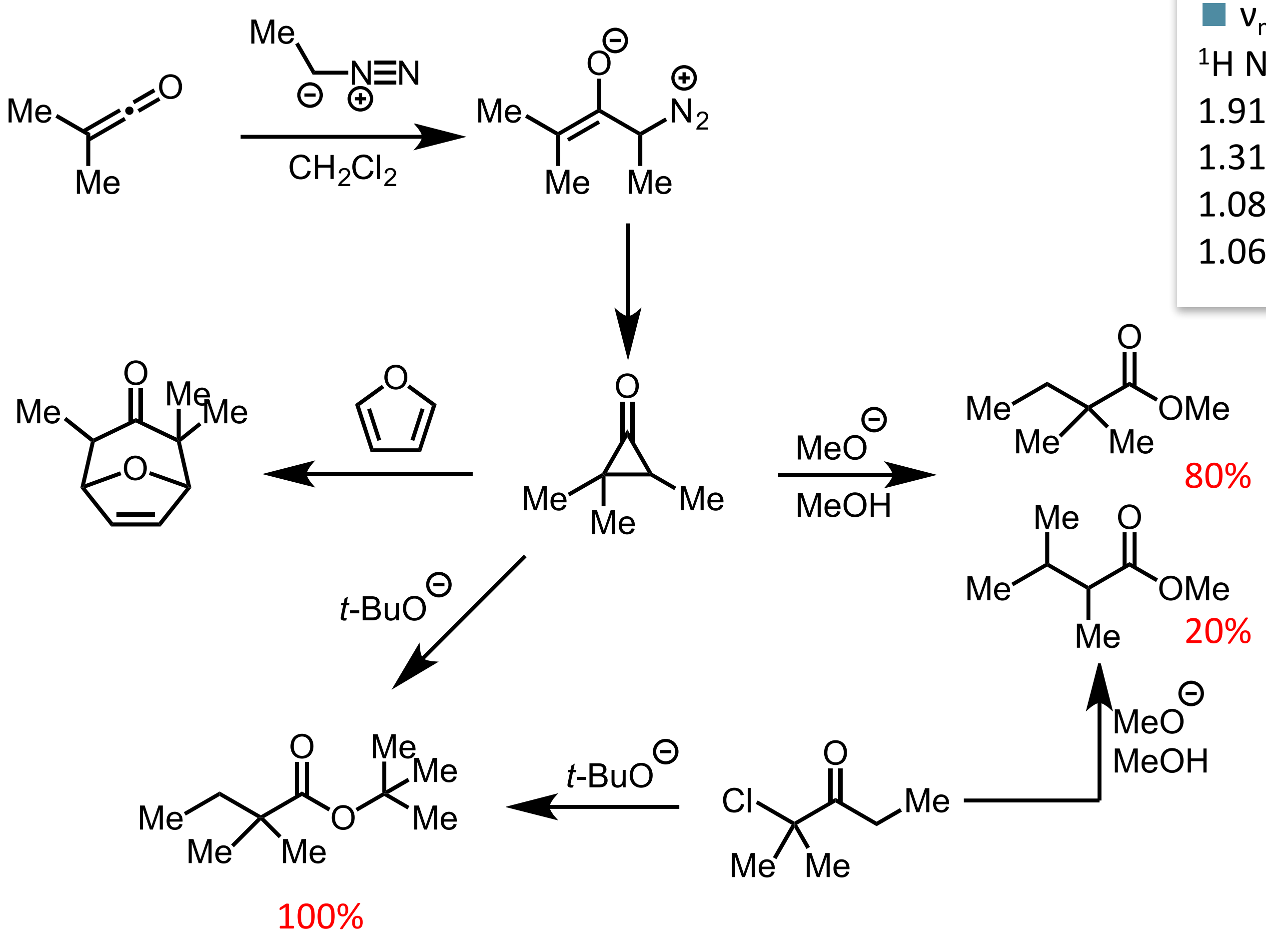
- use of a non-hydroxylic solvent restores the stereospecificity



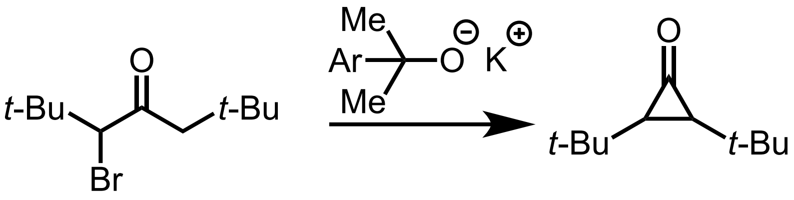
- further evidence – cyclopropanones can be isolated and they give the same distribution of products as the Favorskii rearrangement of α-haloketones under the same reaction conditions

- $\nu_{max} = 1850\ cm^{-1}$
  ^1H NMR: δ_H =
  1.91 (q, J = 7.5 Hz, 1H),
  1.31 (s, 3H),
  1.08 (d, J = 7.5 Hz, 3H),
  1.06 (s, 3H)

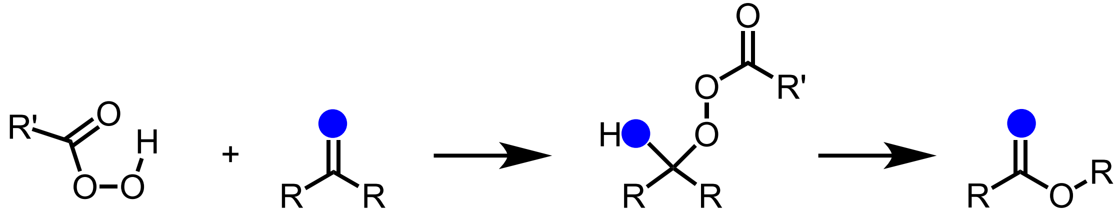




- cyclopropanones can also be isolated under Favorskii rearrangement conditions

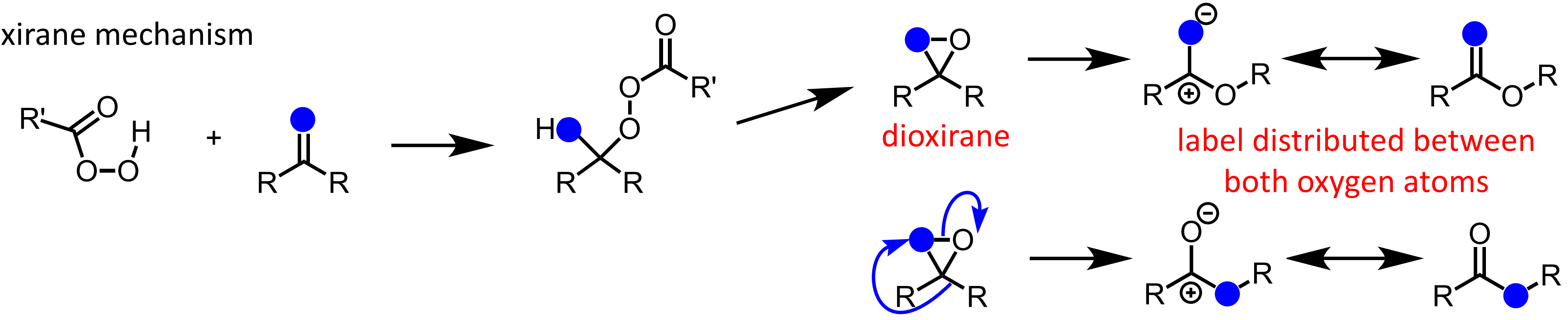


- Baeyer-Villiger oxidation - the group which best supports a positive charge migrates
- accepted mechanism (Criegee mechanism)



label in carbonyl oxygen

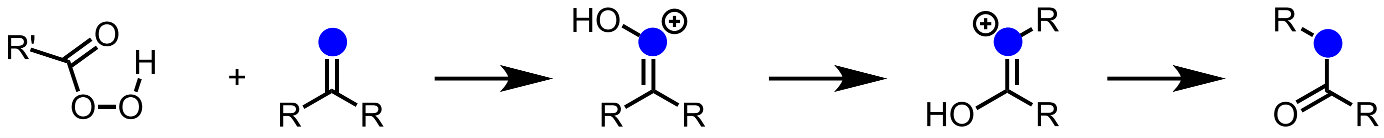
- some other reasonable mechanisms were originally proposed
- dioxirane mechanism



dioxirane

label distributed between both oxygen atoms

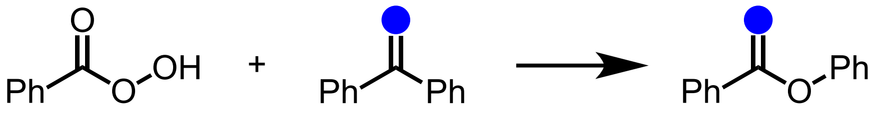
- peroxide mechanism



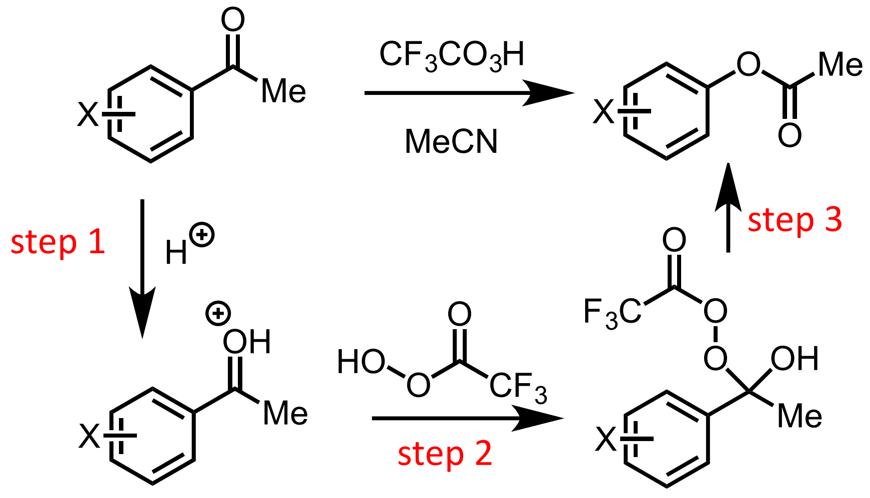
peroxide

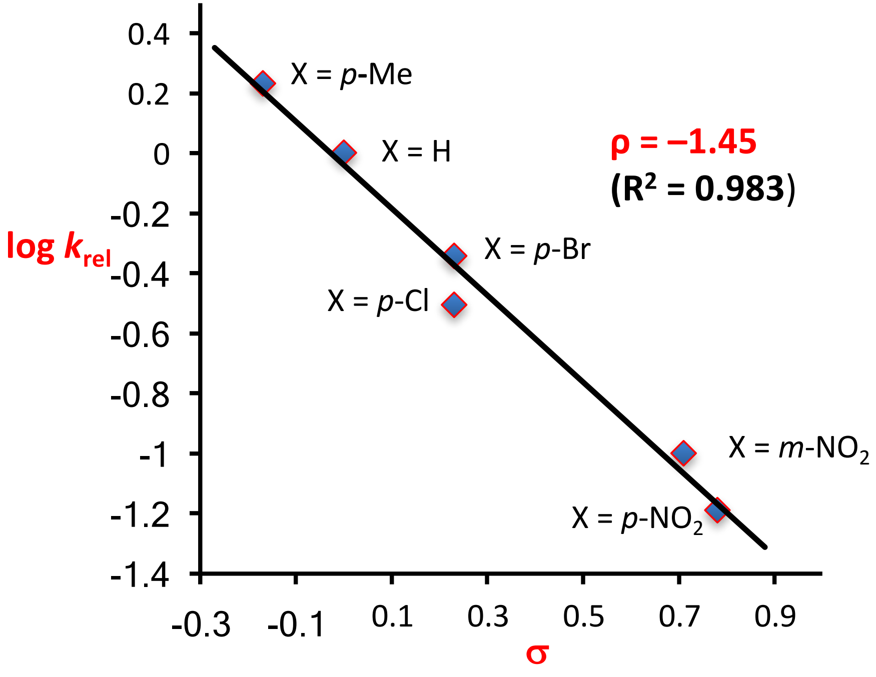
label in non-carbonyl oxygen

- isotope labeling studies are only consistent with the Criegee mechanism (● = ^{18}O)



- Baeyer-Villiger oxidation – nature of the rate determining step





- Hammett plot for the above rearrangement has **ρ = –1.45**

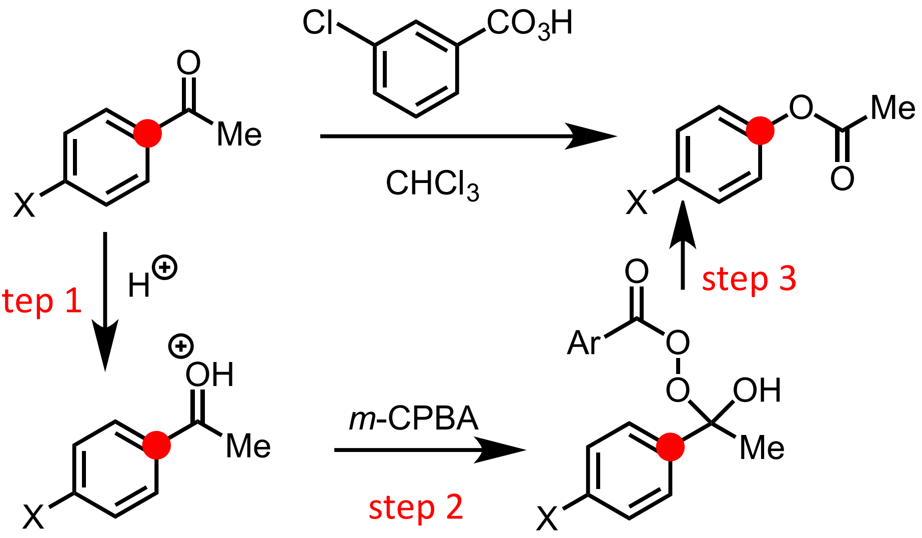
- typical Hammett values for acid catalysed addition of heteroatoms to carbonyl groups (steps 1 and 2) have positive **ρ** values - e.g. acid catalysed hydrolysis of ethylbenzoates ($ArCO_2Et$) has **ρ = + 0.144**

- for above Baeyer-Villiger reaction **ρ = –1.45** ∴ likely step 3 is rate determining

- remember positive **ρ** electrons flow into transition state, negative **ρ** electrons flow out of transition state

- negative **ρ** for step 3 makes sense – reaction is accelerated by electron donating aryl groups

- Baeyer-Villiger oxidation – nature of the rate determining step (● = ^{14}C)



X	k_{12}/k_{14}
CN	1.085
Cl	1.052
H	1.048
CH_3	1.003
CH_3O	0.998

- kinetic isotope effect demonstrates that rate determining step is **step 3** for all the substituents except **X = OCH_3** i.e. there is significant alteration in the bonding to the labelled carbon in the rate determining step giving rise to the observed kinetic isotope effect

- lack of kinetic isotope effect for **X = OCH_3** indicates formation of the tetrahedral intermediate is rate determining for **X = OCH_3**

- with **X = OCH_3** step 3 becomes fast (EDG increase rate of Baeyer-Villiger reaction) and step 2 becomes rate determining – i.e. attack of *m*-CPBA on activated carbonyl group is slower than rearrangement

- in general, rearrangement is the rate determining step