Rearrangements and Reactive Intermediates
Hilary Term

1A Organic Chemistry

Handout 1

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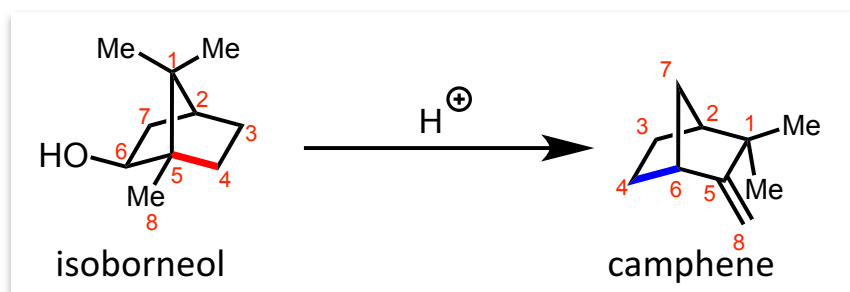
- *Polar Rearrangements*, Oxford Chemistry Primer no. 5; L. M. Harwood
- *Organic Chemistry* J. Clayden, N. Greeves, S. Warren – Chapters 36-41
- *Reactive Intermediates,* Oxford Chemistry Primer no. 8; C. J. Moody, G. H. Whitham

- *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.

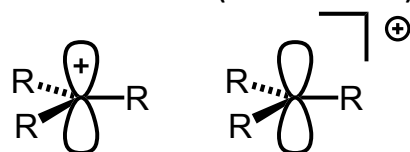## Types of High Energy Intermediates
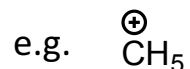
■ Electron Deficient Cations
Two classes of carbocations

reactive towards
a) nucleophiles
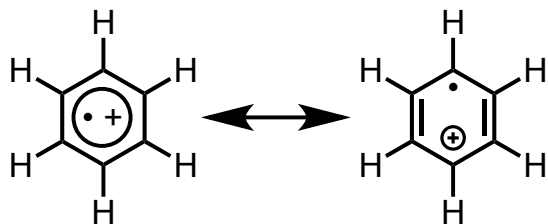b) bases
c) reducing agents
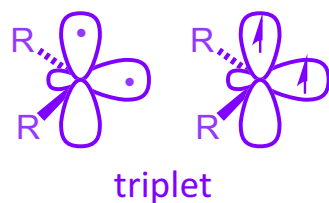
Carbenium ion (6 electrons)

Carbonium ion (8 electrons)
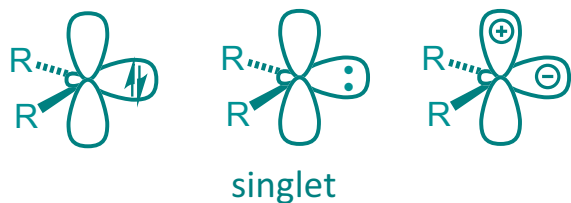
e.g. $\overset{\oplus}{C}H_5$

Radical cation

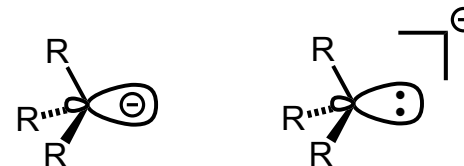■ Neutral species
Carbenes (6 electrons)

singlet   triplet

■ Electron Rich Anions
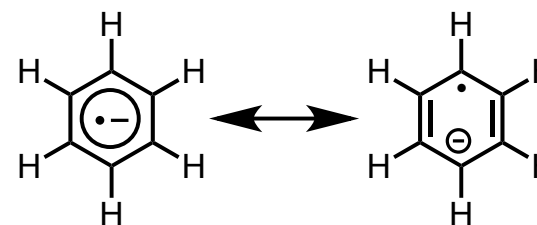Carbanion (8 electrons)

reactive towards
a) electrophiles
b) acids
c) oxidising agents
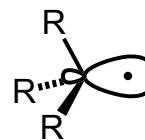
■ Electron Rich Anions
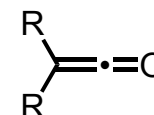Radical Anion

■ Neutral species
Radical (7 electrons)

reactive towards
a) electrophiles or nucleophiles
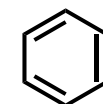b) other high energy agents
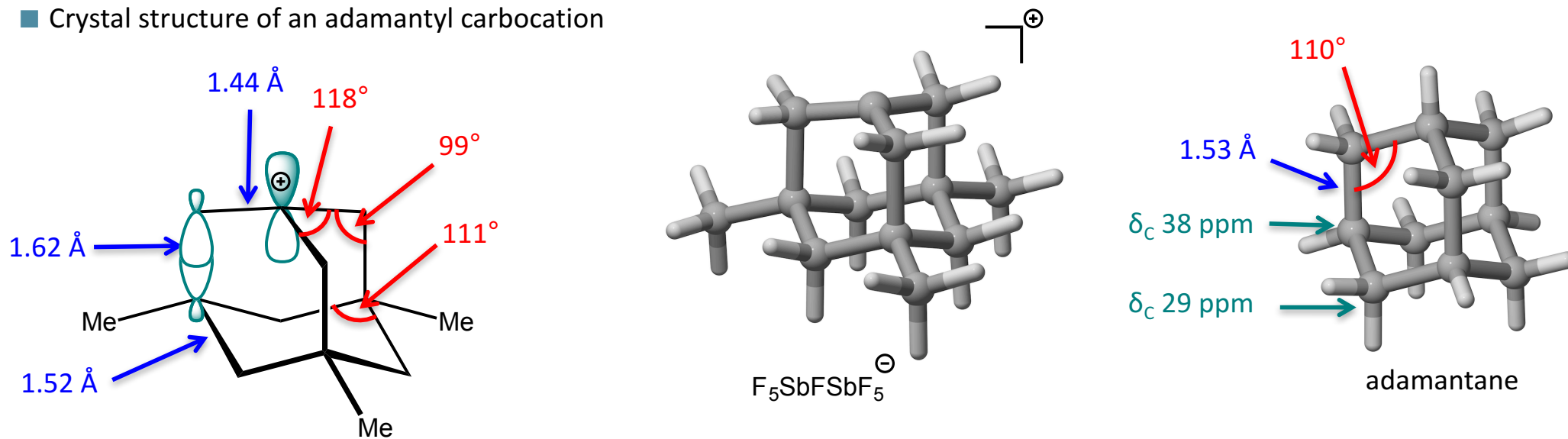c) oxidising or reducing agents

■ Neutral species
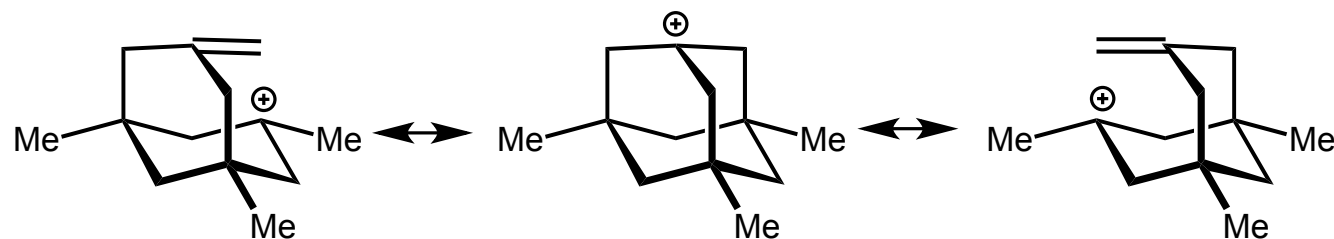ketenes

■ Neutral species
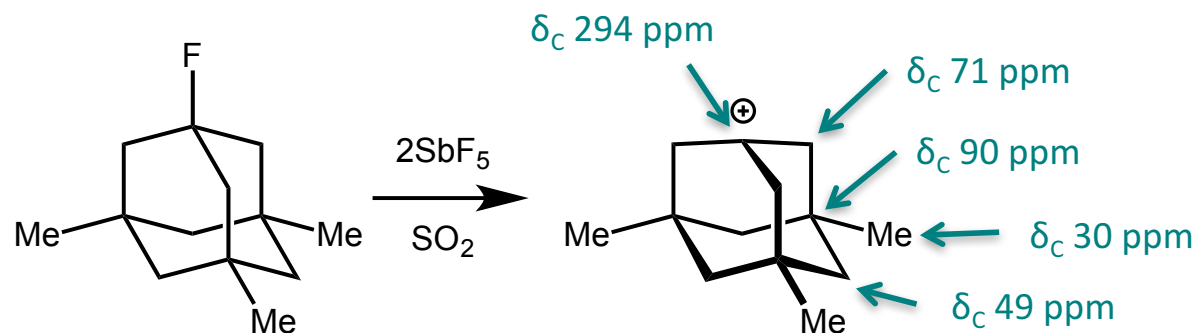arynes

Stuctures of Carbocations
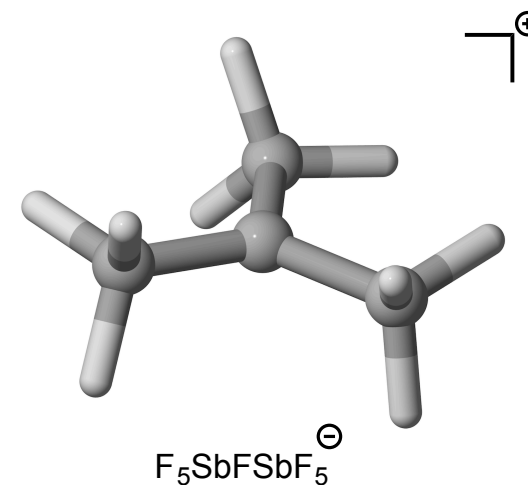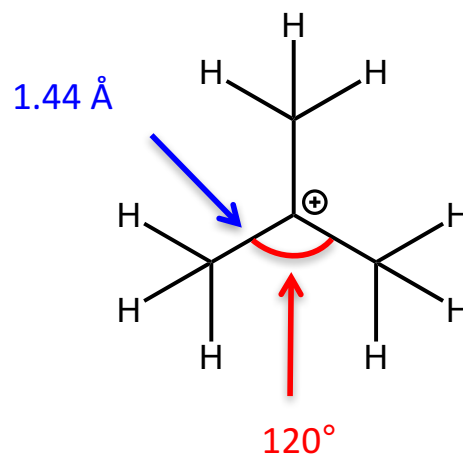
■ Crystal structure of an adamantyl carbocation

1.44 Å
118°
99°
111°
1.62 Å
1.52 Å
Me
Me
Me

$F_5SbFSbF_5^{\ominus}$

110°
1.53 Å
δ_C 38 ppm
δ_C 29 ppm

adamantane

■ C-C σ to empty p

Me — Me — Me ⟷ Me — Me — Me ⟷ Me — Me — Me
Me   Me   Me

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

F
Me — Me
Me

$\xrightarrow[\text{SO}_2]{2SbF_5}$

δ_C 294 ppm
δ_C 71 ppm
δ_C 90 ppm
δ_C 30 ppm
δ_C 49 ppm
Me — Me
Me

■ Bond lengths and bond angles provide evidence of hyperconjugation (T. Laube, *Angew. Chem. Int. Ed.* **1986**, *25*, 349).
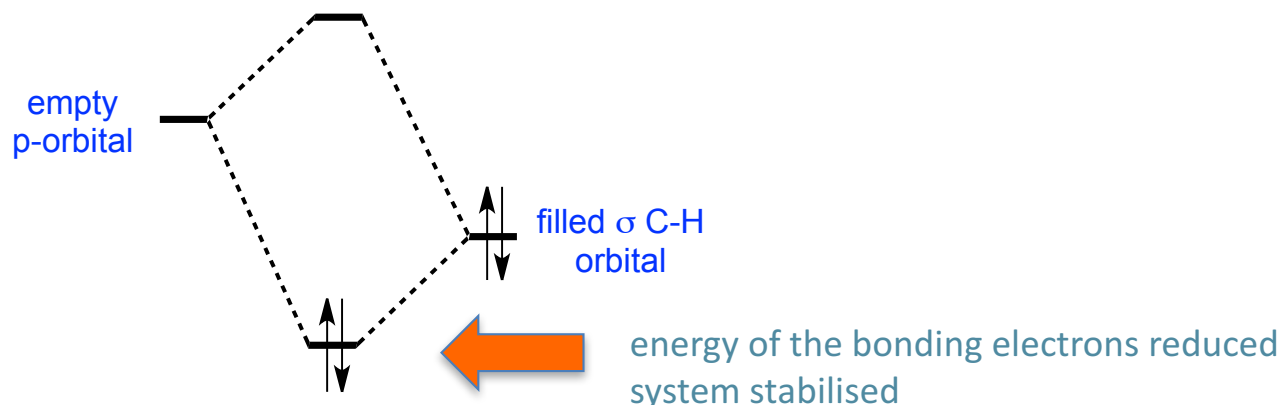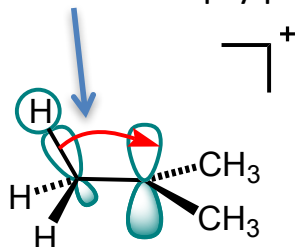
■ Crystal structure of a *t*-butyl carbocation

C-C	sp³-sp³	1.54 Å
C-C	sp³-sp²	1.50 Å
C-C	sp²-sp²	1.46 Å
C=C		1.34 Å

1.44 Å

120°

$F_5SbFSbF_5$

δ_C = 335 ppm

δ_C = 94 ppm

δ_C = 28 ppm

2SbF₅

SO₂

2SbF₅

SO₂

δ_C = 47 ppm

δ_H = 4.35 ppm

δ_C = 171 ppm
(pivalic acid fluoride)

δ_C = 320 ppm

δ_H = 13.5 ppm

SbF₅

SO₂

δ_C = 51.5 ppm

δ_H = 5 ppm
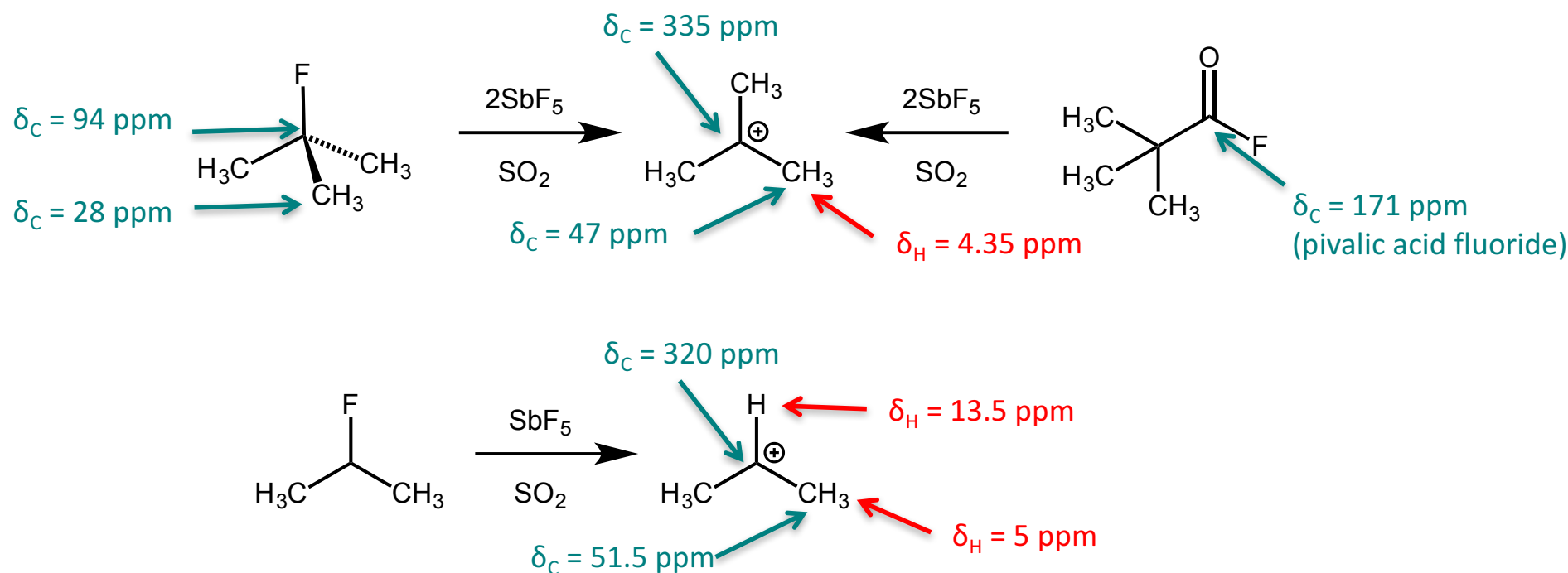
■ Bond lengths provide evidence of hyperconjugation   (T. Laube, *J. Am. Chem. Soc.* **1993**, *115*, 7240).

■ Hyperconjugation

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

empty p-orbital

filled σ C-H 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:

tertiary   secondary   primary

$$R\overset{\oplus}{\underset{R}{C}}R \;>\; R\overset{\oplus}{C}R \;>\; R{-}\overset{\oplus}{C}$$
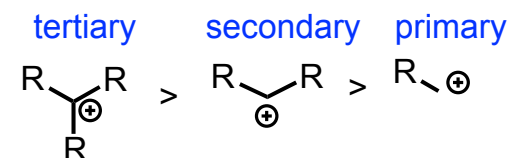
■ conjugation with alkenes, arenes and lone pairs, also stabilises carbenium ions

■ 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

Ph—C(Ph)(Ph)—OH →(H₂SO₄, CH₂Cl₂)→ trityl cation HSO₄⁻ ↔ ...

δ_C = 212 ppm

$\overset{\ominus}{B}(CN)_4$
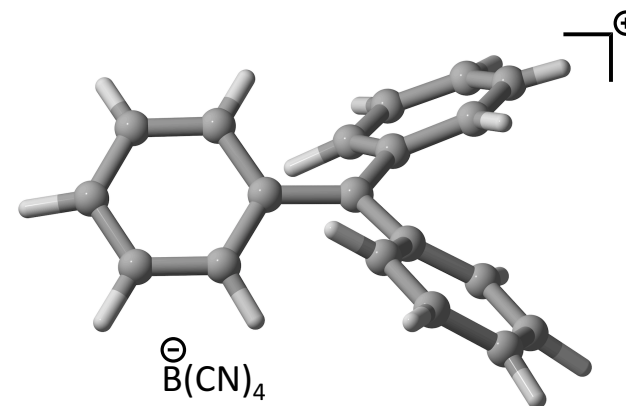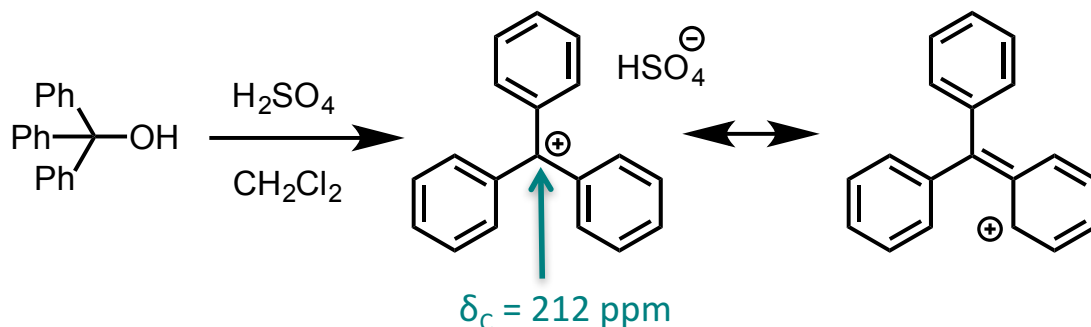
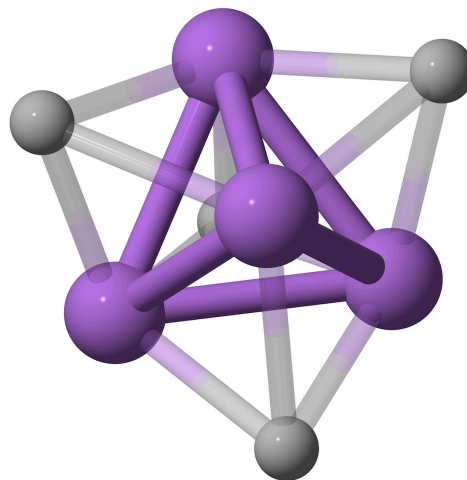**Structures of Carbanions**
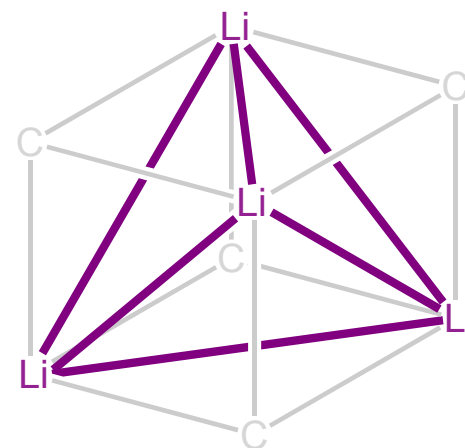
- generally aggregated in the solid state and in solution

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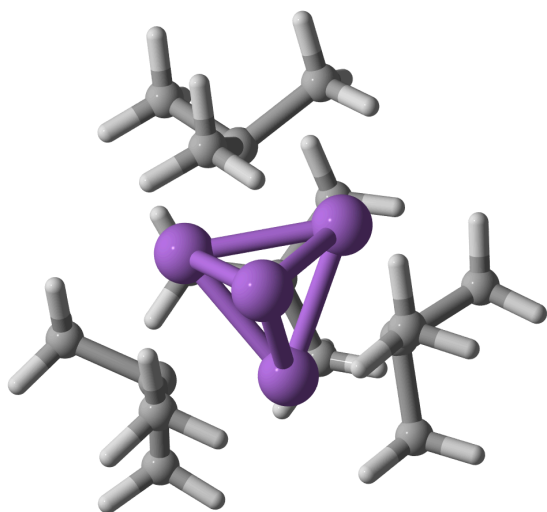
t-butyllithium
(t-BuLi)$_4$
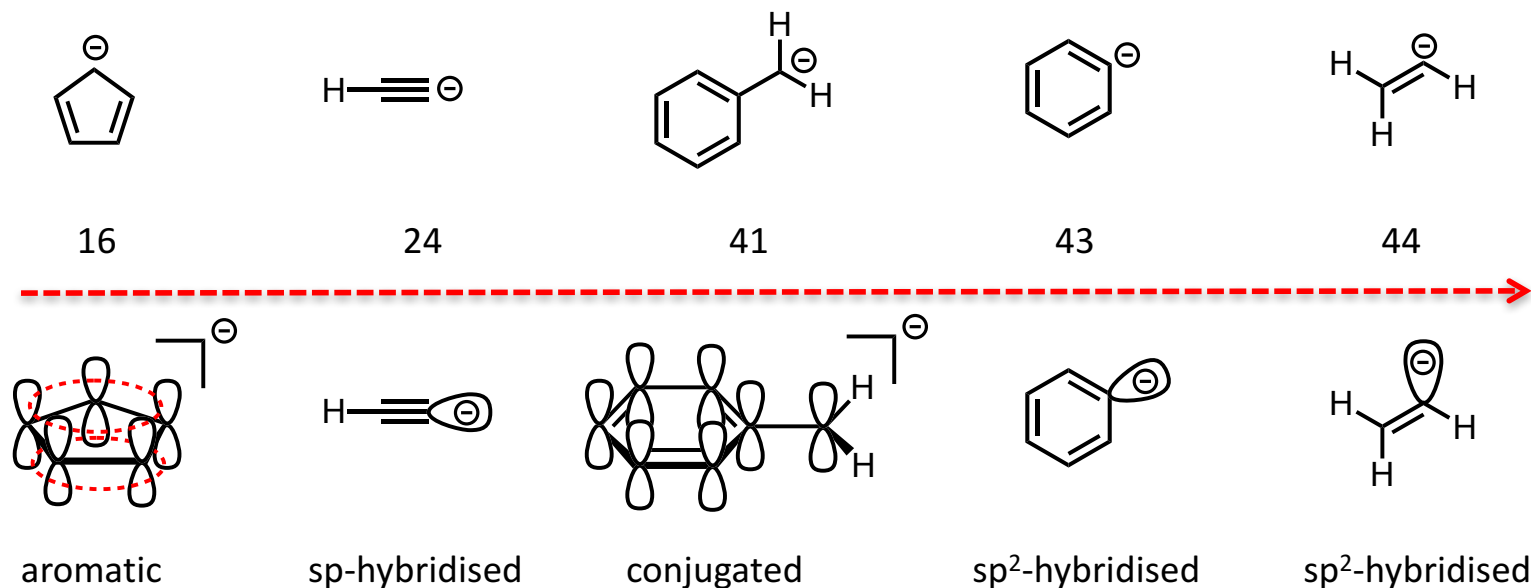
methyllithium
$(MeLi)_4$
(H-atoms removed
for clarity)

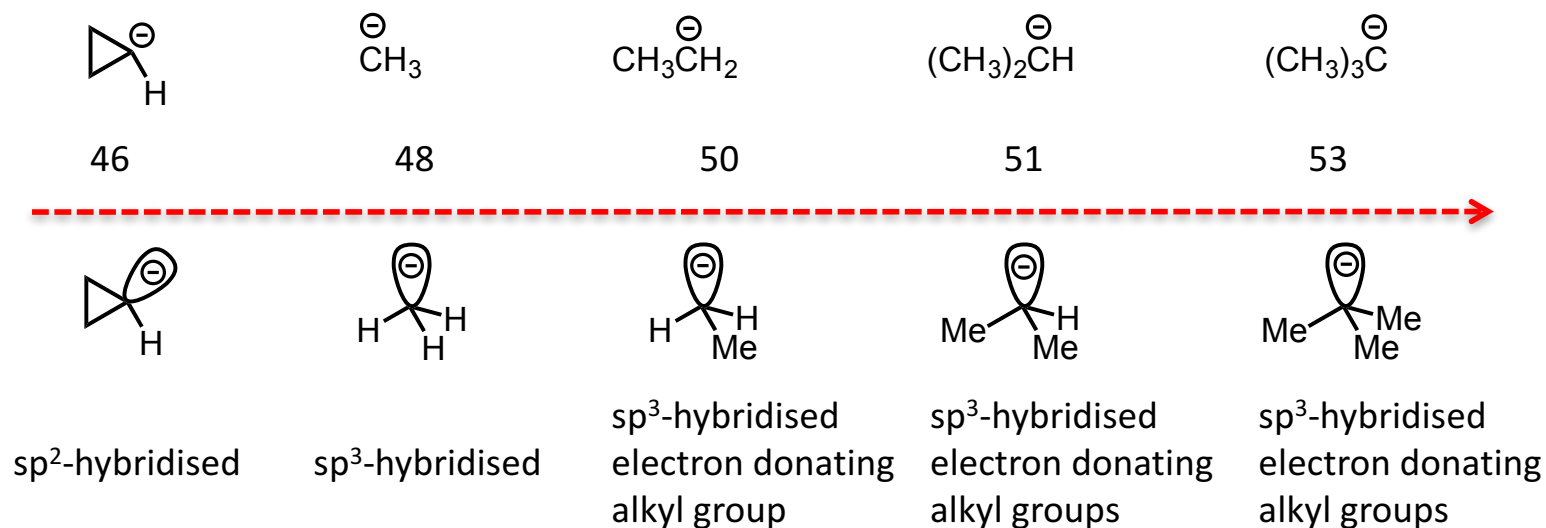idealised arrangement of
lithium and carbon atoms

- 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

CH_3	CH_3CH_2	$(CH_3)_2CH$	$(CH_3)_3C$	
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 sp³ hybridised carbanions (they are isoelectronic with NH_3) and hence chiral carbanions generally undergo rapid racemisation.
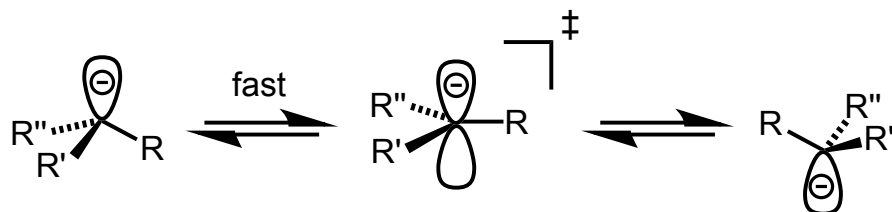
■ vinyl anions and cyclopropyl anions are the exceptions and are generally considered configurationally stable

■ lithium halogen exchange with alkenyl iodides and bromides is a stereospecific process
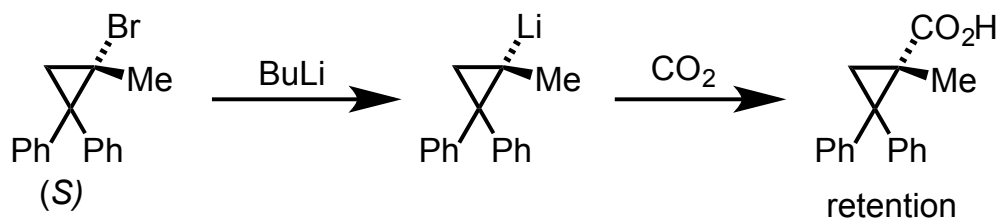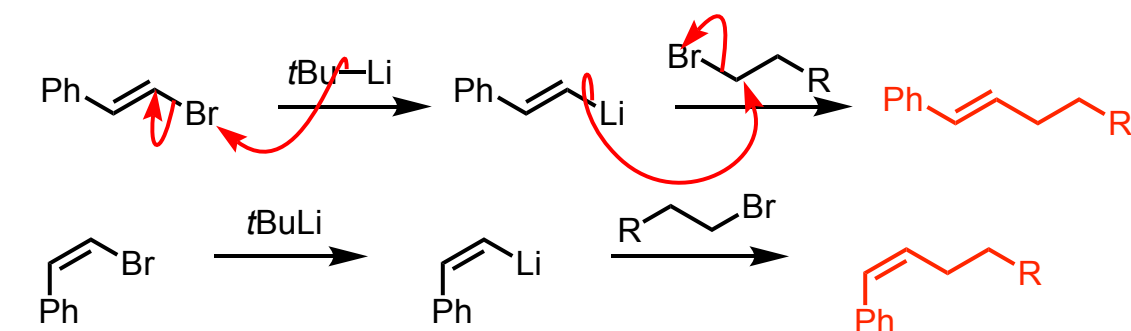
■ sp² hybridisation at transition state for pyramidal inversion
■ ideal 120 ° angles only ca. 60° for cyclopropane
■ transition state highly strained therefore slow rate of inversion
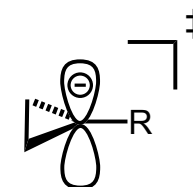
Reactions of Carbocations and Carbanions

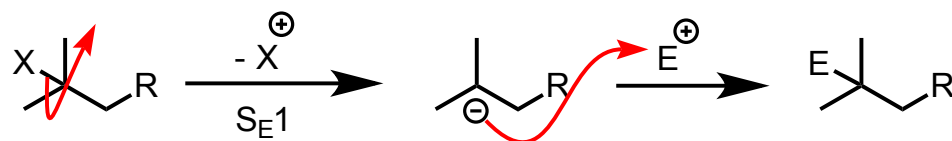■ Generic reaction map of carbocations and carbanions
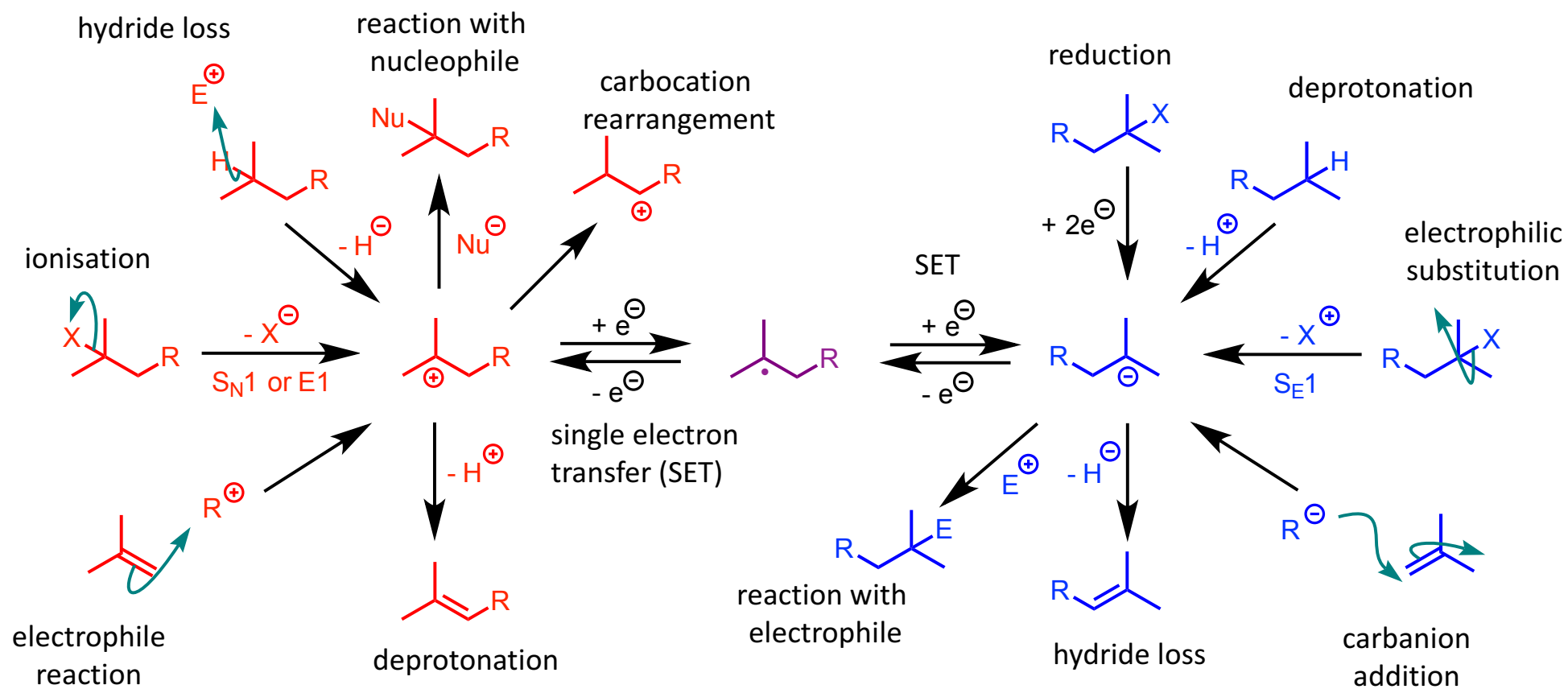
■ most common reaction of carbanions is reaction with electrophiles (e.g. RLi or RMgBr plus $E^{\oplus}$) which is amply covered elsewhere
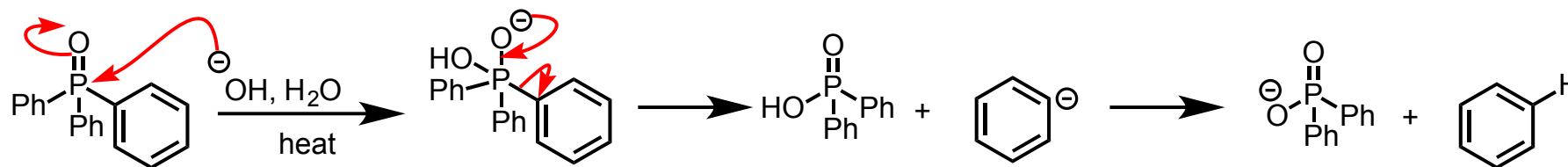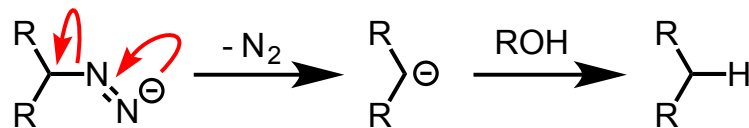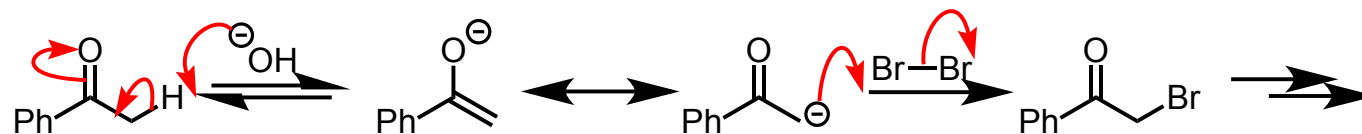
■ some other reactions are shown below

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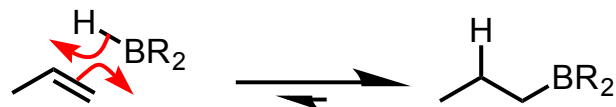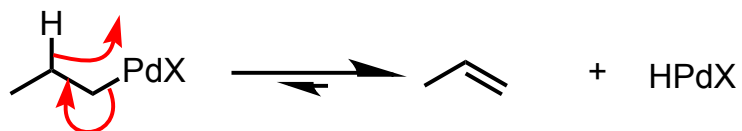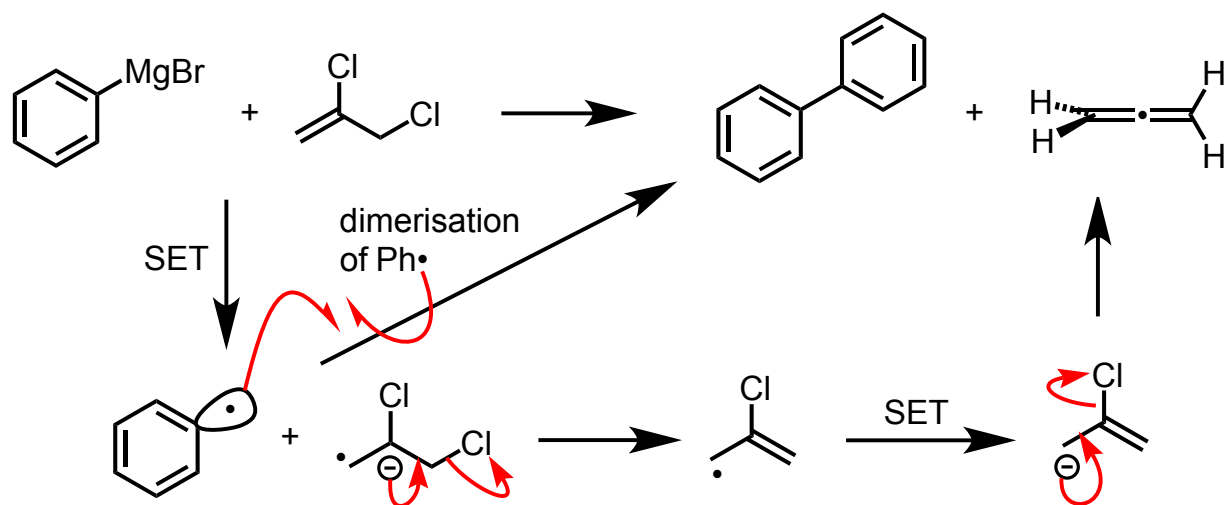
■ generic mechanism

■ examples

■ 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
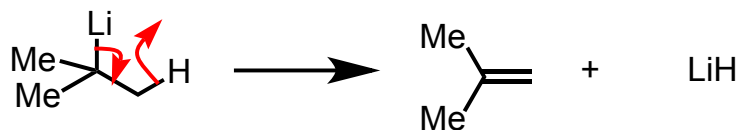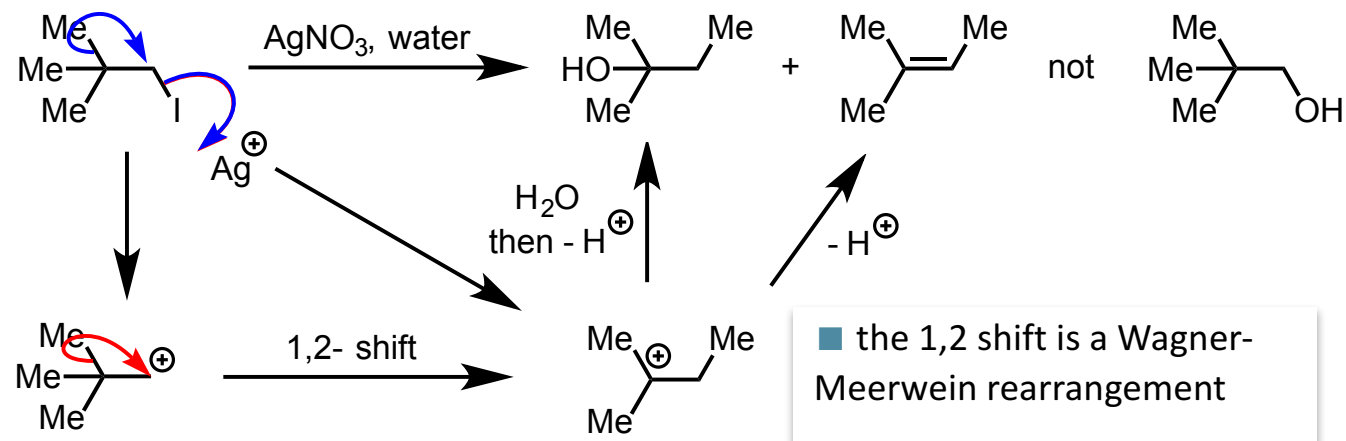
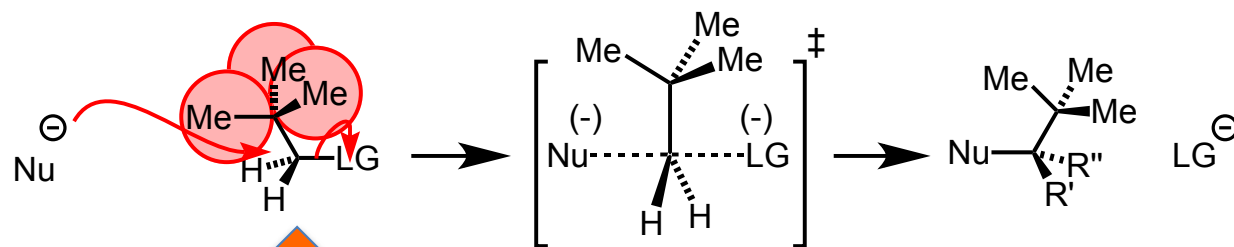

- redox reactions – Single Electron Transfer - SET

- rearrangement of carbocations
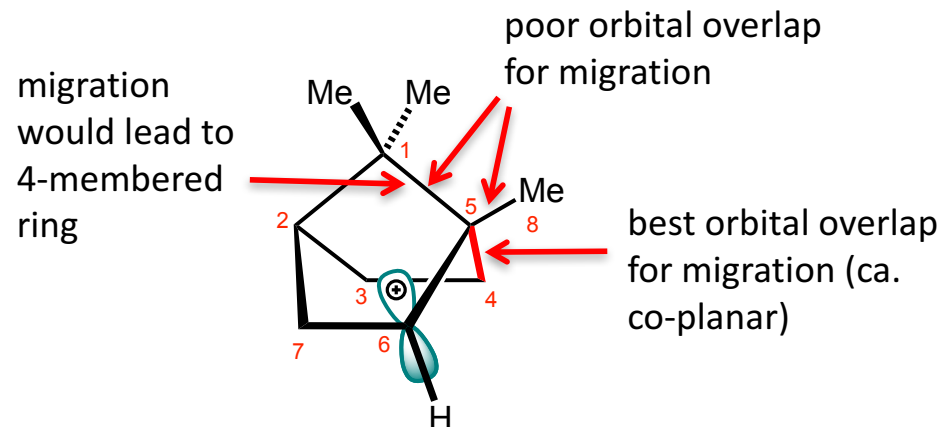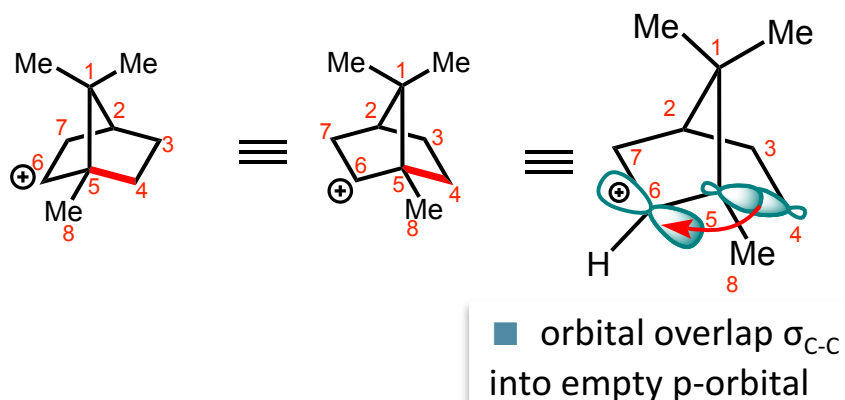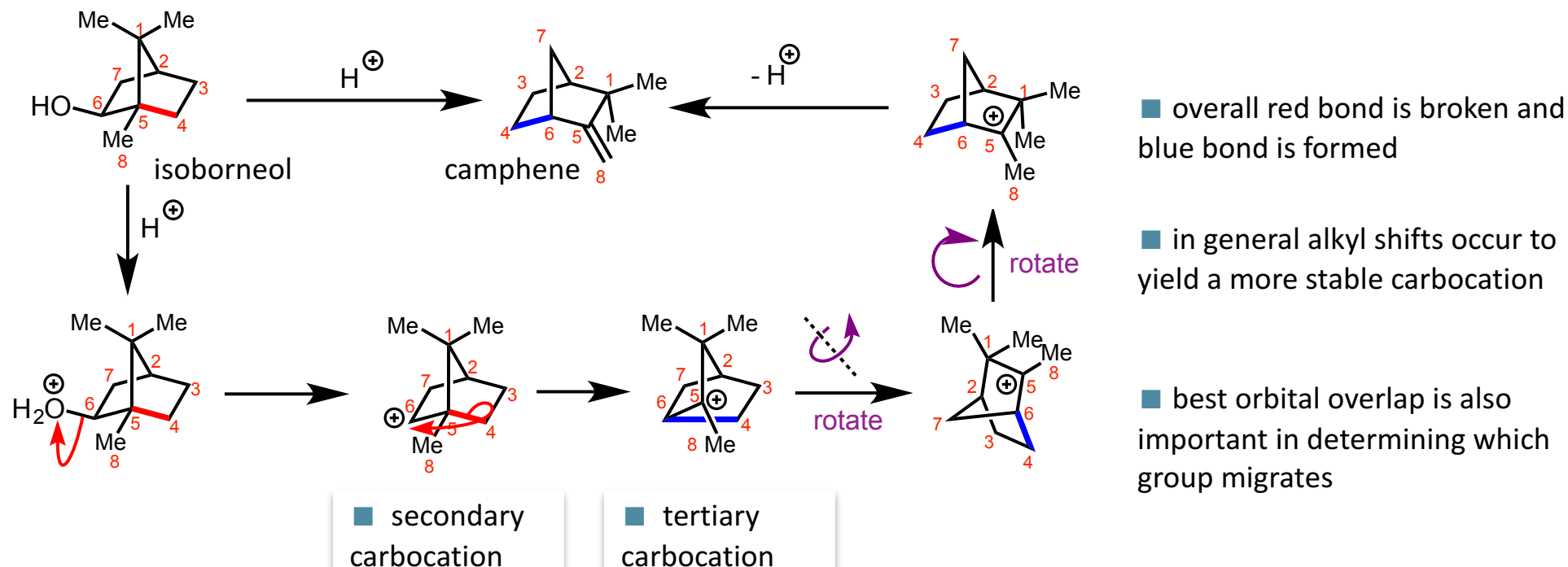
- the neopentyl system

AgNO$_3$, water

HO — Me, Me, Me + Me, Me = Me, Me   not   Me, Me — OH

H$_2$O then - H$^{\oplus}$

- H$^{\oplus}$

Ag$^{\oplus}$

1,2- shift

- 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
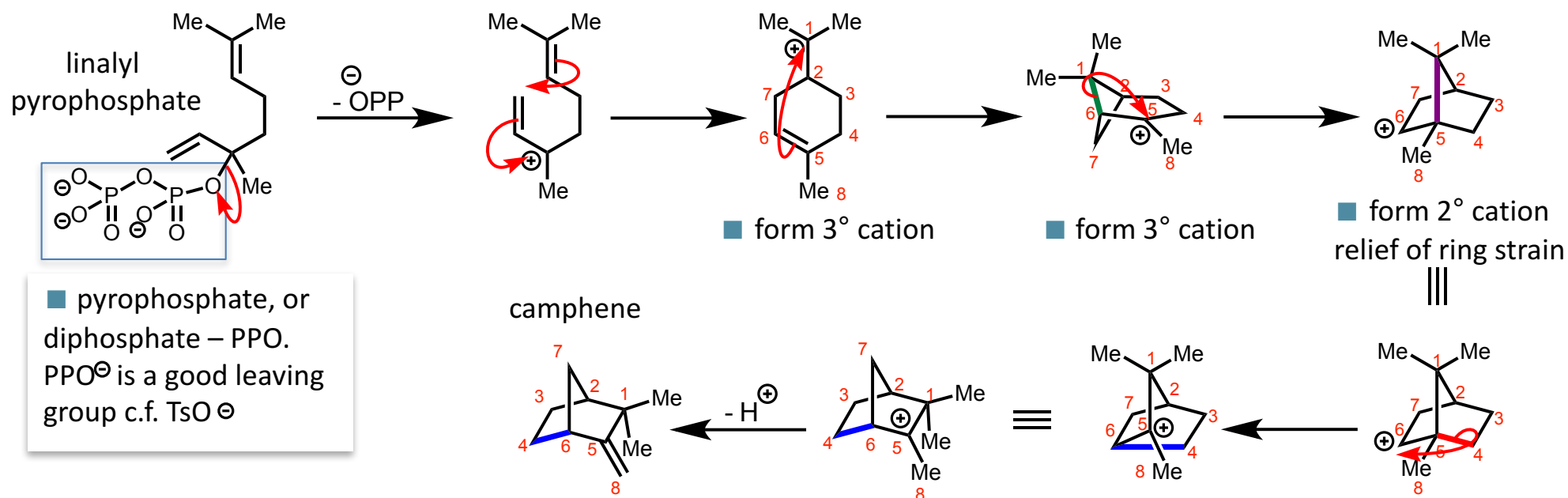

Nu$^{\ominus}$

$\left[\begin{array}{c} \text{Me, Me, Me} \\ (-) \quad (-) \\ \text{Nu} \cdots \cdots \text{LG} \\ \text{H} \quad \text{H} \end{array} \right]^{\ddagger}$

Nu — Me, Me, Me, R", R'   LG$^{\ominus}$

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

■ Wagner-Meerwein rearrangements exemplified

isoborneol

camphene

■ overall red bond is broken and blue bond is formed

■ in general alkyl shifts occur to yield a more stable carbocation

rotate

■ best orbital overlap is also important in determining which group migrates

■ secondary carbocation

■ tertiary carbocation

rotate

■ orbital overlap σ$_{C-C}$ 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

- OPP

■ form 3° cation

■ form 3° cation

■ form 2° cation
relief of ring strain

■ pyrophosphate, or
diphosphate – PPO.
PPO$^{\ominus}$ is a good leaving
group c.f. TsO $^{\ominus}$

camphene

- H$^{\oplus}$

■ 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
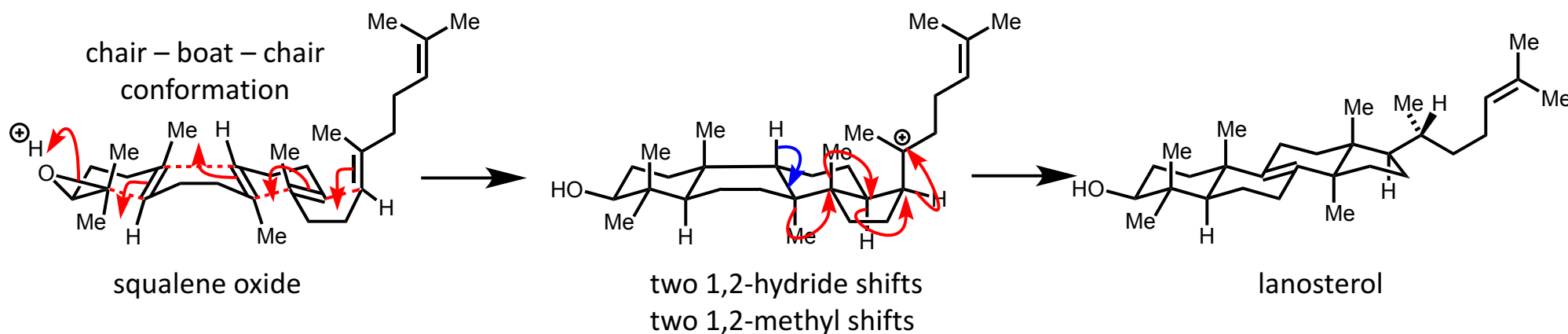
lanosterol

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

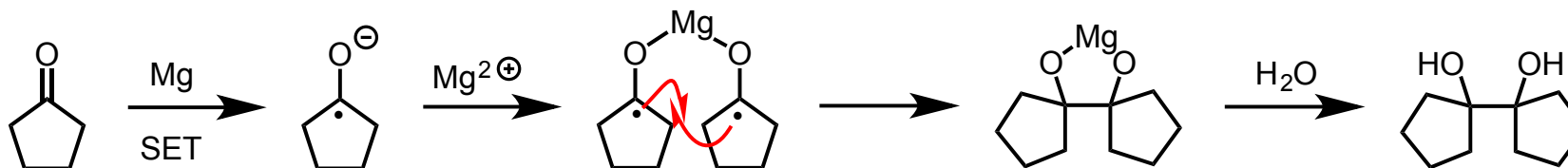■ Pinacol and semi-pinacol rearrangements
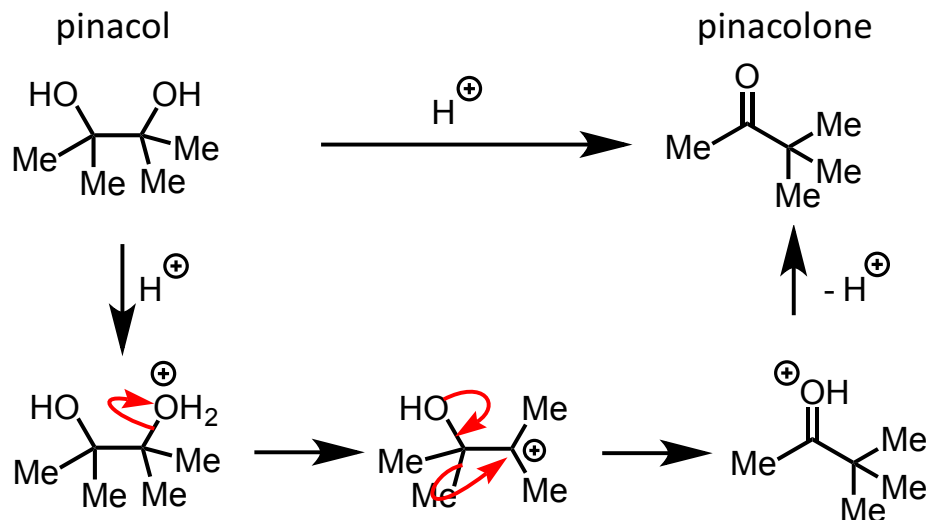
pinacol   pinacolone

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

■ mechanism in more detail
correct orbital overlap required for migration

$\sigma_{C\text{-}C}$ to empty p
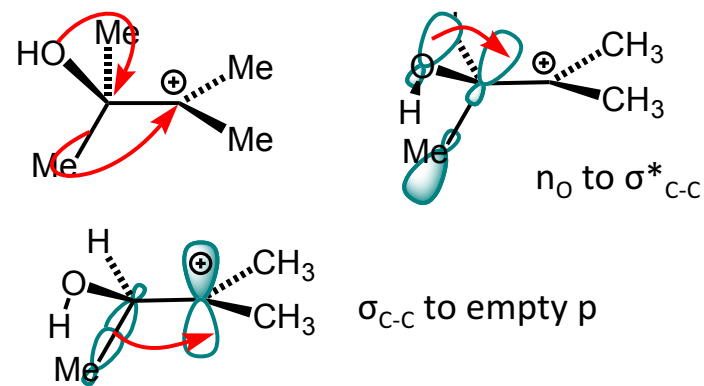
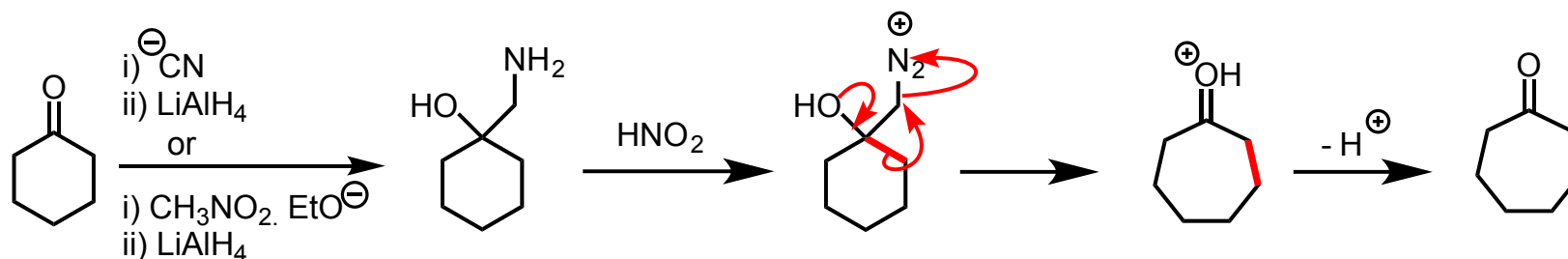■ useful method for the preparation of spirocyclic ketones.
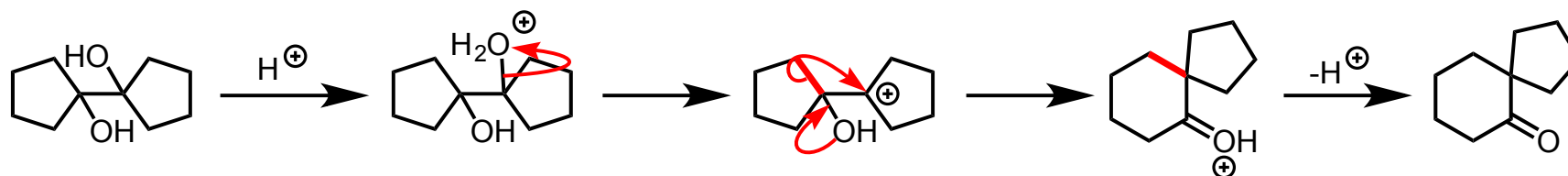
■ the starting diols can be readily prepared by the pinacol reaction

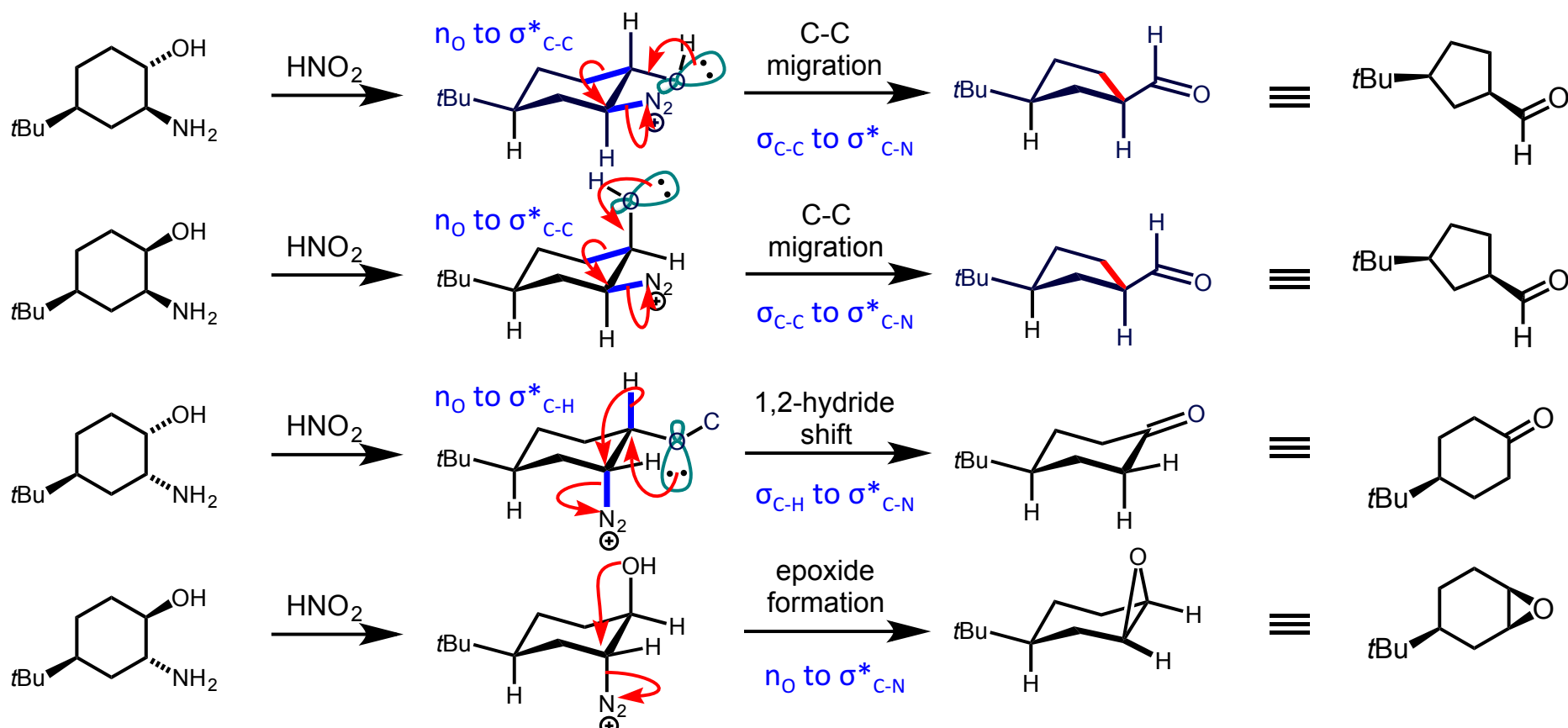■ epoxides and halohydrins can be substrates for the pinacol rearrangement

■ 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
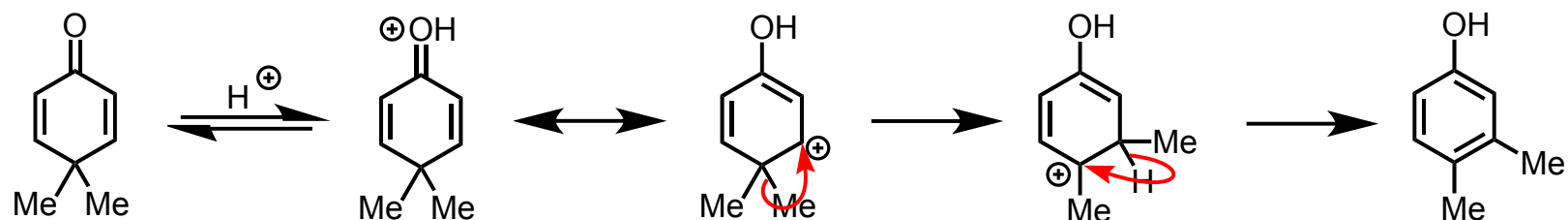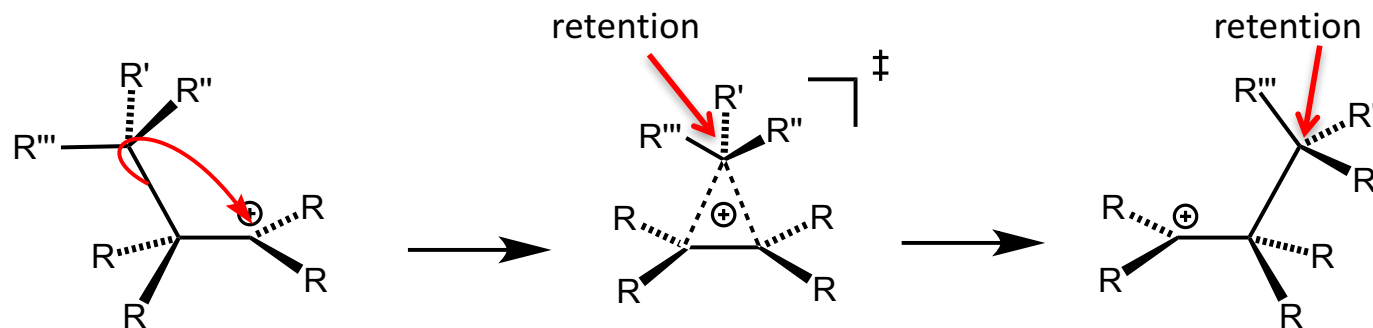

■ the pinacol rearrangement is driven by formation of a strong C=O bond

■ the dienone-phenol rearrangement involves loss of a C=O bond and gain of an aromatic ring

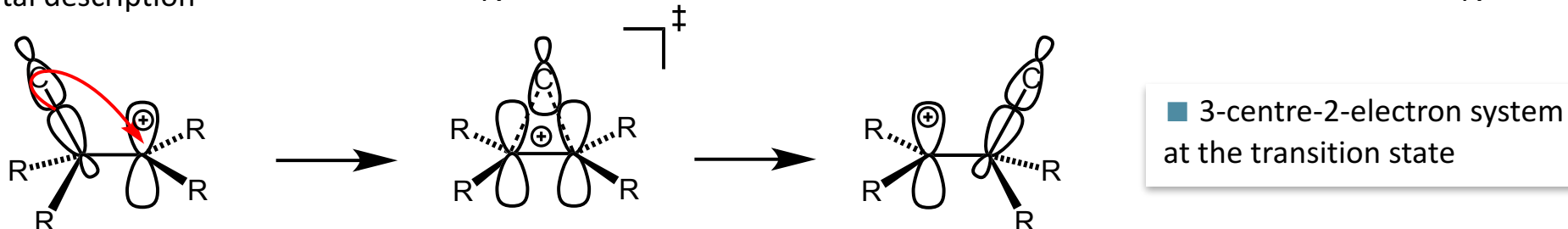■ the dienone-phenol rearrangement provides a method for ring annulation
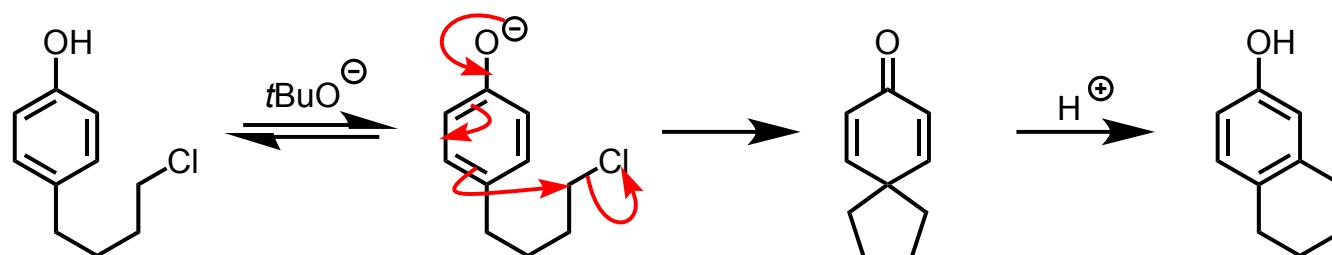
Theory of 1,2-shifts
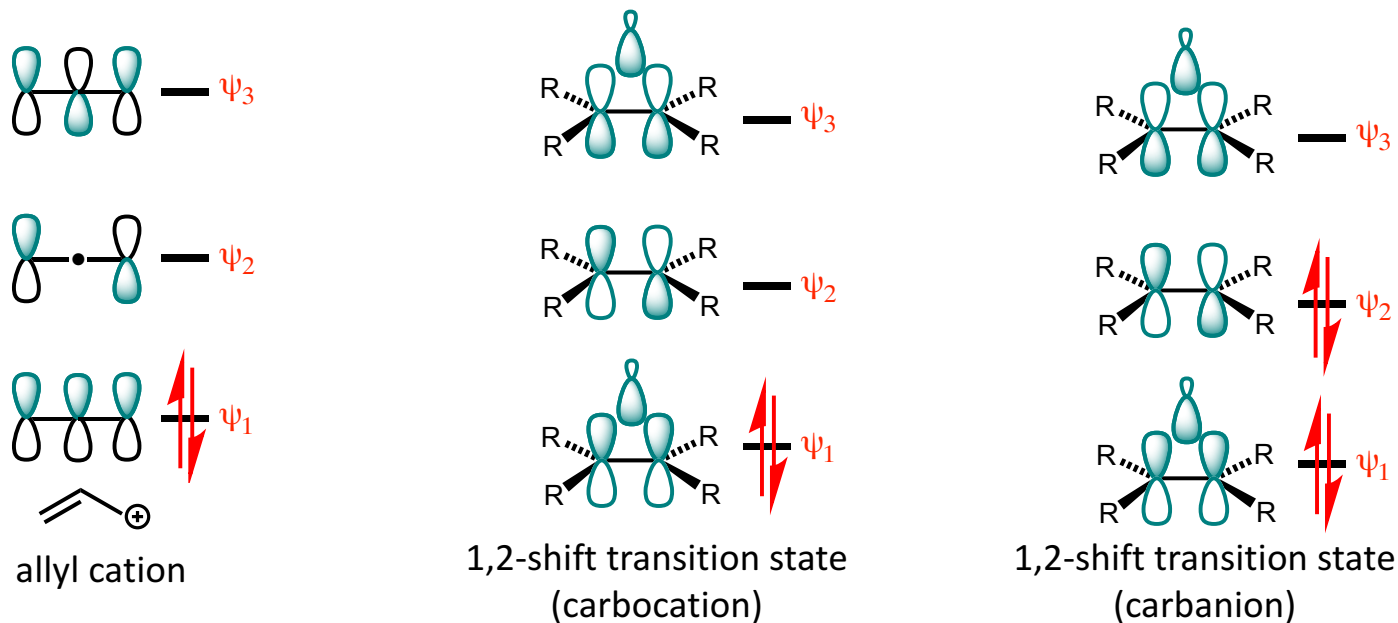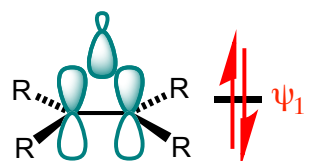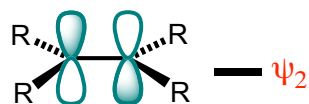- curly arrow mechanism

retention

‡

retention
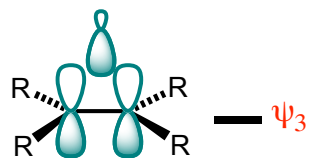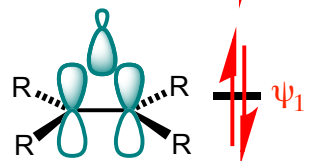
- orbital description

‡

- 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

ψ_3

ψ_2

ψ_1

allyl cation

ψ_3

ψ_2

ψ_1

1,2-shift transition state (carbocation)

ψ_3

ψ_2

ψ_1

1,2-shift transition state (carbanion)

■ 1,2-cation and 1,2-anion shifts

ψ_3

ψ_2

ψ_1
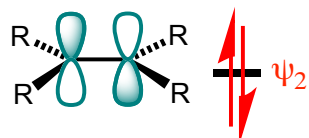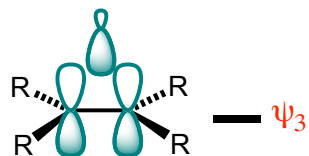
1,2-shift transition state
carbocation

■ 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*

ψ_3

ψ_2

ψ_1

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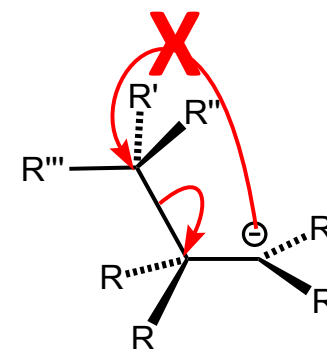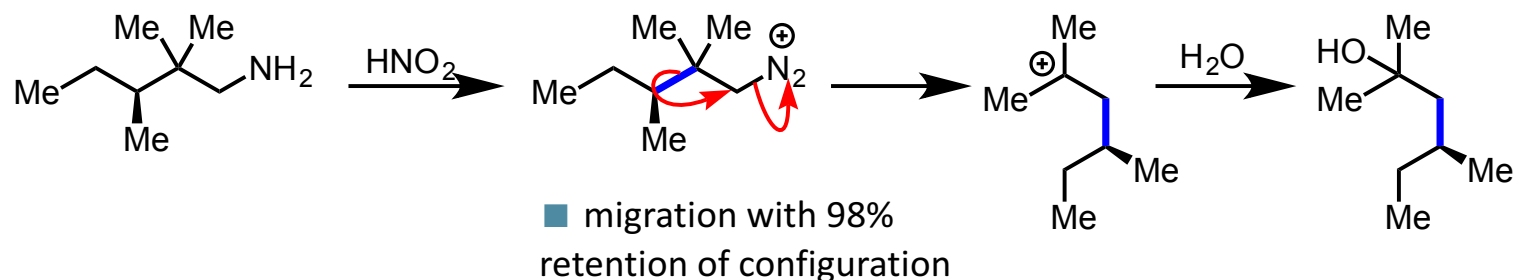
- as we have seen, for efficient rearrangement orbital alignment is critical

- all three indicated hydrogen atoms are in the same plane -
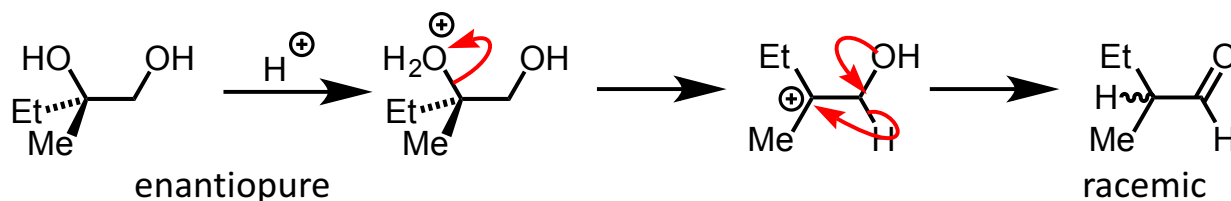rearrangement to the more stable 3° carbocation does not occur
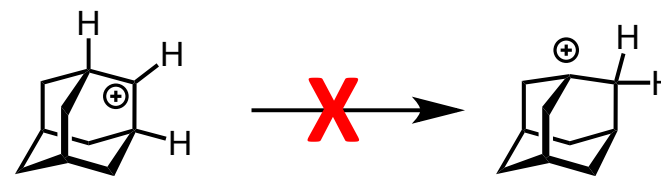
- retention of configuration at the migrating centre is observed

- migration with 98%
retention of configuration

- at the migrating terminus inversion or racemisation can occur

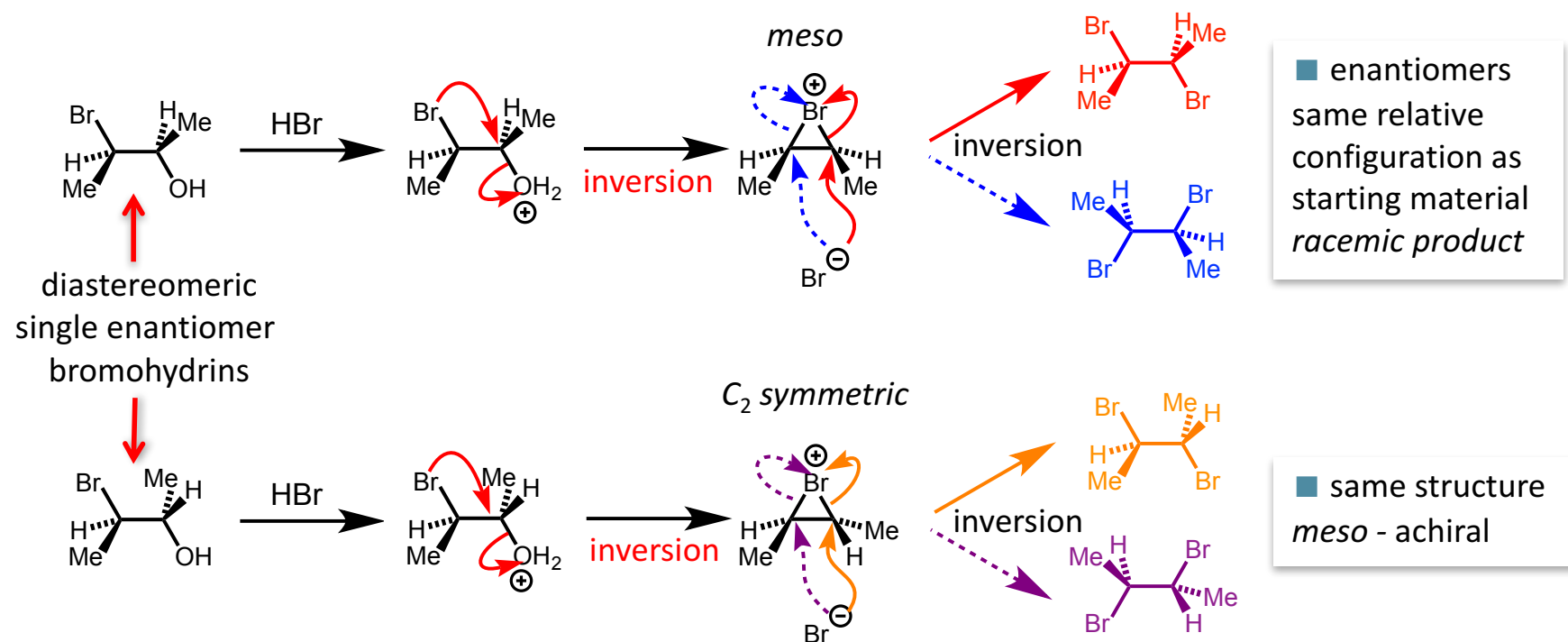- racemisation will occur if the mechanism is S$_N$1-like i.e. *via* a full carbocation

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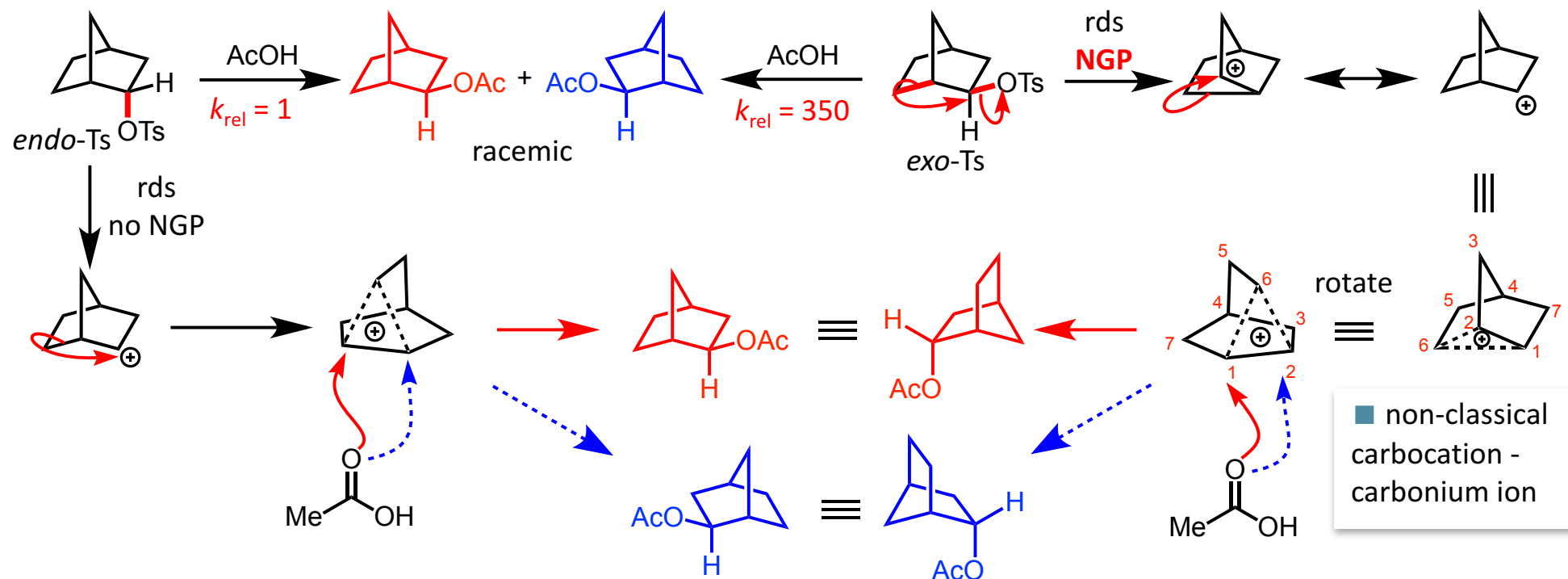
A rate increase due to neighbouring group participation is known as 'anchimeric assistance'
neighbouring group participation and anchimeric assistance are often used interchangeably

meso

inversion

inversion

diastereomeric
single enantiomer
bromohydrins

■ enantiomers
same relative
configuration as
starting material
racemic product

C₂ symmetric

C_2 symmetric

inversion

inversion

■ 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

AcOH

$k_{rel} = 1$

endo-Ts OTs

racemic

AcOH

$k_{rel} = 350$

exo-Ts

rds
NGP

rds
no NGP

rotate

Me OH

AcO

AcO

Me OH

- non-classical carbocation - carbonium ion

- alternative perspective of **NGP**

1.8 Å

H

TsO

- 3-centre-2-electron bond
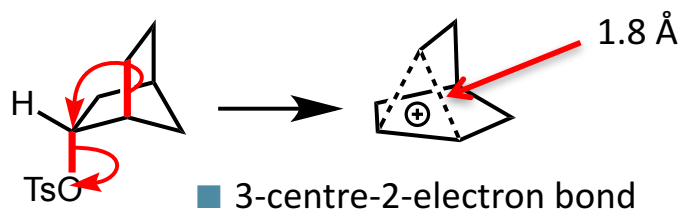
- *exo*-Ts reacts faster due to NGP of antiperiplanar C-C sigma bond
- *endo*-Ts ionises slower to give classical carbocation followed by non-classical carbocation formation
- non-classical cation has plane of symmetry leading to racemic products

■ 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
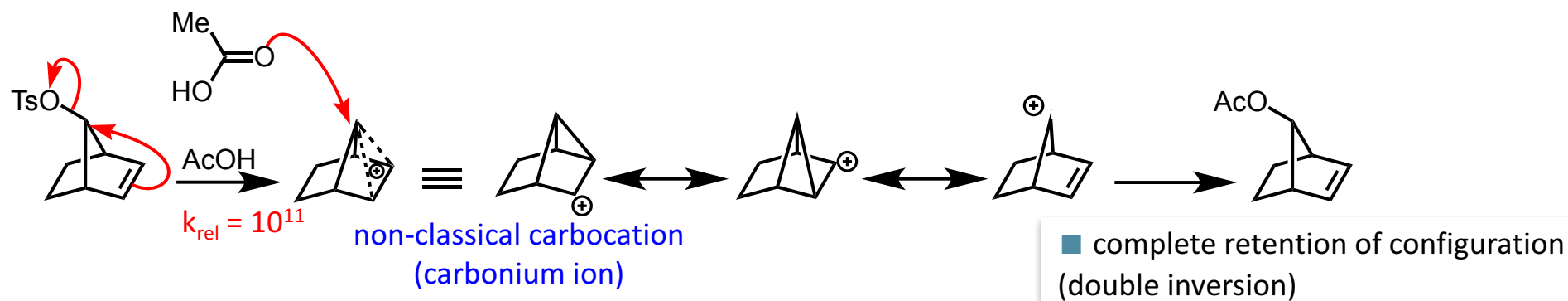

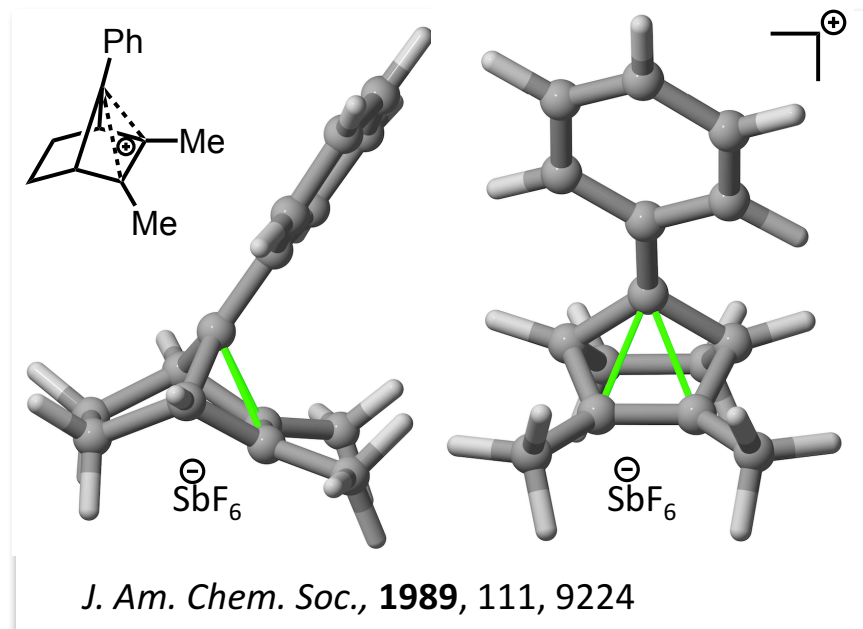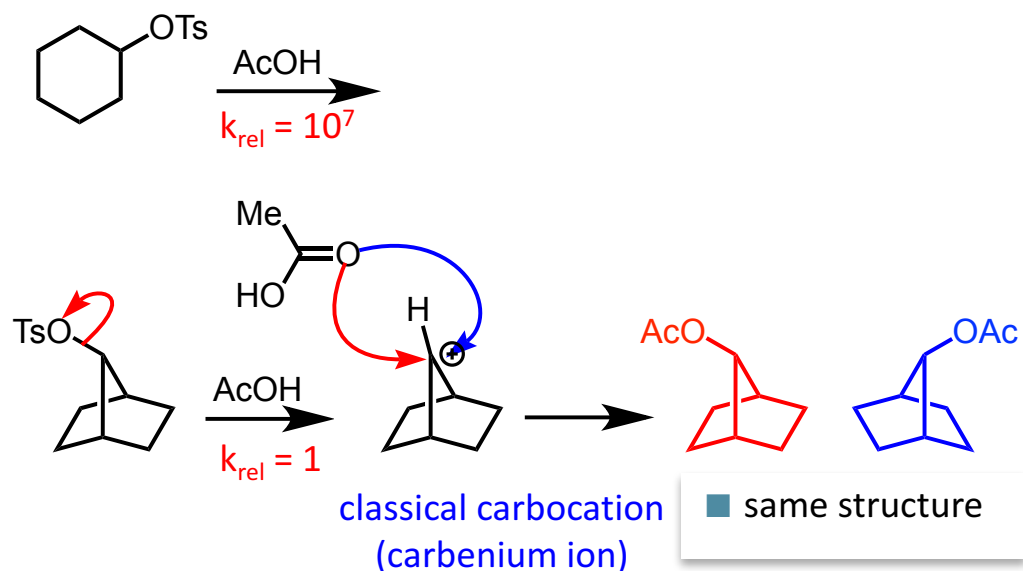
1.8 Å

$δ_C$ 125 ppm

$Br_3AlBrAlBr_3^{\ominus}$
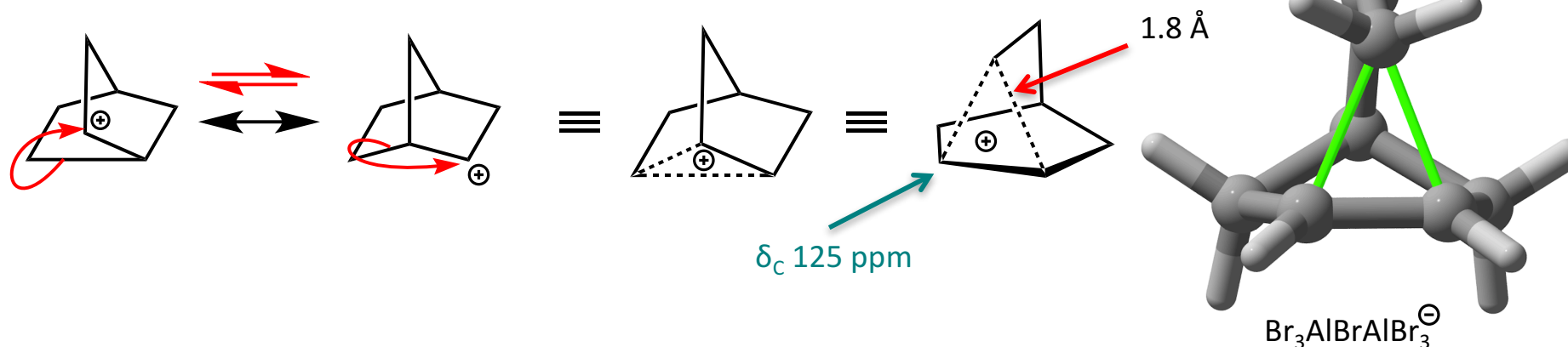
■ *Note:* non-classical carbocations are only formed if they are ***more*** stable than their classical counterparts

■ 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.

2.1 Å   Me   1.7 Å

Me   Me   Me

Me   Me

$F_5SbFSbF_5^{\ominus}$
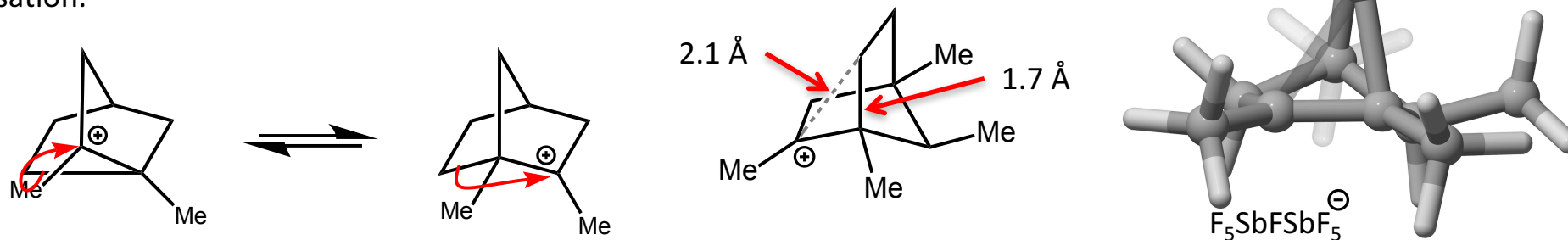
- π-bonds are better donors than σ-bonds

$k_{rel} = 10^7$

$k_{rel} = 1$

classical carbocation
(carbenium ion)

- same structure

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

$k_{rel} = 10^{11}$

non-classical carbocation
(carbonium ion)

- complete retention of configuration
(double inversion)

$k_{rel} = 10^4$

allyl cation
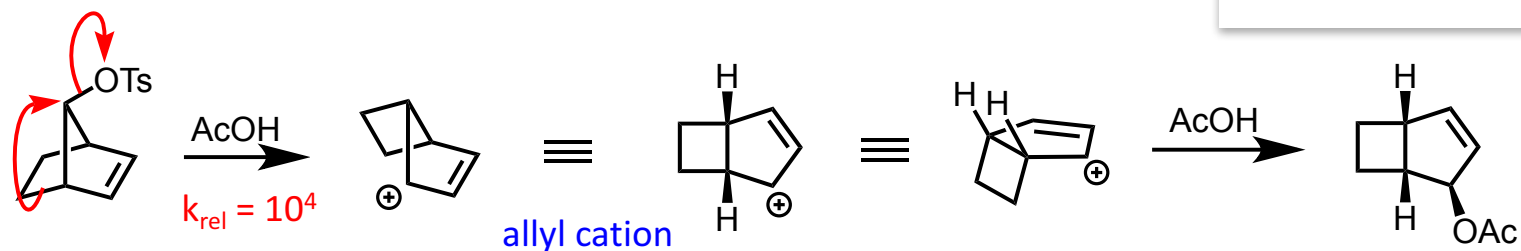
■ More neighbouring group participation with π-bonds – phenonium ions

■ *meso* phenonium ion
(σ-plane)

AcOH

inversion

inversion

■ enantiomers
racemic product

diastereomeric
single enantiomer
substrates

■ C_2-symmetric
phenonium ion

AcOH

inversion

inversion

■ same single
enantiomer product

133 ppm

155 ppm

172 ppm

69 ppm

δ_C = 60 ppm
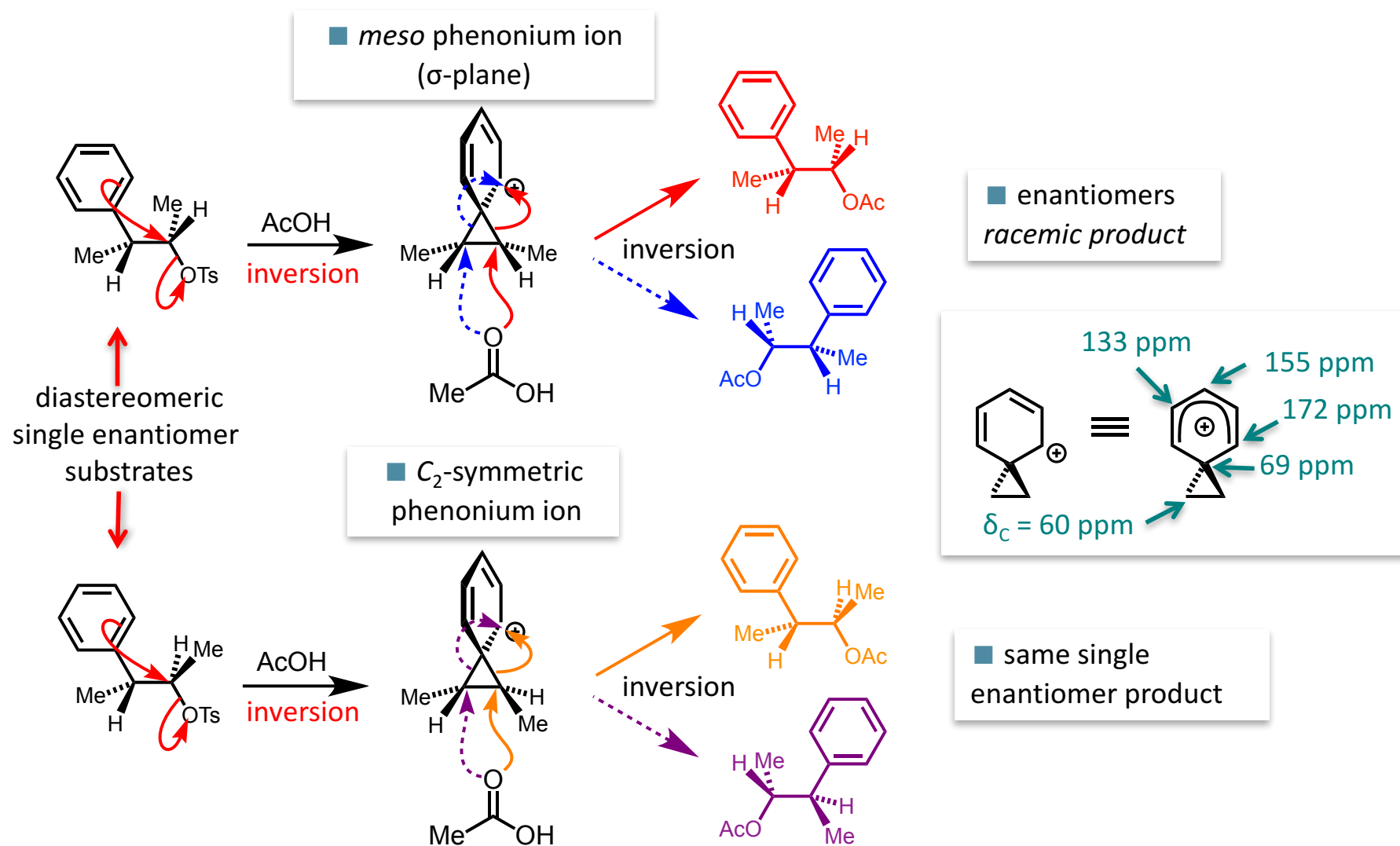
- multiple 1,2-shifts
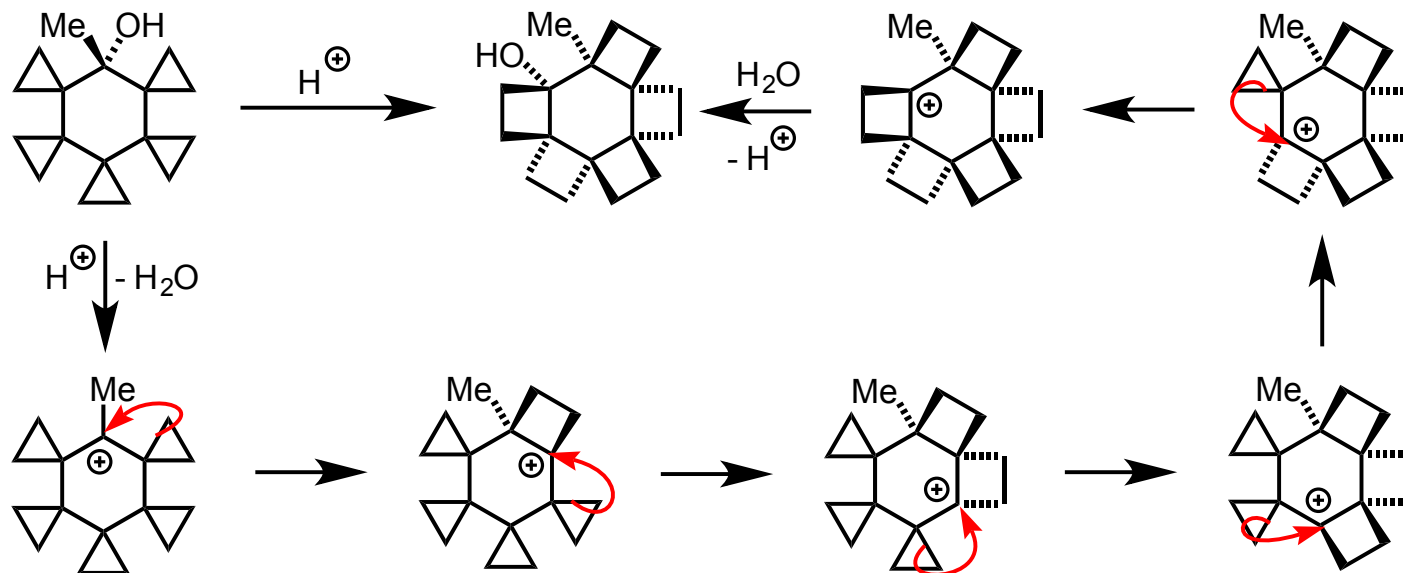
- formation of adamantane

$C_{10}H_{16}$ adamantane $C_{10}H_{16}$
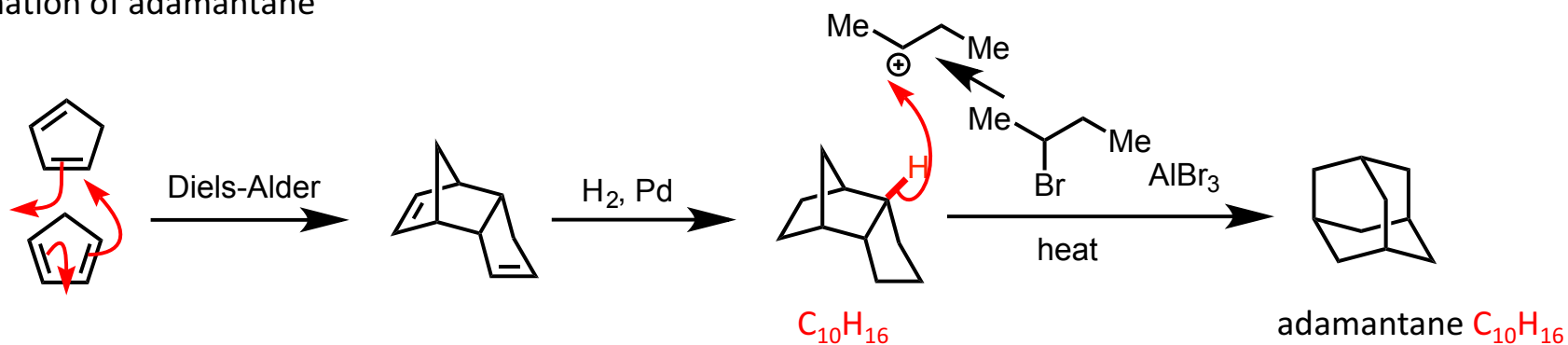
- all $C_{10}H_{16}$ hydrocarbons rearrange to adamantane on treatment with Lewis acid

- adamantane is the thermodynamically most stable $C_{10}H_{16}$ isomer – it possess repeating units of the diamond lattice

■ transannular hydride shifts
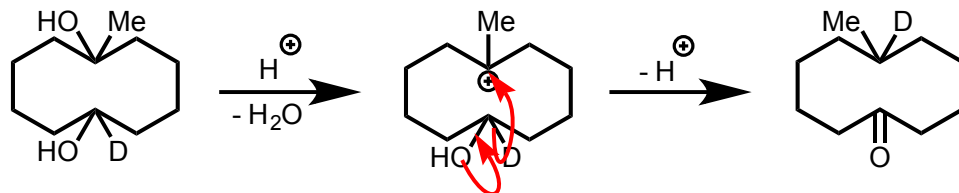
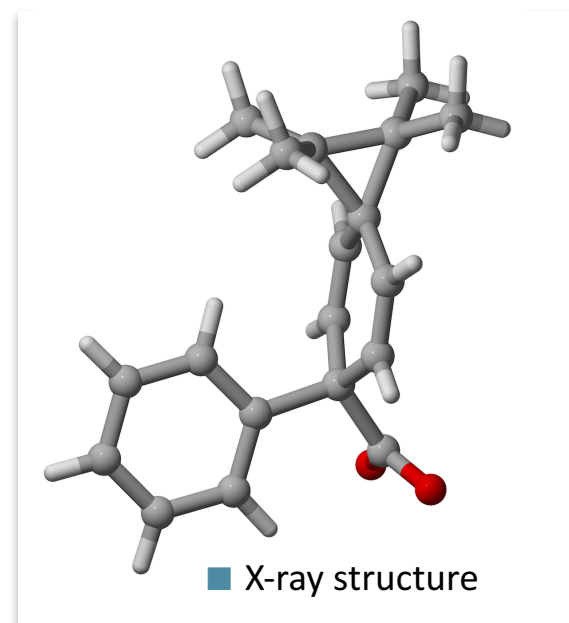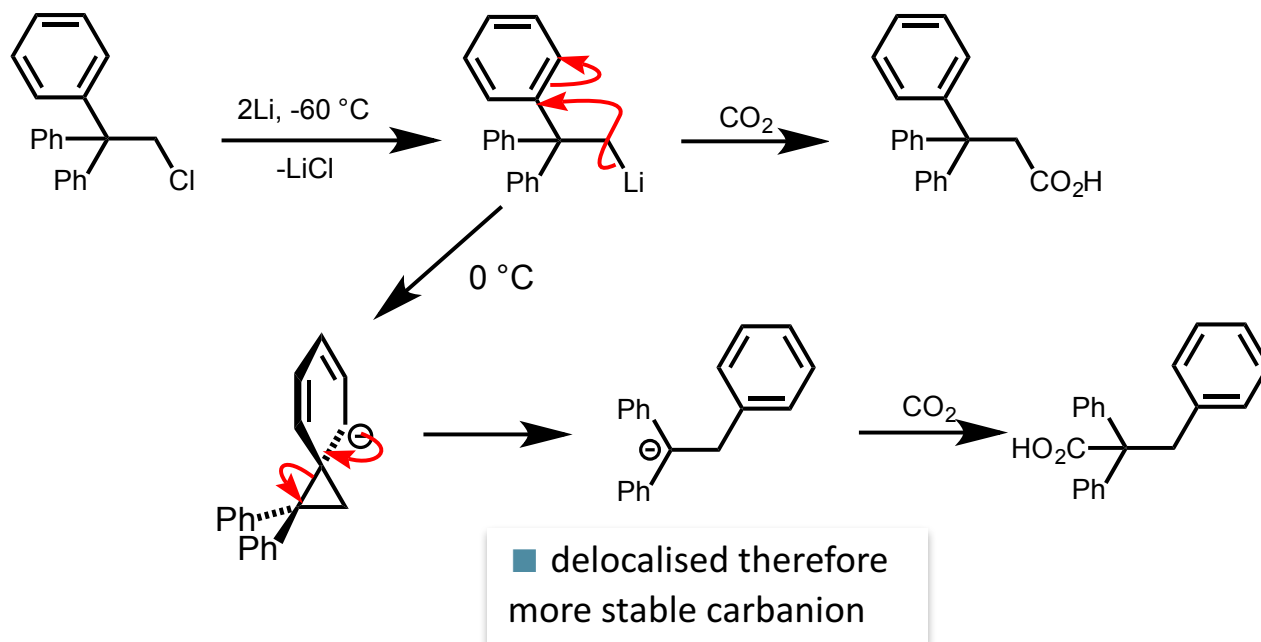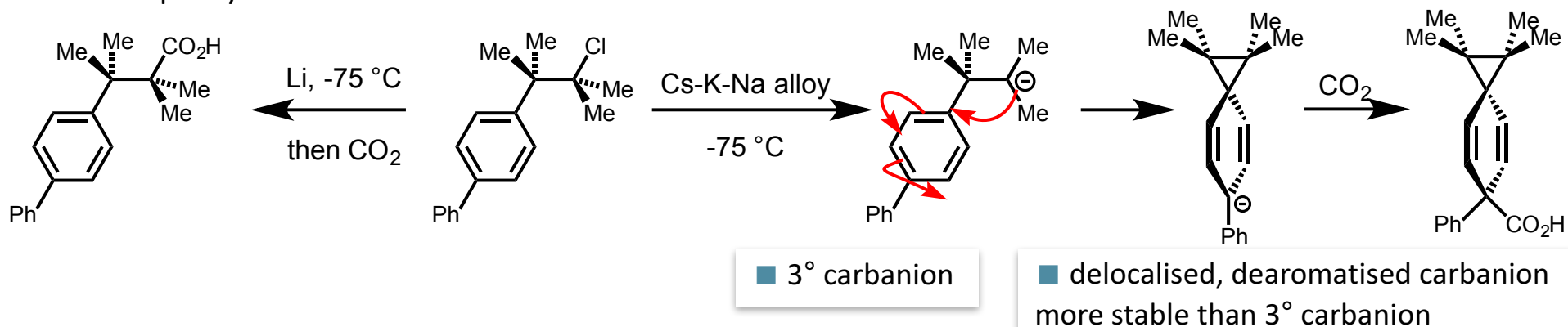■ cyclodecyl cation – 3-centre-2-electron bond c.f. diborane

$\delta_H = +4.0$ ppm

$\delta_H = -3.9$ ppm

$\delta_C = 142$ ppm

$\delta_H = -0.51$ ppm

SbF$_5$, FSO$_3$H
-140 °C

$\delta_H = -6.85$ ppm

$\delta_C = 153$ ppm

SbF$_5$, FSO$_3$H
-140 °C

$\delta_H = +6.80$ ppm
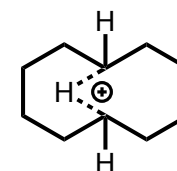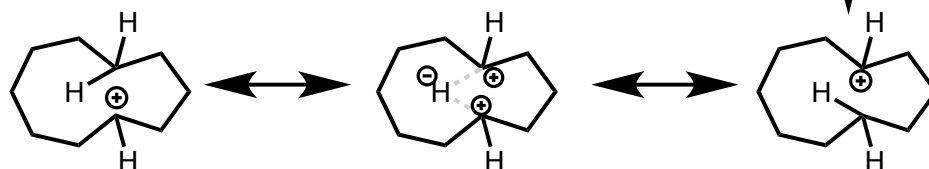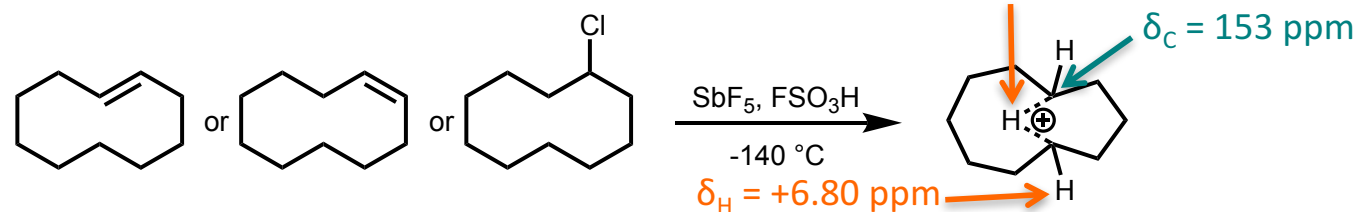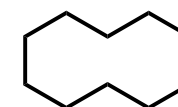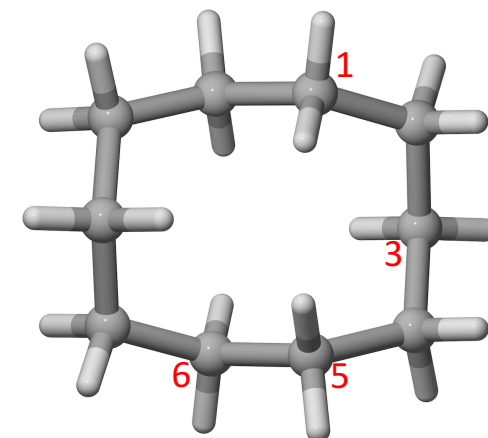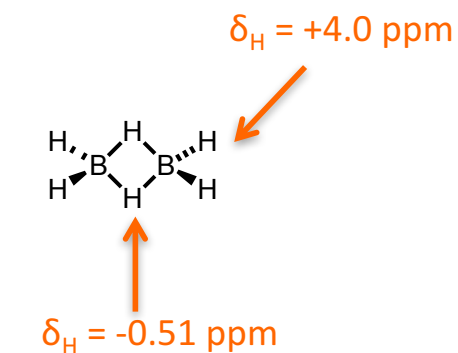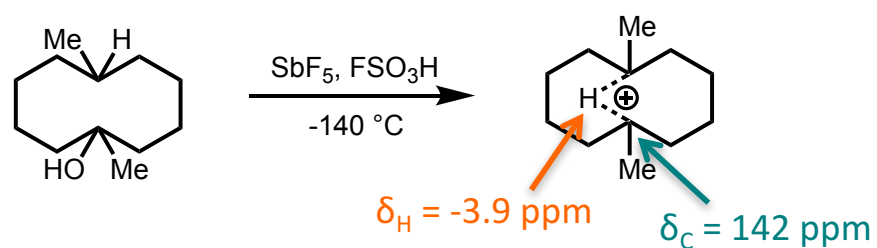
■ 1,6-cation slightly higher in energy than 1,5-cation

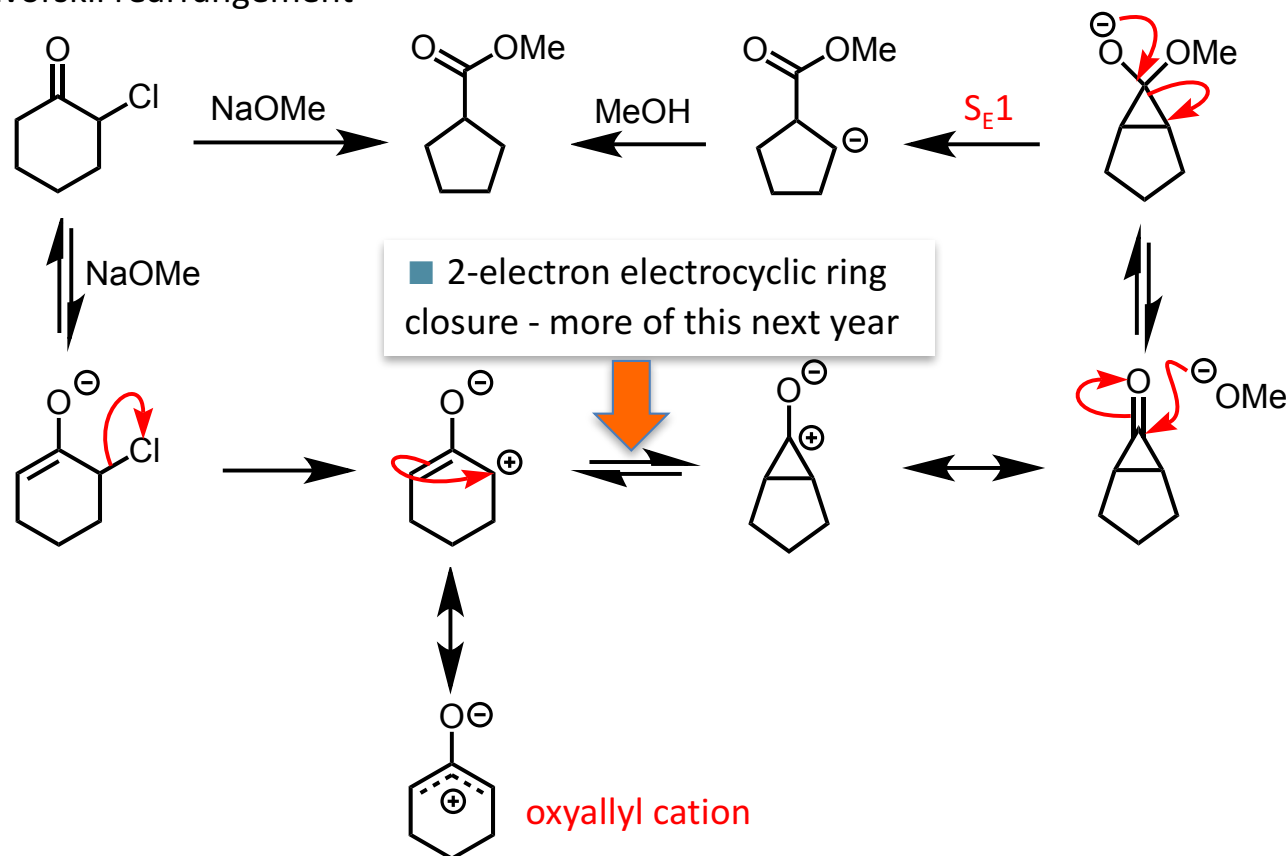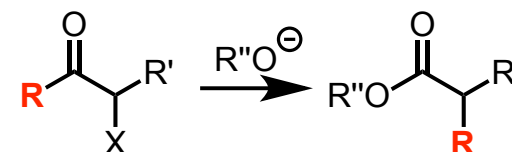- Carbanion rearrangements – carbanions are much less prone to rearrangement than carbocations

- 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

oxyallyl cation

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

■ 1:1 mixture

MeOH
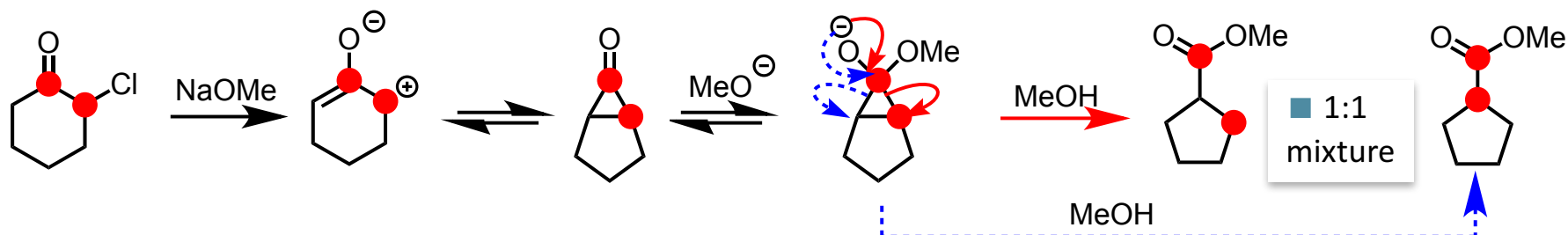
■ quasi-Favorskii rearrangement – Favorskii rearrangement on substrates with no enolisable hydrogen atoms
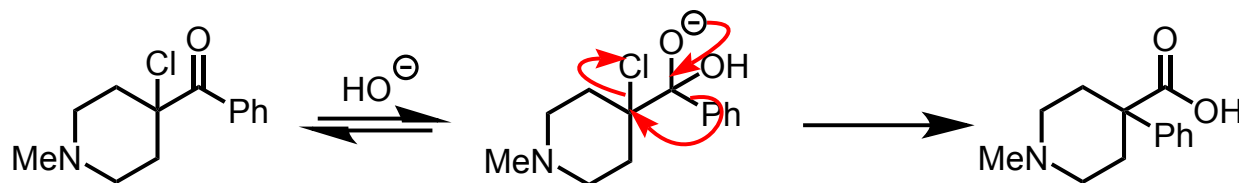
■ the mechanism is a base catalysed semi-pinacol rearrangement and is closely related to the mechanism of the benzil-benzillic acid rearrangement

■ Ramberg-Bäcklund reaction
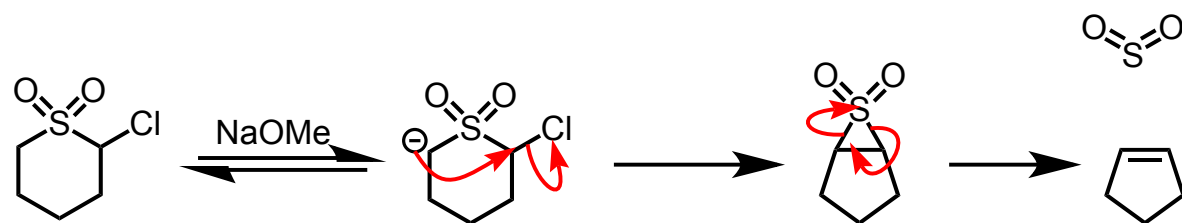
■ cheletropic extrusion of SO_2
 – more next year

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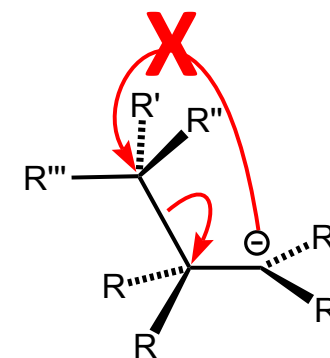
■ Concerted 1,2-shifts of carbanions are geometrically impossible - as the carbanion cannot reach to perform an intramolecular S_N2 reaction with inversion of configuration

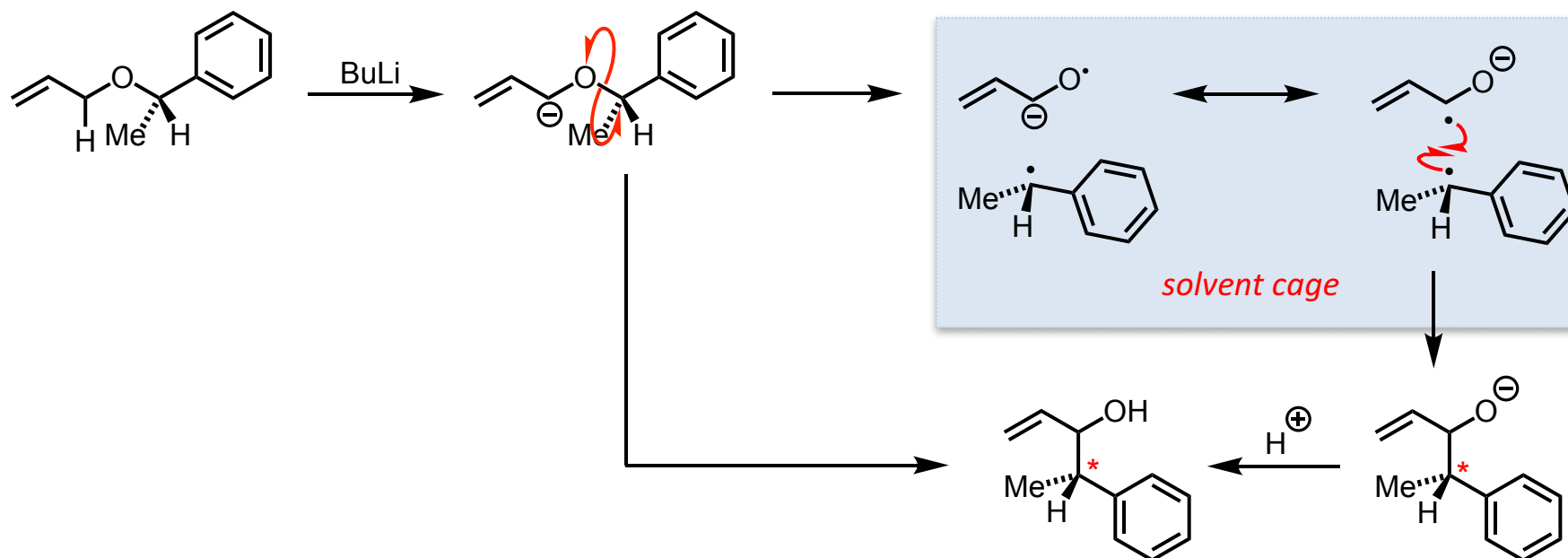■ 1,2-Shifts of carbanions occur by a radical mechanism – 1,2-Wittig, 1,2-Stevens and related rearrangements

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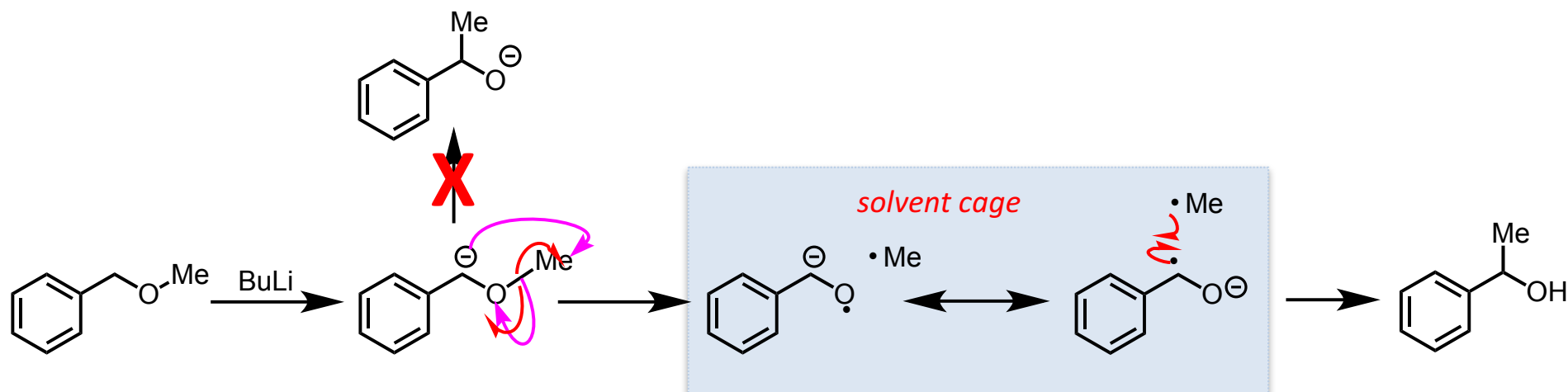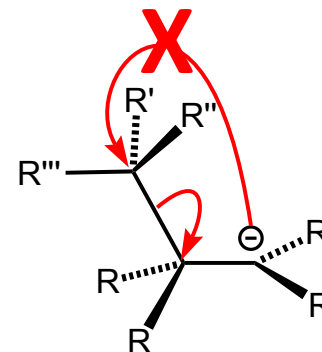
■ Stevens rearrangement
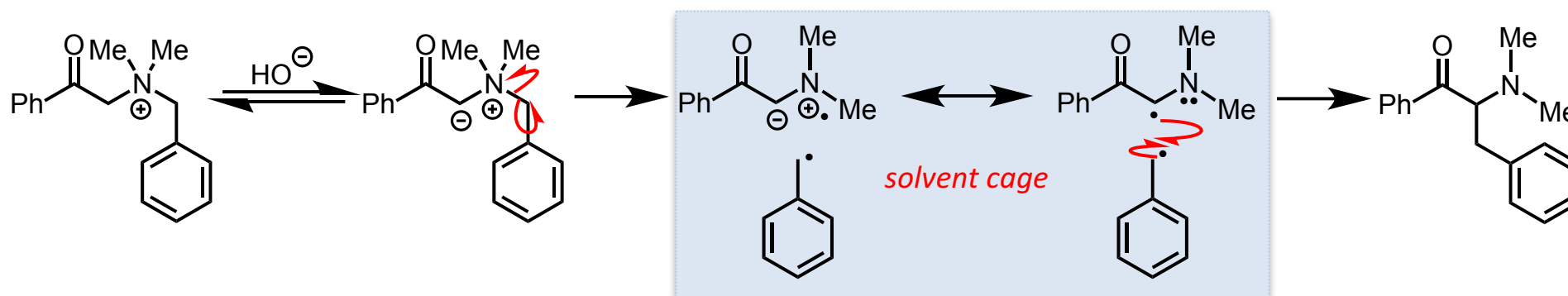
■ the 1,2-Wittig rearrangement occurs predominantly with retention of configuration in the migrating group
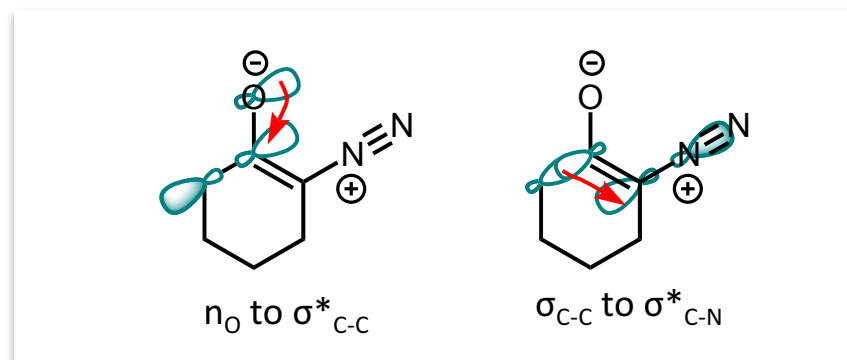

solvent cage

■ predominant retention of configuration at the migrating centre *

Rearrangements and Reactive Intermediates

1A Organic Chemistry

Handout 2 - Carbenes and Nitrenes

n_O to σ^*_{C-C} σ_{C-C} to σ^*_{C-N}

Carbenes

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

■ structure – singlet carbenes

singlet

■ 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

■ 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

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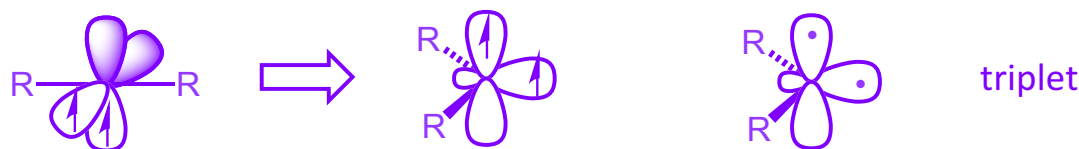
■ bending the linear state leads to one of the unpaired electrons gaining some s-character and being lowered in energy – here one of the p-orbitals becomes an sp^n hybrid orbital (a σ-orbtial)

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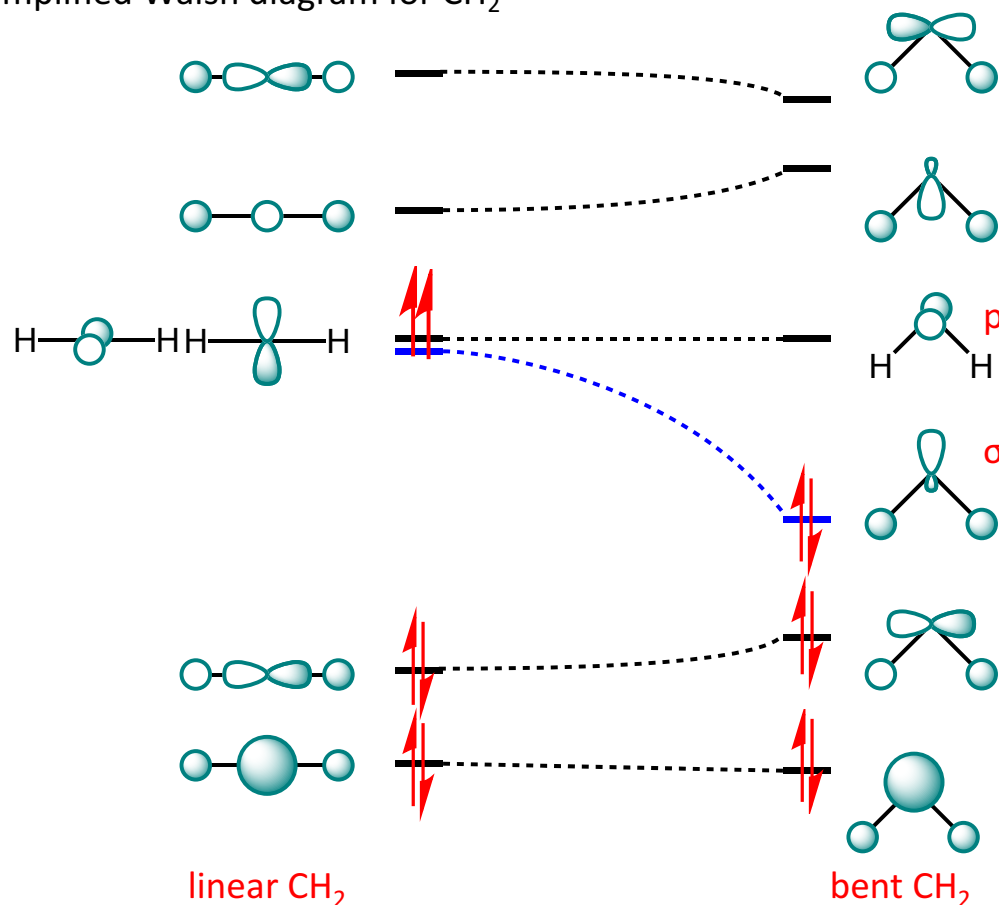
■ beginning with linear CH_2, MO diagram predicts a triplet ground state

■ 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

singlet

triplet

linear CH_2 bent CH_2
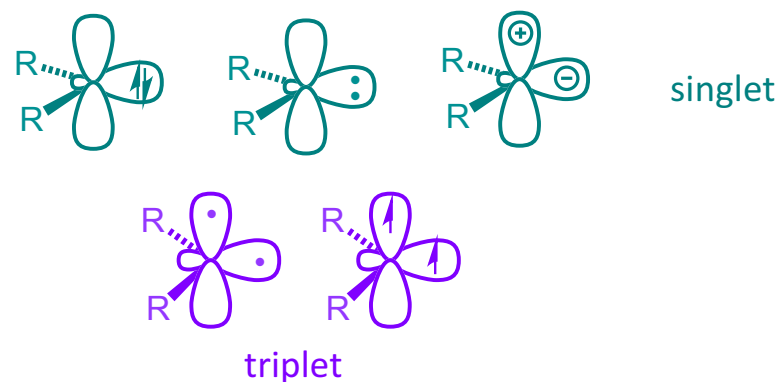
■ *take home message* – triplet carbenes and singlet carbenes are bent – we will consider them both to be sp² hybridised
■ triplet carbenes have a larger bond angle than singlet carbenes
■ the above representations are adequate for our purposes
■ neither Walsh diagram nor hybridisation allows us to predict 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

134° ⟶   triplet   102° ⟶   singlet

■ dialkylcarbenes, arylalkylcarbenes and some diarylcarbenes have triplet ground states

■ heteroatom substituted carbenes have singlet ground states due to delocalisation

n_{Cl} to empty p

:CH_2 Ph_2C: singlet

triplet
ground state

singlet
ground state

N-heterocyclic carbenes

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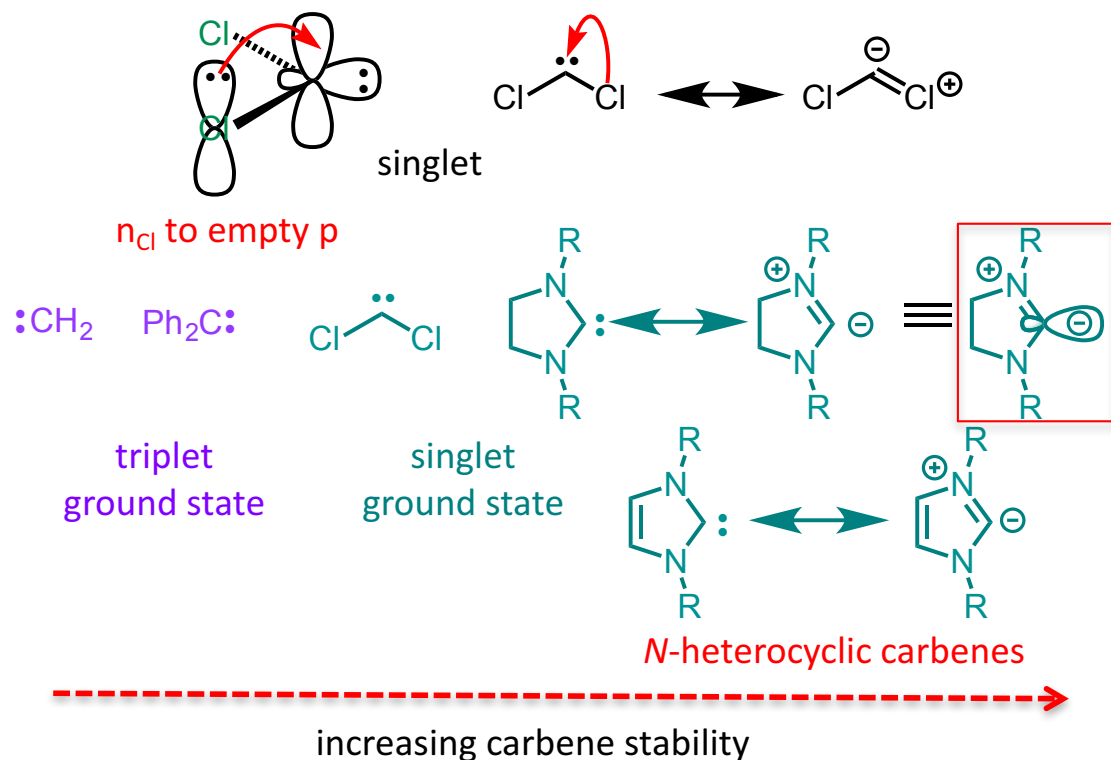
■ first X-ray structure of a carbene (*J. Am. Chem. Soc.*, **1991**, *113*, 361).

■ carbene or ylid? c.f.

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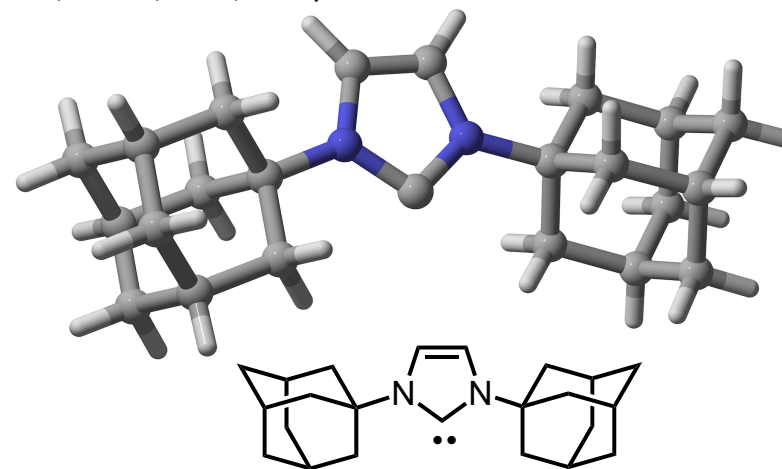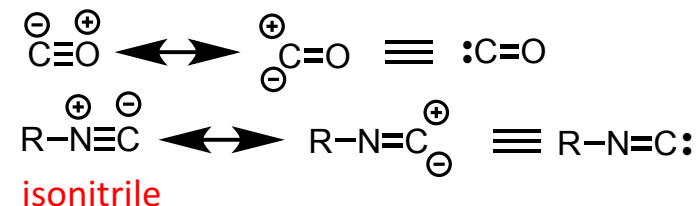
- the majority of carbenes are electrophilic – there are six electrons around the central carbon and hence they are electron deficient

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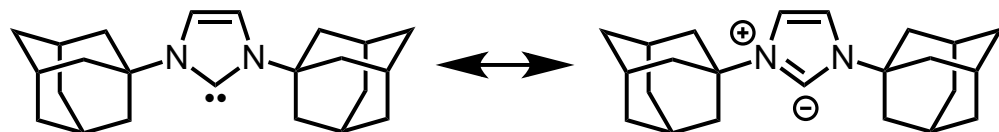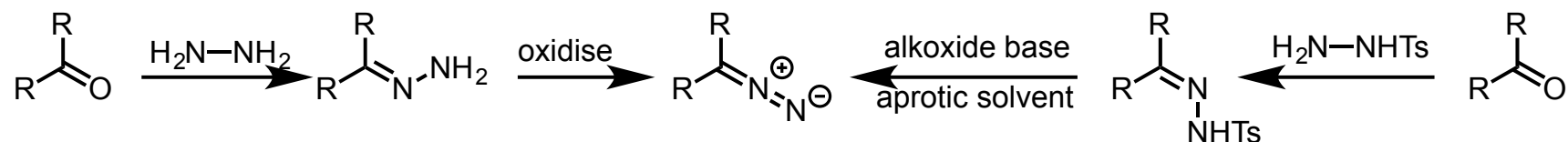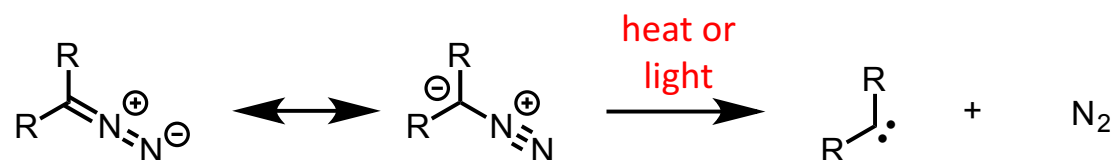

- Nature was here before us with nucleophilic carbenes – thiamine pyrophosphate (vitamin B1) – more next year

nucleophilic carbene
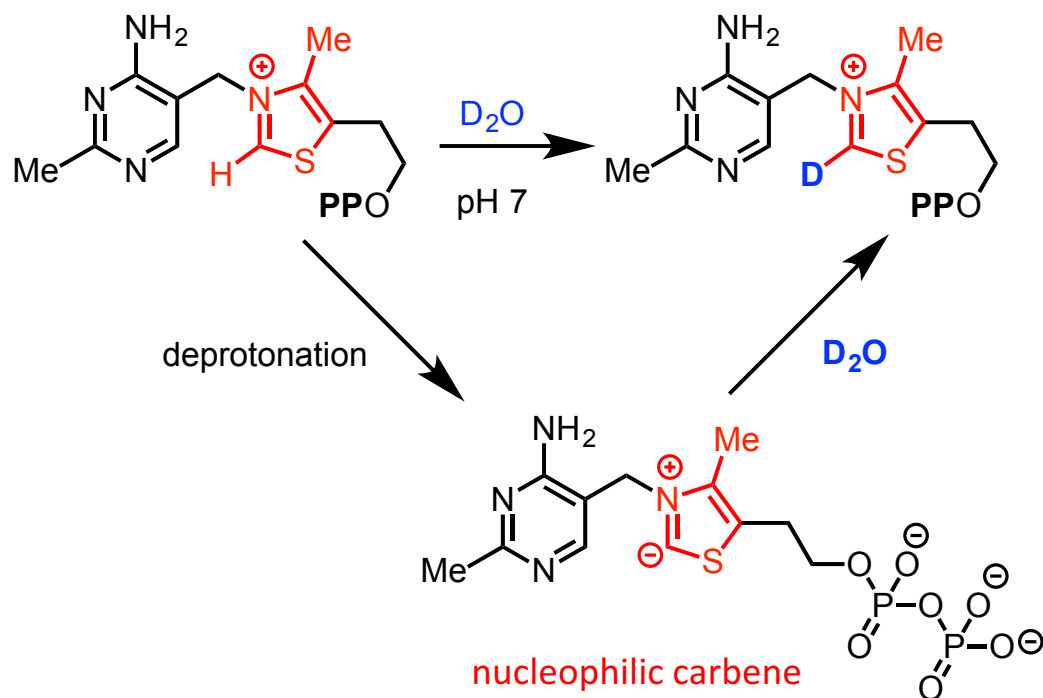
- Grubbs-Hoveyda 2nd generation metathesis catalyst (*J. Am. Chem. Soc.*, **2000**, *122*, 8168) – more next year
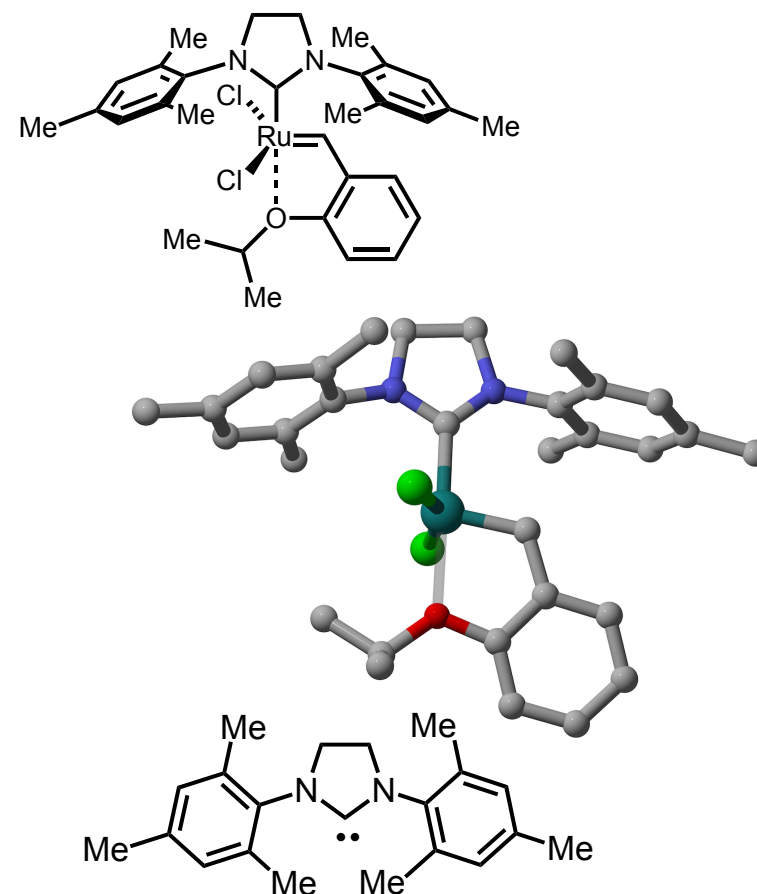
■ some methods for carbene formation

heat or light

N_2

H_2N-NH_2 oxidise alkoxide base aprotic solvent $H_2N-NHTs$

NHTs

heat or light

N=N

diazirene

N_2

:base

$Cl^\ominus$

CO

MeO OMe

cycloreversion

MeO OMe +
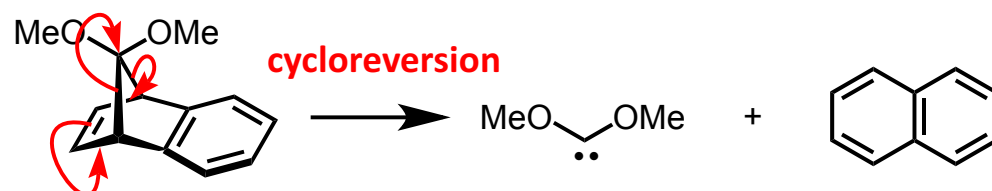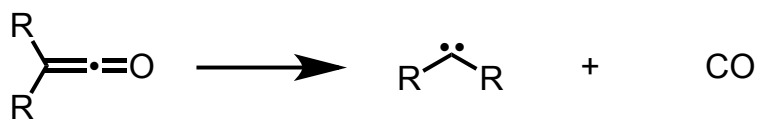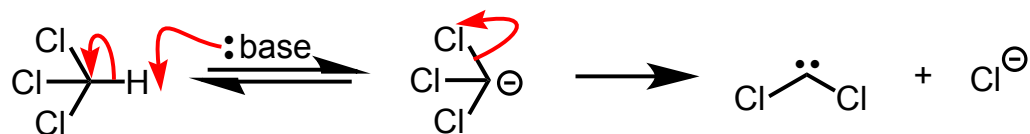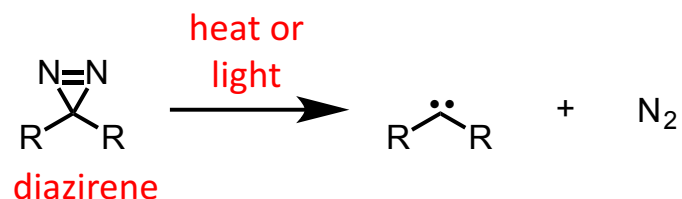
■ direct irradiation normally produces a carbene in the singlet excited state

■ 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

n-BuLi, *t*-BuOK

Schlosser's base - a very strong base

carbenoid

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

hν

1,2-migration

R≡H ⇌ high temperature

alkylidene carbene

■ carbene 1,2-shift ■ cation 1,2-shift
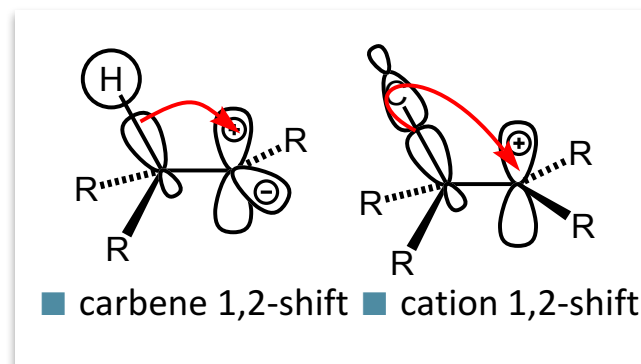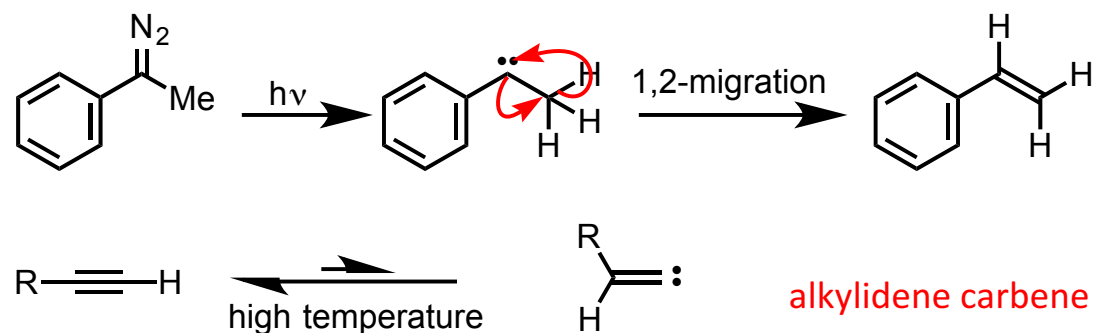
■ insertion into XH bonds is common using transition metal catalysis

Rh₂(OAc)₄
- N₂

C-H insertion
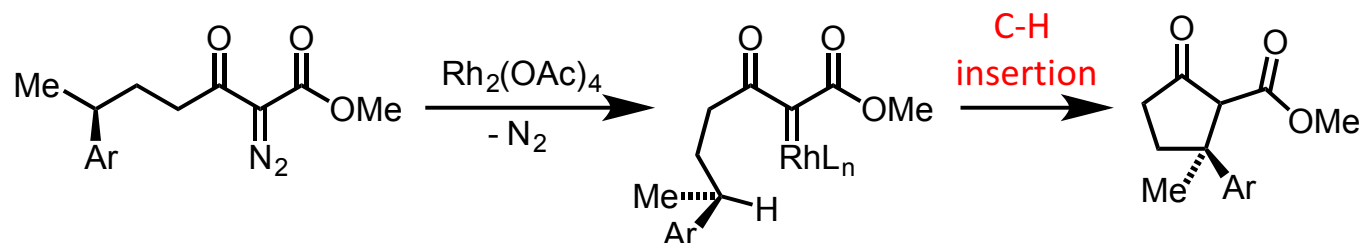
■ rhodium carbenoid is equivalent to a carbene

Rh₂(OAc)₄
- N₂
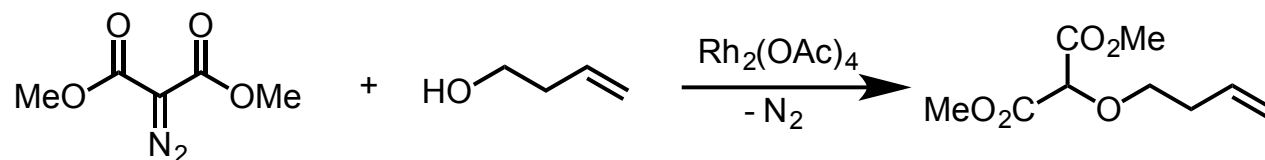
■ here the (rhodium) carbene is attacked by the nucleophilic alcohol followed by proton transfer

■ Wolff rearrangement
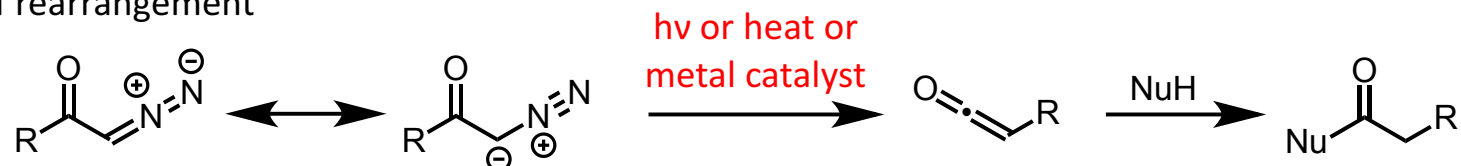
■ concerted or stepwise mechanism – depends on substrate and reaction conditions

■ as a rule of thumb, the thermal reactions are concerted and the photochemical reactions proceed *via* carbenes

concerted

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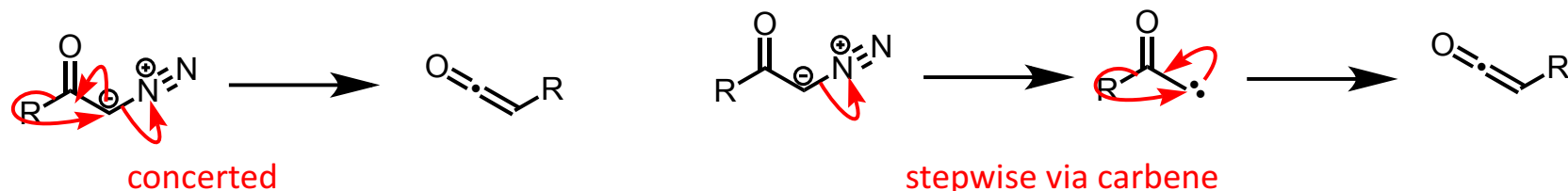
■ the acyl carbenes are also in equilibrium with an oxirene in some cases (● = ^{13}C)

oxirene

mixture
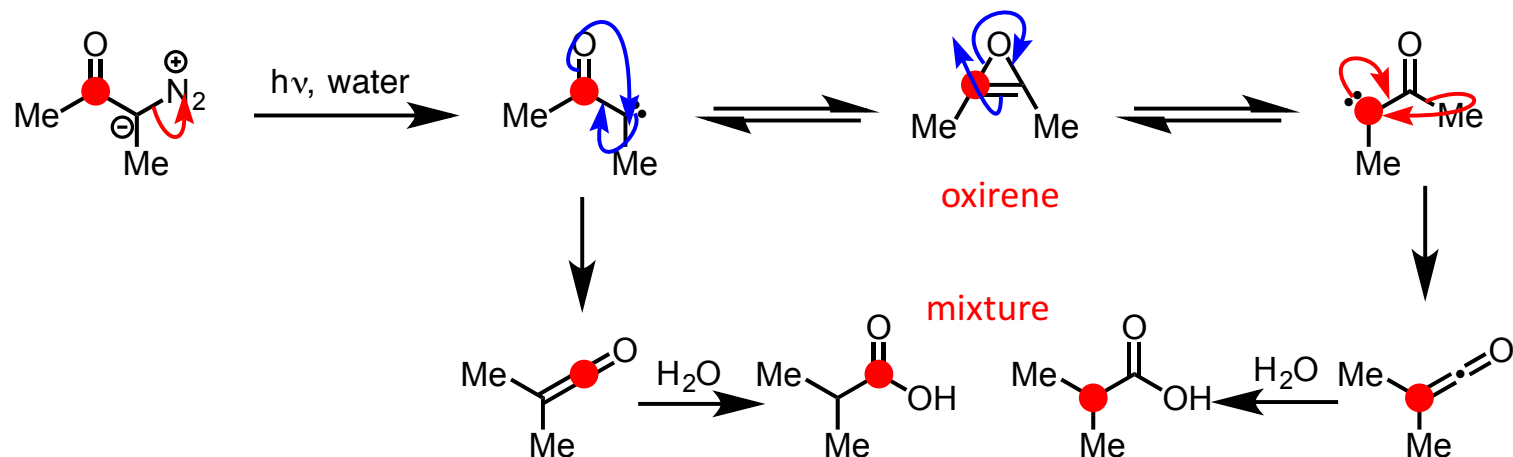
■ Arndt-Eistert homologation
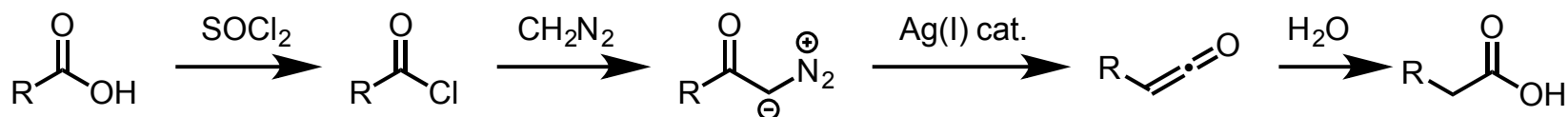
■ Wolff rearrangement – a look at the orbitals
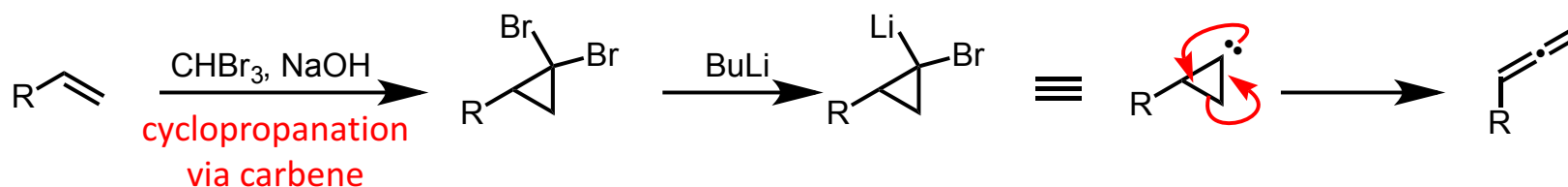
■ with cyclic ketones the reaction is likely to be concerted under most conditions
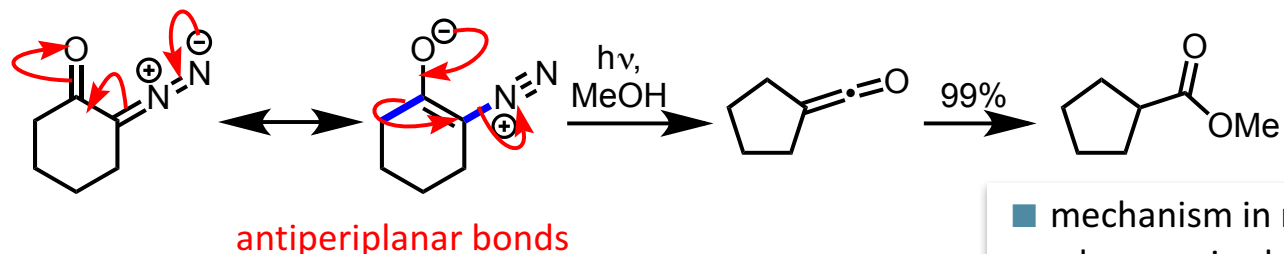
antiperiplanar bonds

■ migration with retention of configuration

■ mechanism in more detail correct orbital overlap required for migration
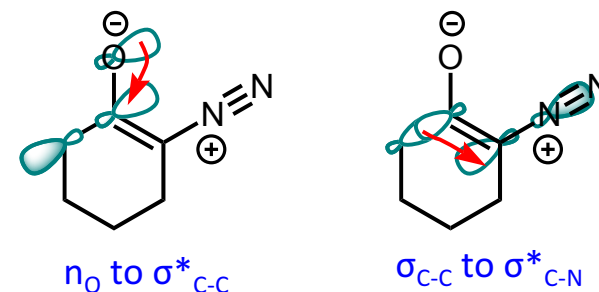
n_O to σ^*_{C-C} σ_{C-C} to σ^*_{C-N}

■ some other rearrangements

■ Doering-LaFlamme allene synthesis

CHBr$_3$, NaOH

cyclopropanation
via carbene

BuLi

■ Skattebol rearrangement

BuLi

C-H insertion
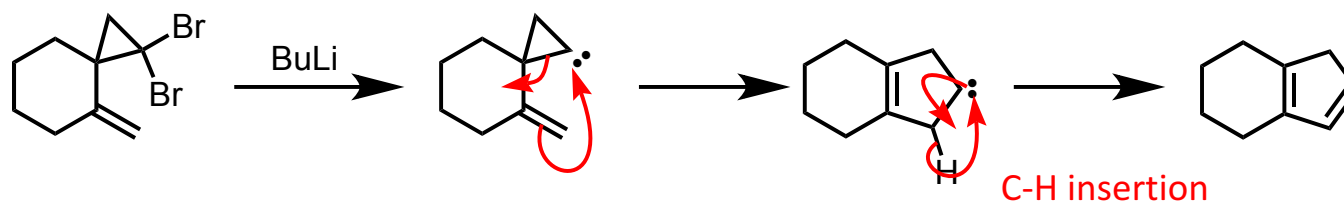
■ carbene addition reactions

■ 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
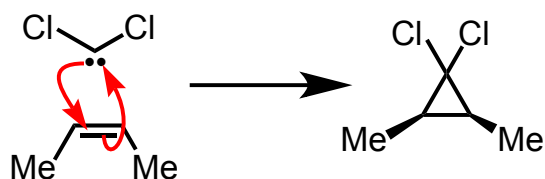
■ orbital picture
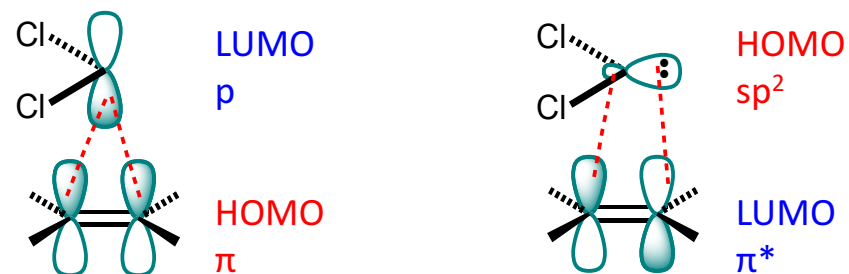
■ triplet carbene – non-concerted radical reaction – spin inversion (requires molecular collision) may be slower than
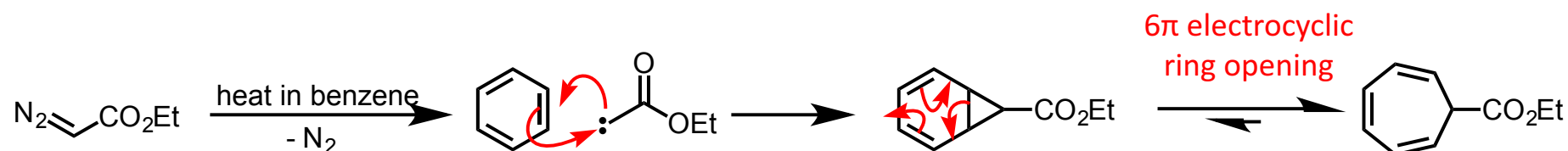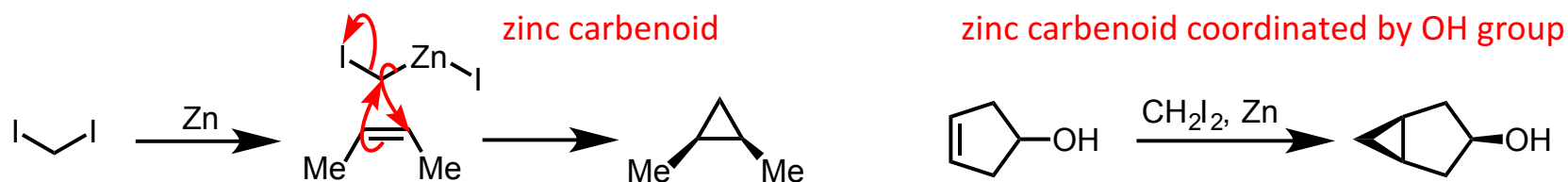bond rotation leading to stereochemical scrambling
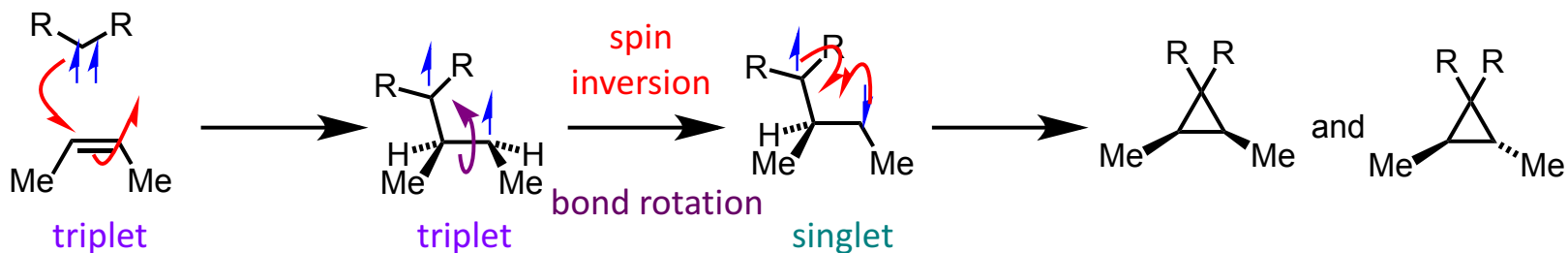
■ Reimer – Tiemann reaction
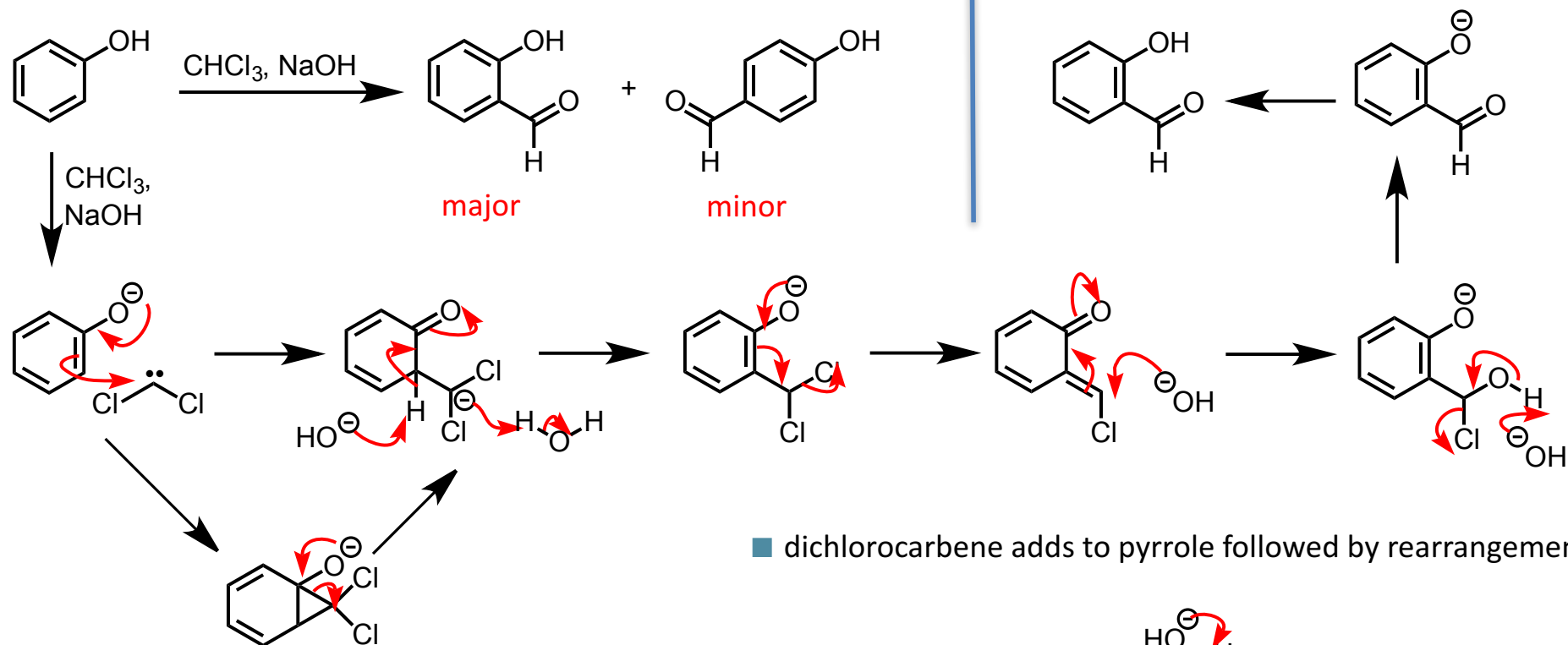
■ dichlorocarbene adds to pyrrole followed by rearrangement
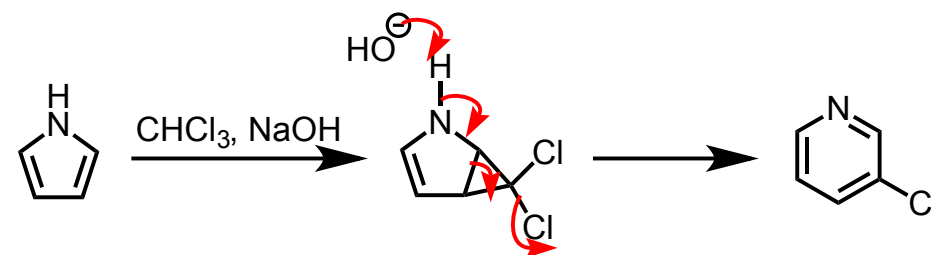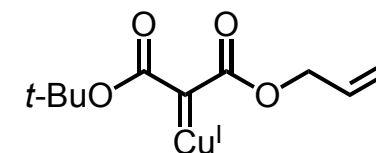

■ very electrophilic carbenes will add to benzene

6π electrocyclic ring opening

- Simmons Smith cyclopropanation

zinc carbenoid

zinc carbenoid coordinated by OH group

CH$_2$I$_2$, Zn

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

Cu

TsN$_3$, K$_2$CO$_3$

CuI

t-BuO

t-BuO

K$_2$CO$_3$

- TsNH

t-BuO

t-BuO

t-BuO

SO$_2$Ar

ArO$_2$S

ArO$_2$S
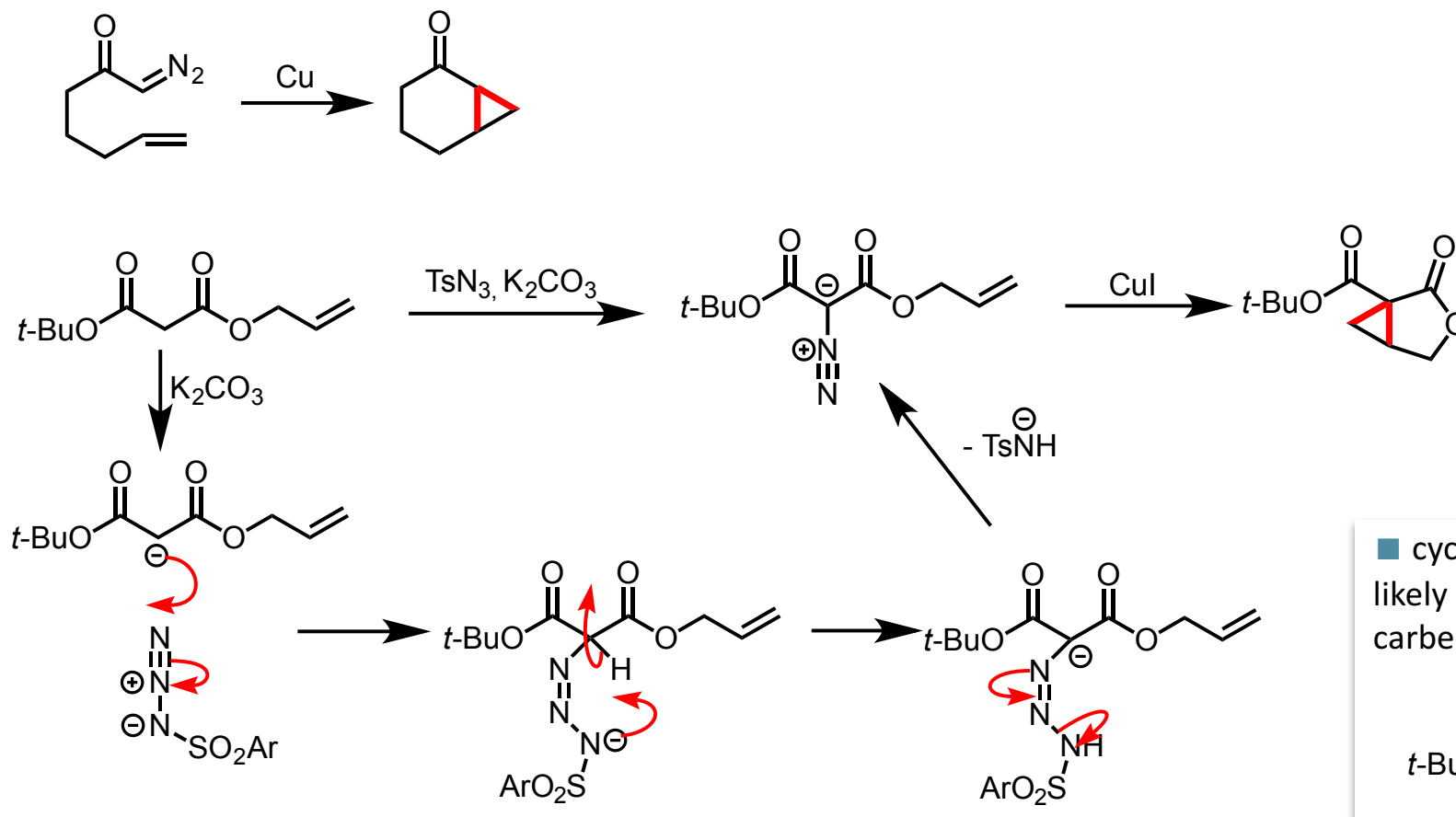
- cyclopropanation most likely proceeds by Cu(I) carbene intermediate

t-BuO

Cu^I

■ carbenes readily react with nucleophiles
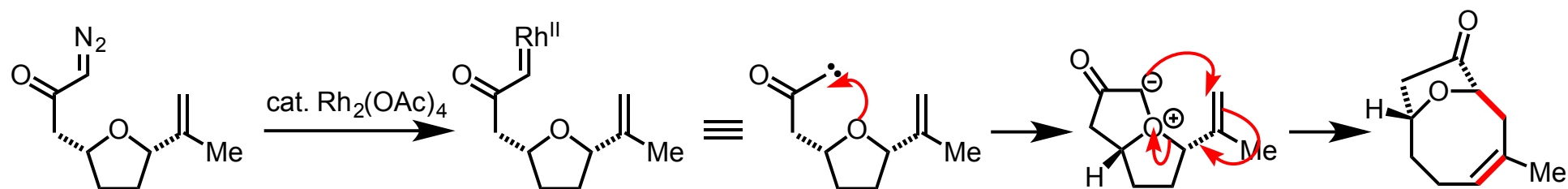
■ nucleophilic carbenes are useful catalysts
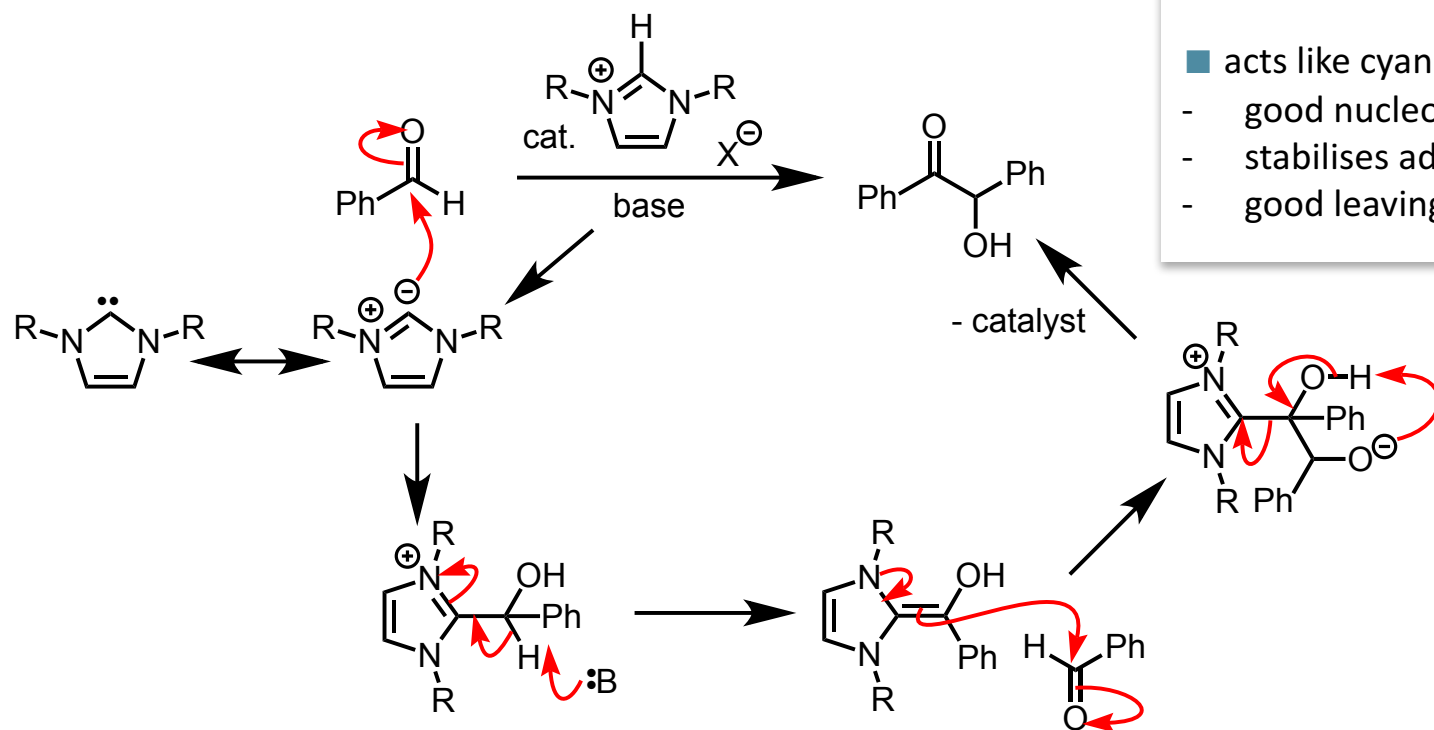
■ *N*-heterocyclic carbene catalyses the benzoin reaction
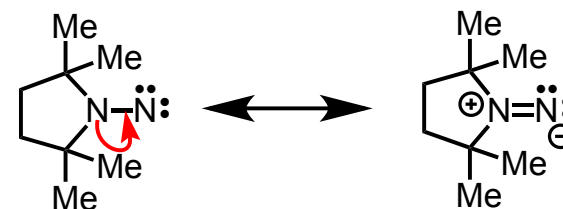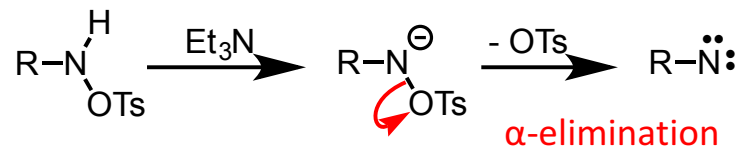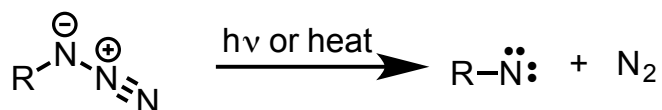
■ acts like cyanide:
- good nucleophile
- stabilises adjacent negative charge
- good leaving group

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

$$R-\ddot{N}: \quad\quad R-\ddot{N}\cdot$$
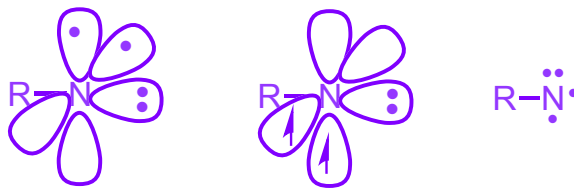
singlet sp^2 　　　　　　　triplet sp

■ 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

$$R-\overset{\ominus}{N}-\overset{\oplus}{N}\equiv N \quad\xrightarrow{h\nu \text{ or heat}}\quad R-\ddot{N}: \quad + \quad N_2$$

$$R-\overset{H}{\underset{OTs}{N}} \quad\xrightarrow{Et_3N}\quad R-\overset{\ominus}{\underset{OTs}{N}} \quad\xrightarrow{-\ OTs}\quad R-\ddot{N}:$$
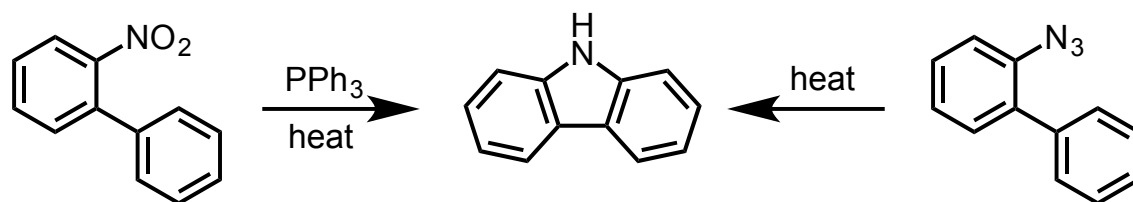
α-elimination

■ a number of methods for nitrene generation, analogous to the methods for carbene generation, are known

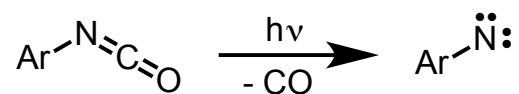■ free nitrenes are not always formed under these conditions
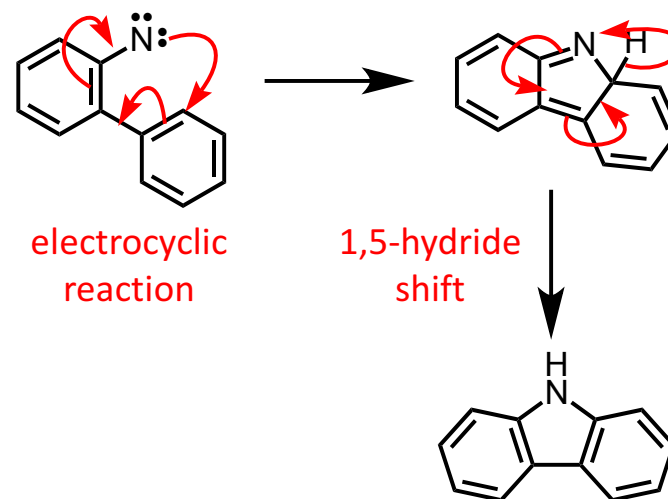
■ generation by reduction of nitro compounds

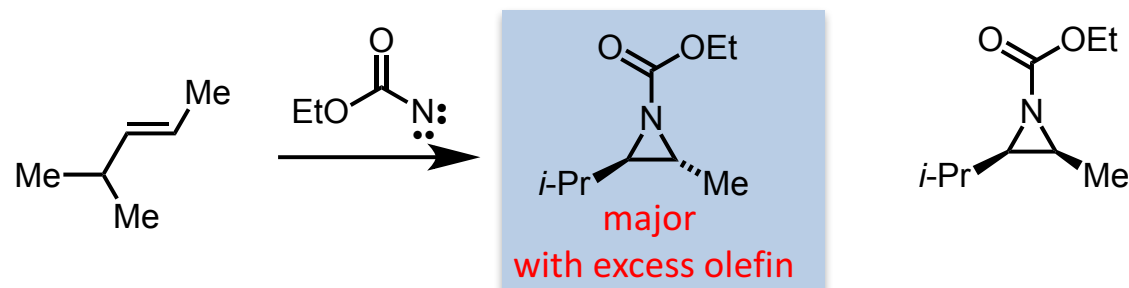α-elimination
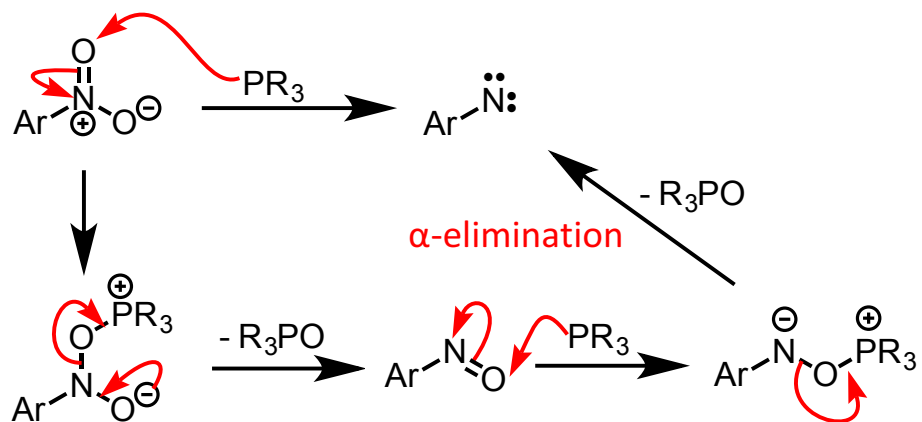
■ carbazole synthesis

■ generation from isocyanates
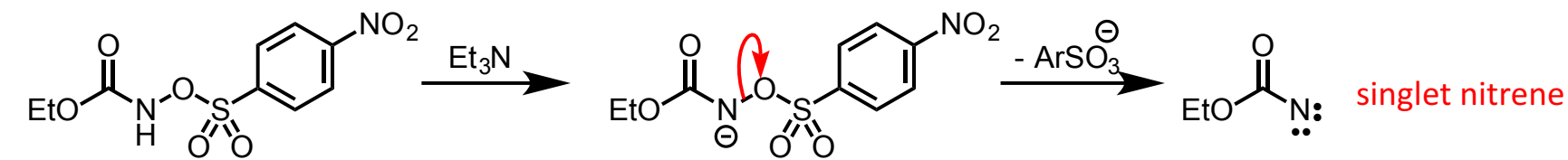

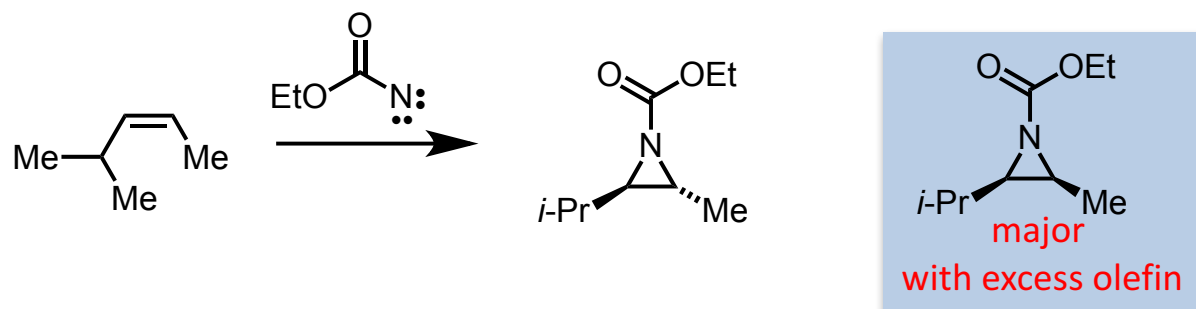■ plausible mechanism

electrocyclic
reaction

1,5-hydride
shift

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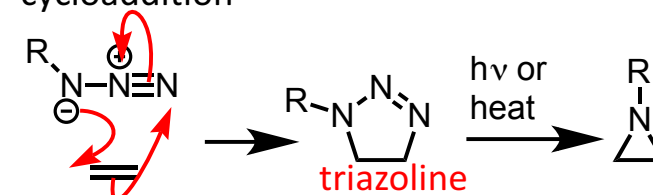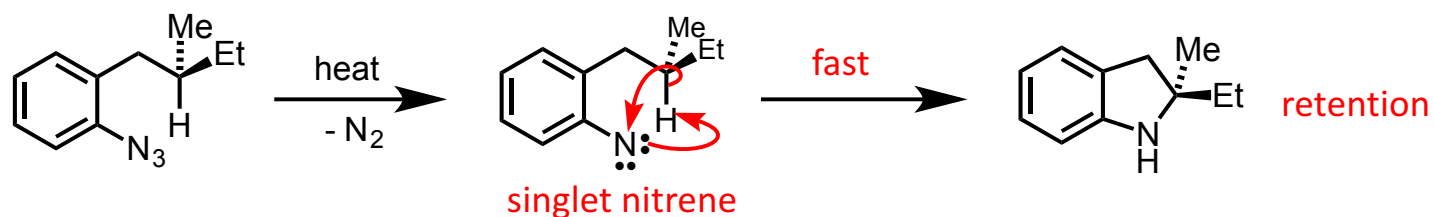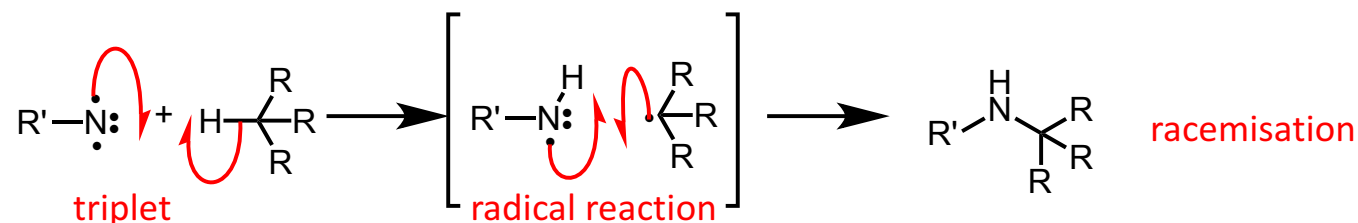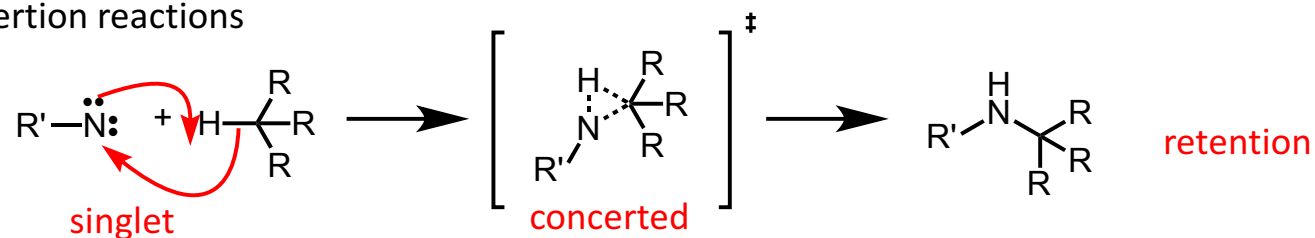
- with high concentration of olefin singlet nitrene reacts stereospecifically to give aziridine products – trans-olefin gives trans-aziridine; cis-olefin gives cis-aziridine
- with low concentraion of olefin singlet nitrene undergoes intersystem crossing to ground state triplet and reacts non-stereospecifically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

■ insertion reactions

singlet   concerted   retention

triplet   radical reaction   racemisation

heat
- N$_2$ fast   retention

singlet nitrene

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

PhI(OAc)$_2$
cat. Rh$_2$(OAc)$_4$ Rh^{II} 86%

iodonium ylid   rhodium nitrenoid   C-H insertion
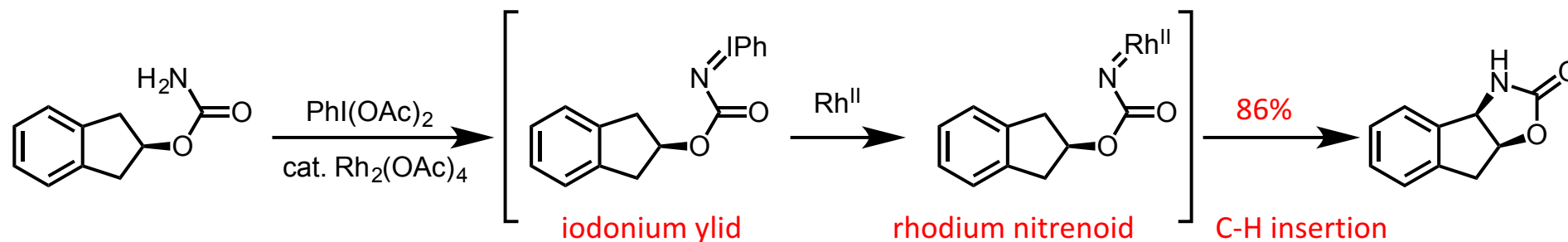
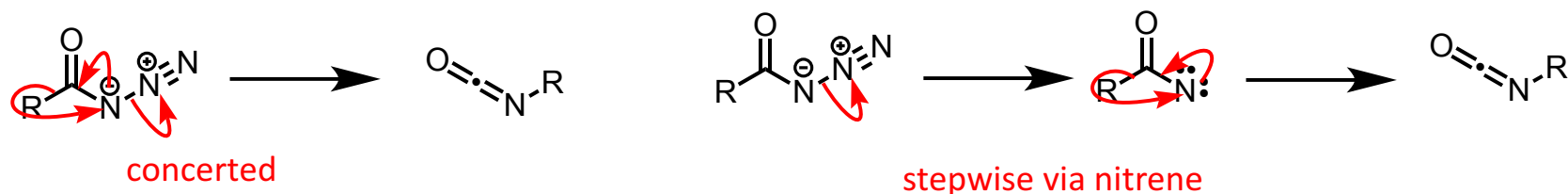■ in a similar manner transition metal nitrenoids react with alkenes to give good yields of aziridines

■ rearrangement of nitrenes

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

concerted 1,2 shift
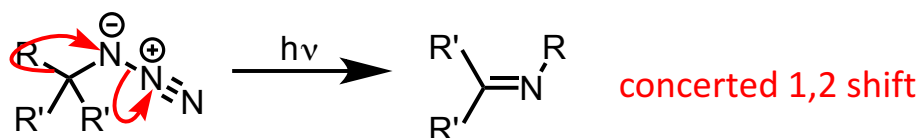
■ Curtius rearrangement or acyl azides
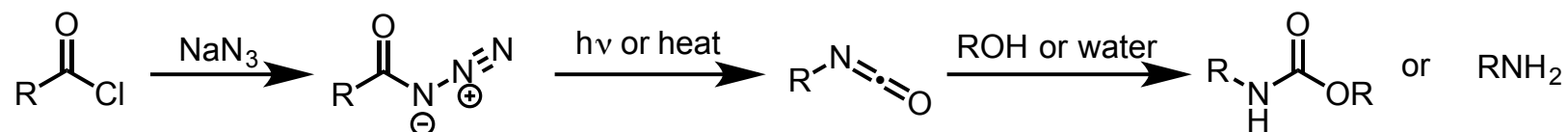
■ there are two plausible mechanisms

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
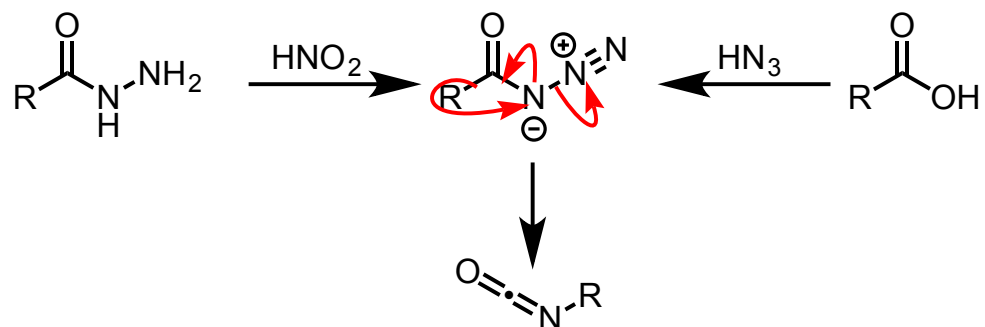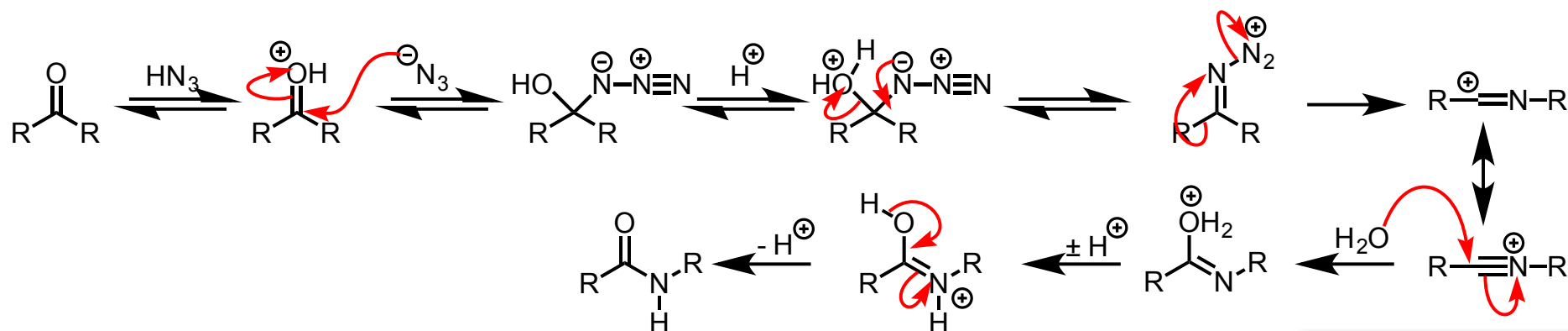
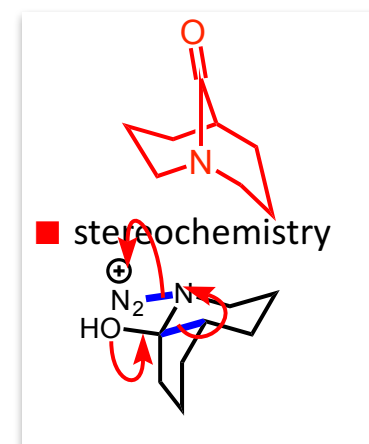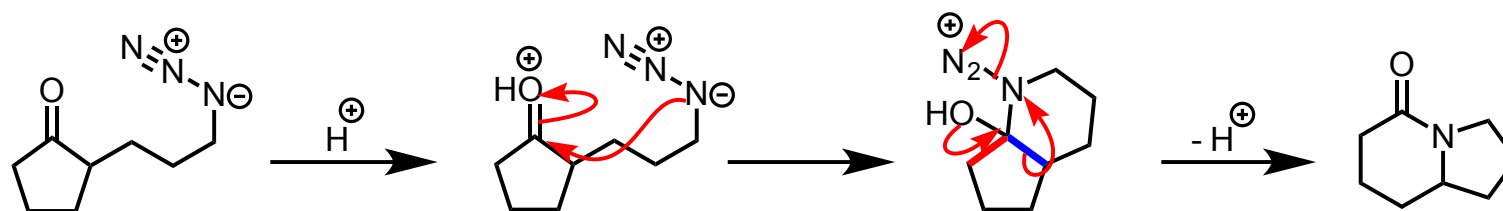- Hoffman rearrangement
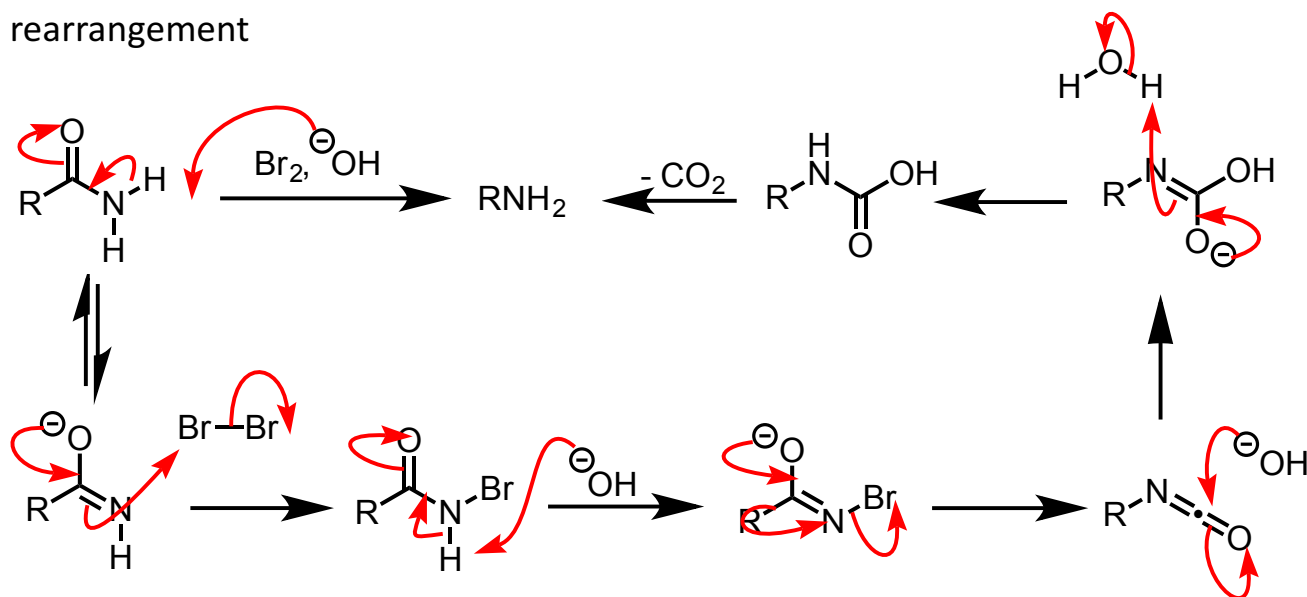
- Lossen rearrangement
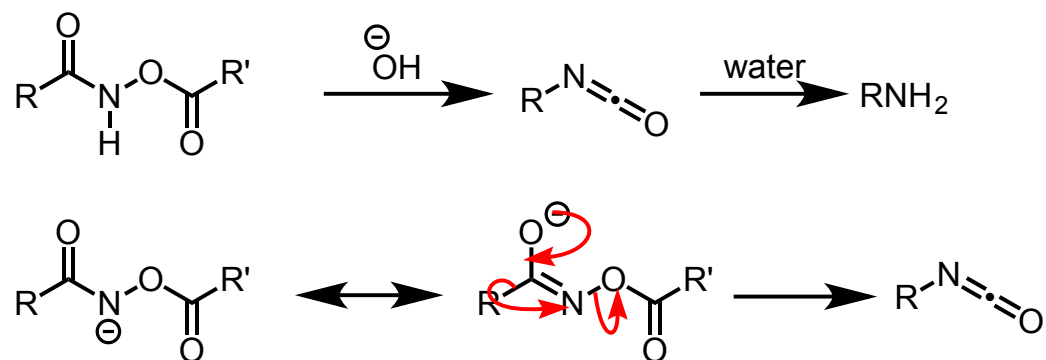
- Schmidt rearrangement

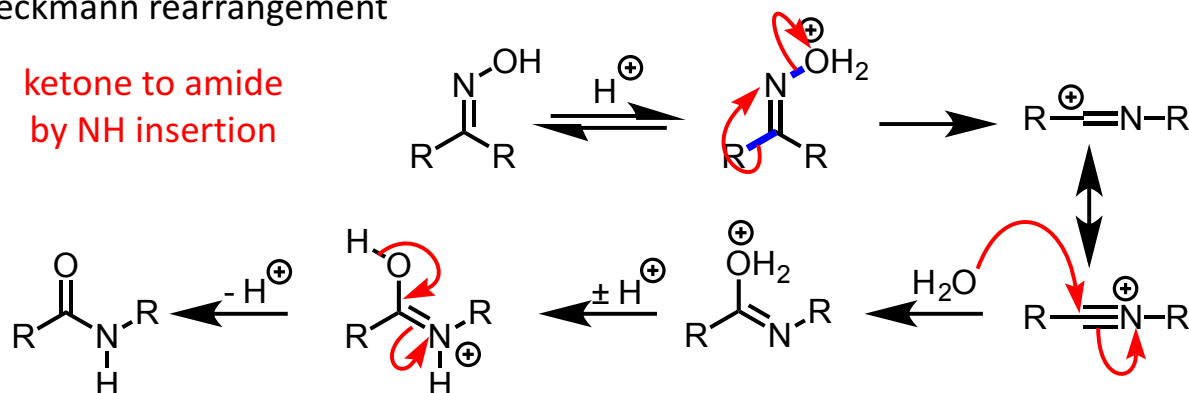- Schmidt rearrangement with ketones (aldehydes give nitriles)

- Intramolecular Schmidt rearrangement with alkyl azides

- stereochemistry

■ **Beckmann rearrangement**
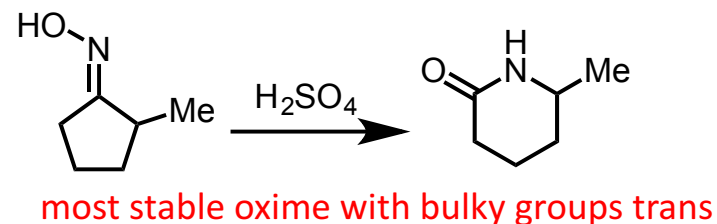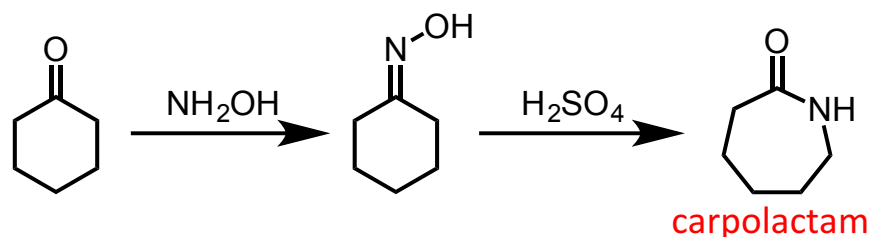
ketone to amide by NH insertion

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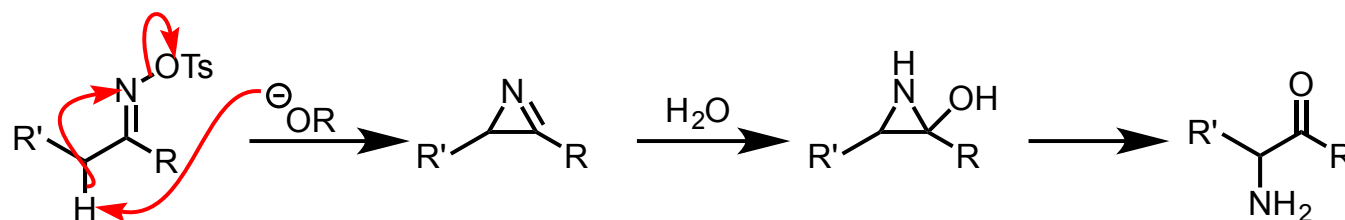
■ oximes can undergo *E/Z* isomerisation under the acidic reactions conditions
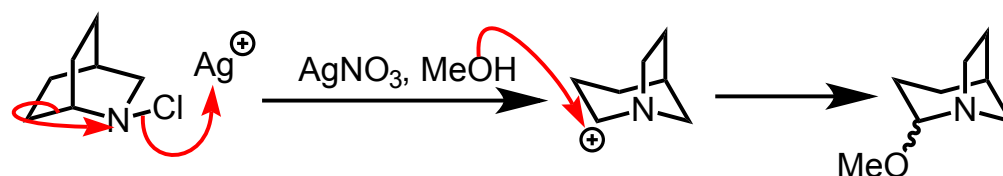
■ migration with retention of configuration

■ Beckmann rearrangement – synthesis of caprolactam, precursor to nylon 6

carpolactam

most stable oxime with bulky groups trans
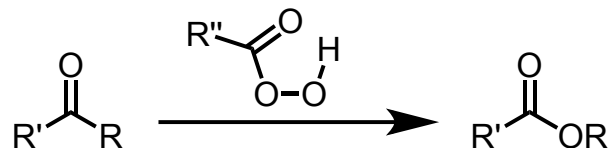
■ Neber rearrangement – substituent possessing most acidic hydrogen migrates

■ Stieglitz rearrangement

■ Baeyer-Villiger

conversion of a ketone into an ester by oxygen insertion

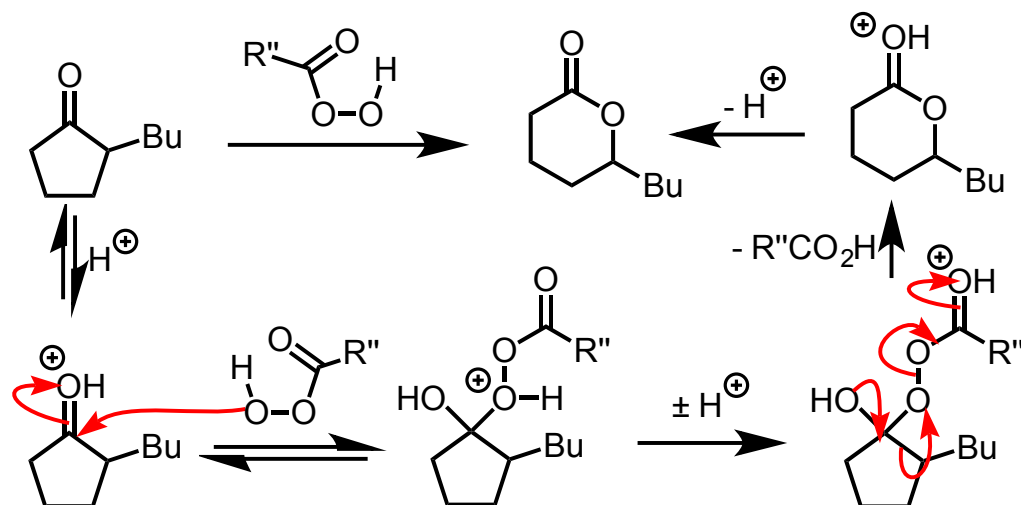■ order of migration A.K.A migratory aptitude
3° alkyl > 2° alkyl > aryl > 1° alkyl > methyl
i.e. the group which best supports a positive charge migrates

■ 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)

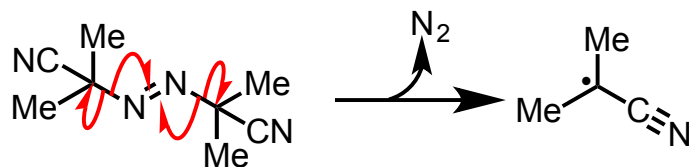■ electron releasing groups stabilise the transition state giving the order of migratory aptitude above
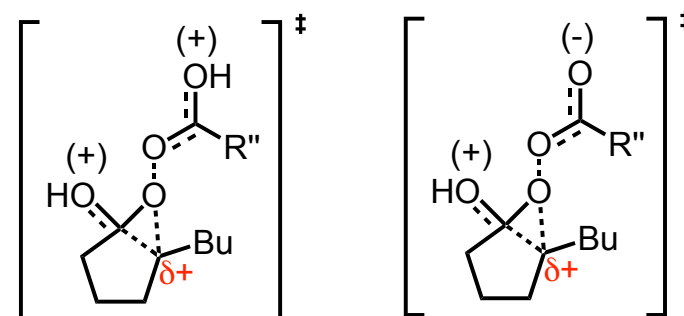
# Rearrangements and Reactive Intermediates

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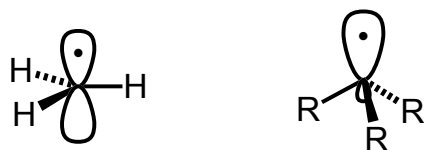
■ stability – a good guide to radical stability comes from C—H (and X-H in general) bond dissociation energies

| 356 | 381 | 395 | 410 | 430 | 427 | 436 | 523 | kJmol^{-1} |
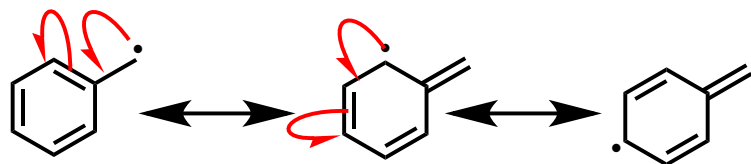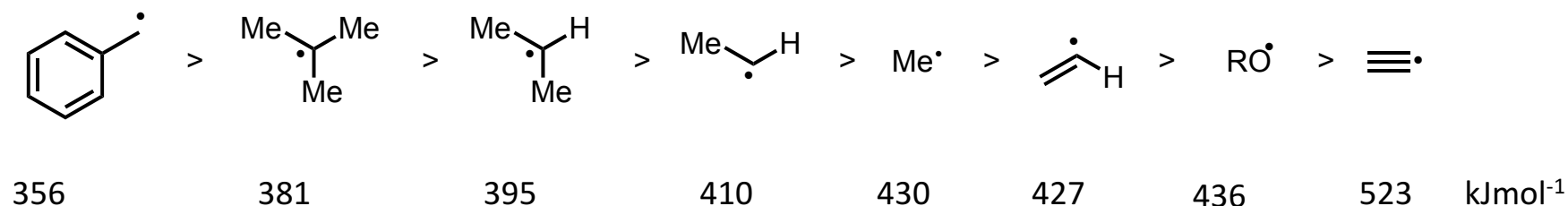
■ stabilised through delocalisation

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

■ stabilised through hyperconjugation

half-filled
sp^n hybrid

filled
σ_{C-H}

overall system stabilised
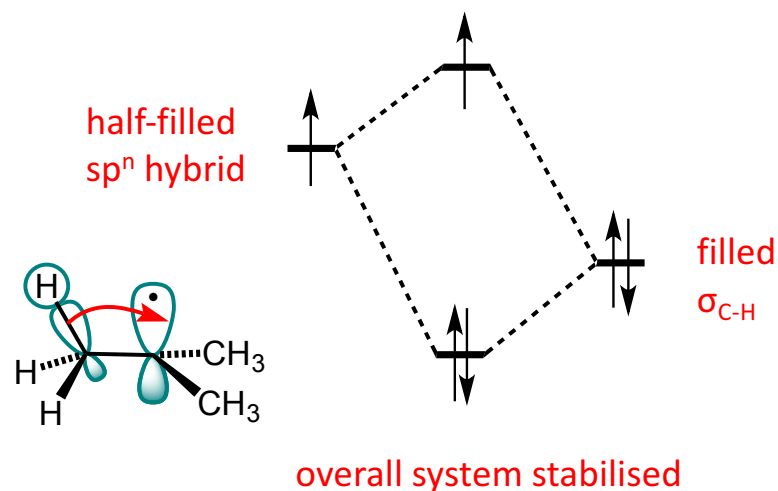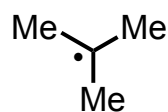
■ some bond dissociation energies − ΔH° for R—R → R• + R•

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—C	330
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=O	750
C=C	585

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?

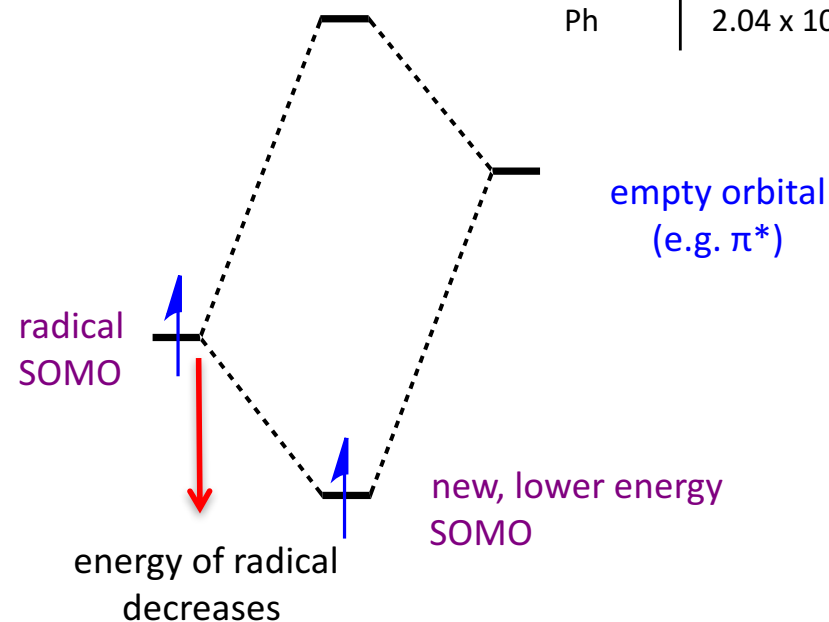| X	k_{rel}
H	1
CH$_3$	501
OMe	5248
CO$_2$R	1.25 x 10^8
CN	1.45 x 10^8
Ph	2.04 x 10^8

energy of radical increases

new, higher energy SOMO (singly occupied molecular orbital)

radical SOMO

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

radical SOMO

empty orbital (e.g. π*)

new, lower energy SOMO

energy of radical decreases
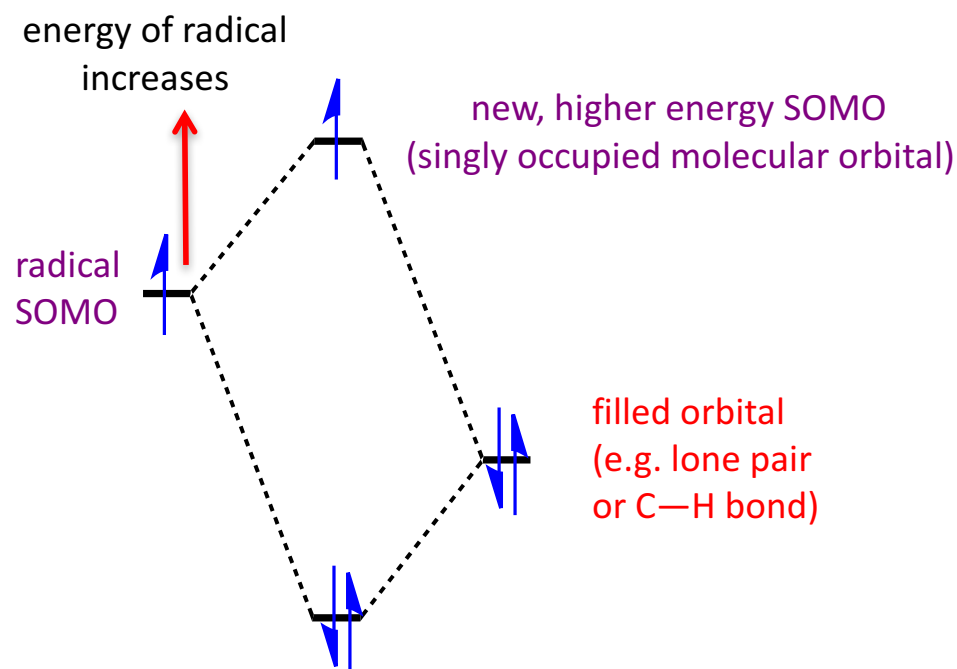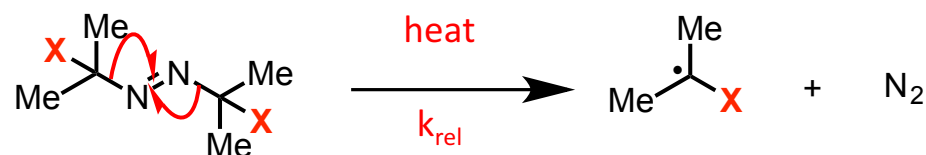
■ radical with adjacent filled orbital SOMO raised, overall system stabilised

■ 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
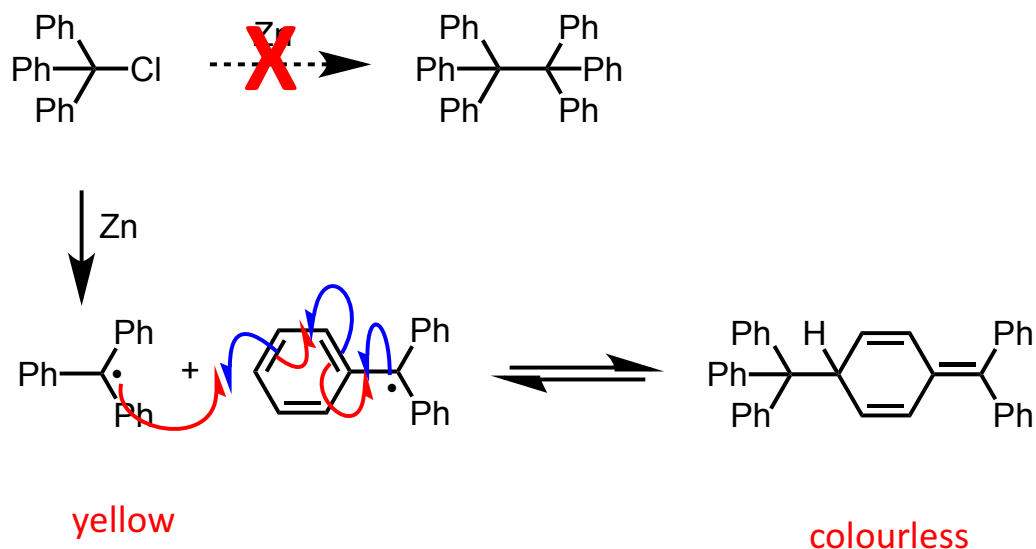
■ An X-ray structure of a substituted trityl radical

1.67 Å

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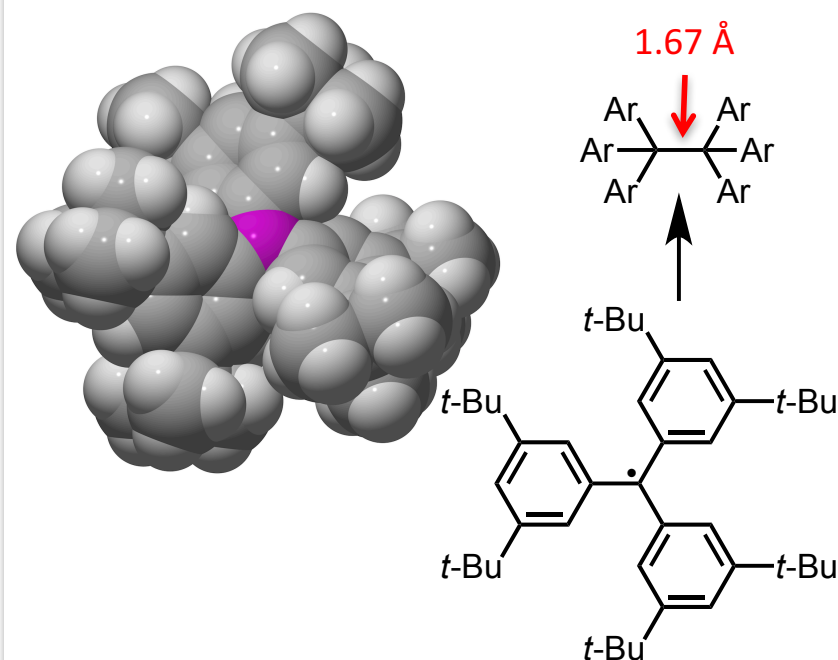
■ most organic radicals are transient (very short lifetimes) – radicals without special stabilisation dimerise or disproportionate

■ trityl radical is a stabilised radical – stabilised radicals include C-centred radicals R• 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
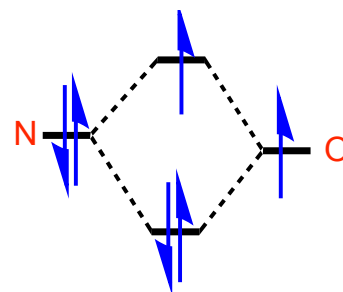
- examples of stable, persistent radicals
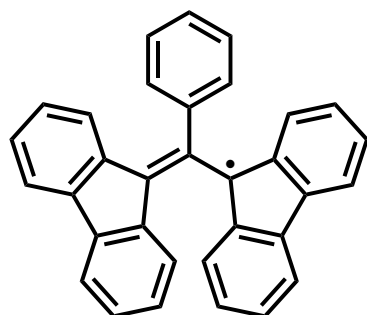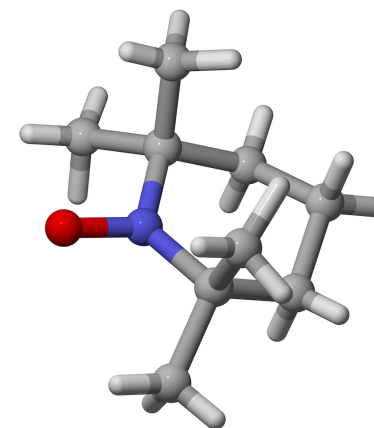
mp 210 °C
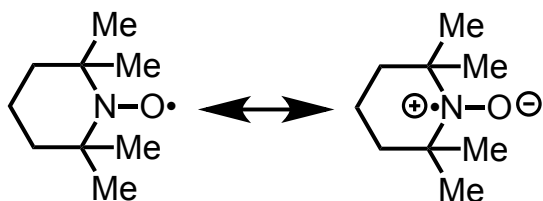
- TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical)
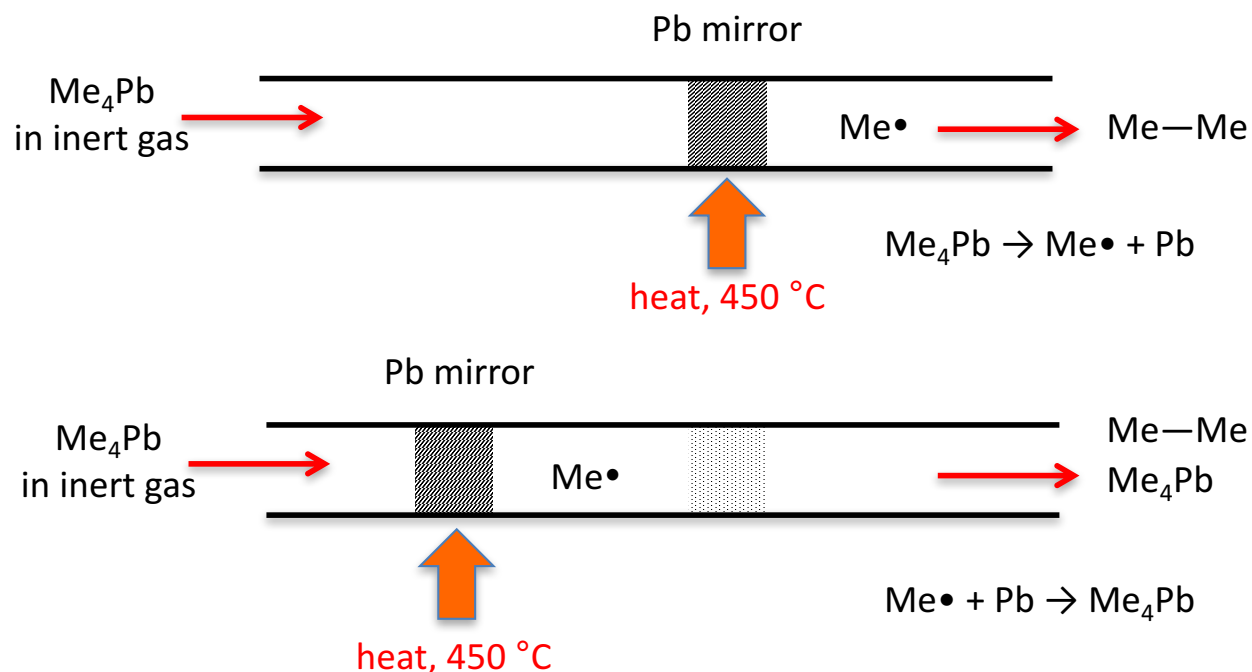
N ⟷ O

- 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

Pb mirror

Me_4Pb
in inert gas

Me• ⟶ Me—Me

heat, 450 °C

$Me_4Pb \rightarrow Me• + Pb$

Pb mirror

Me_4Pb
in inert gas

Me•

Me—Me
Me_4Pb

heat, 450 °C

$Me• + Pb \rightarrow Me_4Pb$

- 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

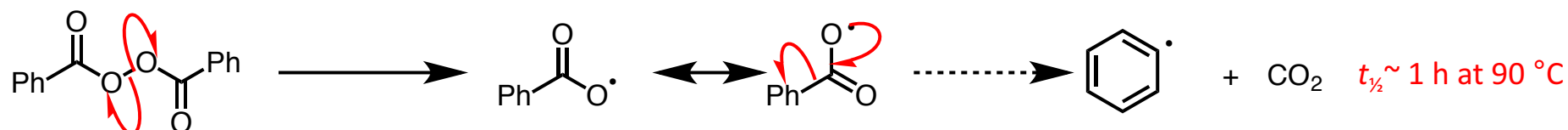- radicals attack univalent and sometimes divalent atoms – very rarely tri- or tetravalent atoms

X–Y $\xrightarrow{\text{heat or h}\nu}$ X• + Y•
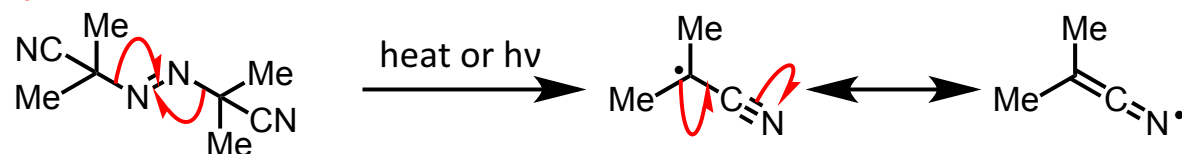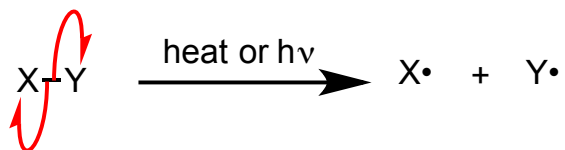
AIBN - azobisidobutyronitrile

$t_{\frac{1}{2}} \sim 1$ h at 80 °C
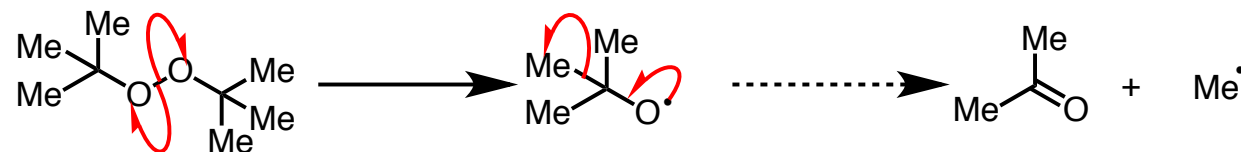
$t_{\frac{1}{2}} \sim 1$ h at 150 °C

+ CO_2 $t_{\frac{1}{2}} \sim 1$ h at 90 °C
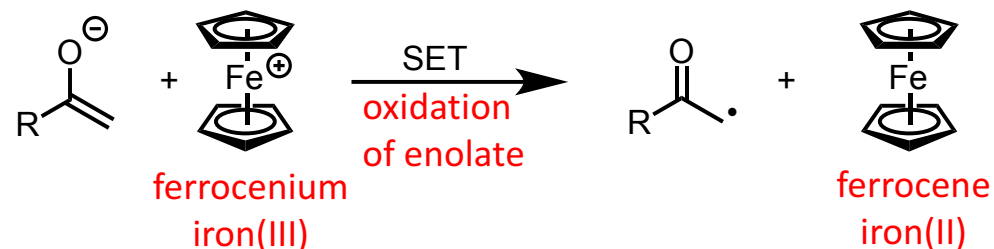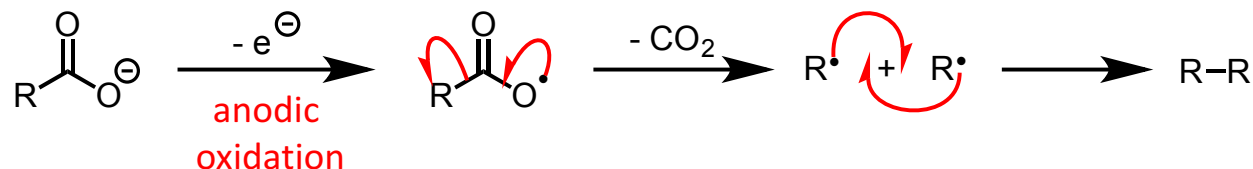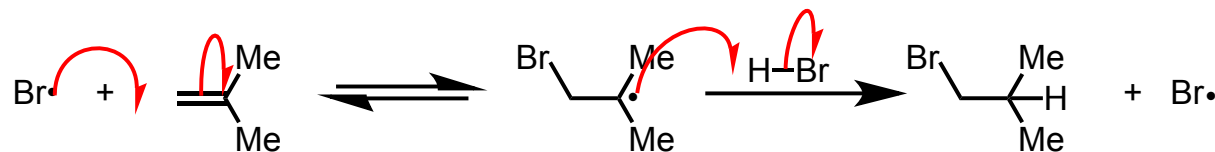
■ redox
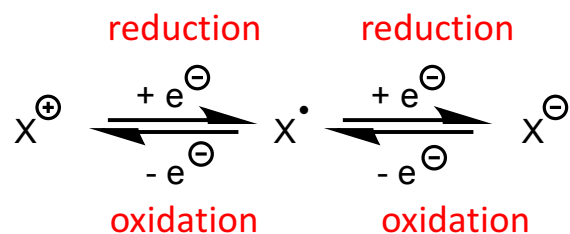
■ many (transition) metal salts are good single electron oxidants for enolates and related functional groups

■ Kolbe electrolysis

■ addition / β-scission
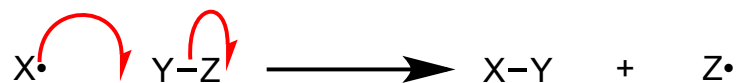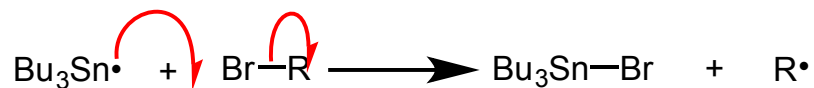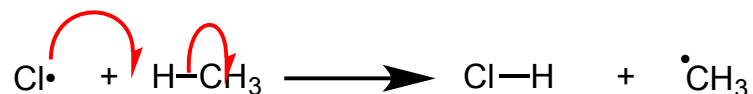

■ example – anti-Markovnikov addition of HBr to alkenes

■ 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)

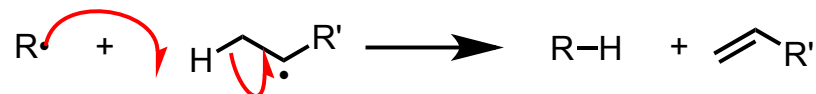■ Y is univalent atom e.g. H or Br occasionally divalent e.g. SPh, SePh – almost never tetravalent atoms

$$X\cdot \quad Y-Z \quad \longrightarrow \quad X-Y \quad + \quad Z\cdot$$

$$Cl\cdot \quad + \quad H-CH_3 \quad \longrightarrow \quad Cl-H \quad + \quad \cdot CH_3$$

$$Bu_3Sn\cdot \quad + \quad Br-R \quad \longrightarrow \quad Bu_3Sn-Br \quad + \quad R\cdot$$

- ■ intramolecular 1,5-hydrogen atom transfer – common for alkoxy radicals with appropriately positioned C—H bond
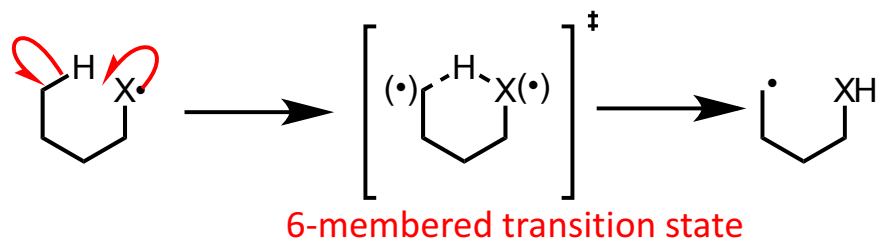
- ■ disproportionation – H-atom abstraction β to radical centre – a type of termination

6-membered transition state

$$R\cdot \quad + \quad H\underset{\cdot}{\diagup}R' \quad \longrightarrow \quad R-H \quad + \quad \diagup\diagup R'$$
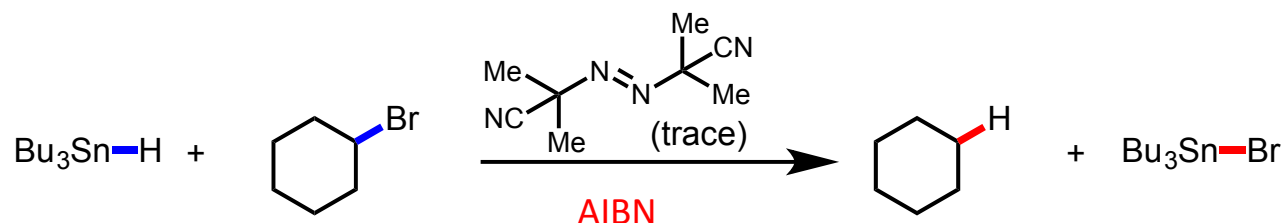
- ■ the majority of radical reactions we will meet will be chain processes which have three steps:

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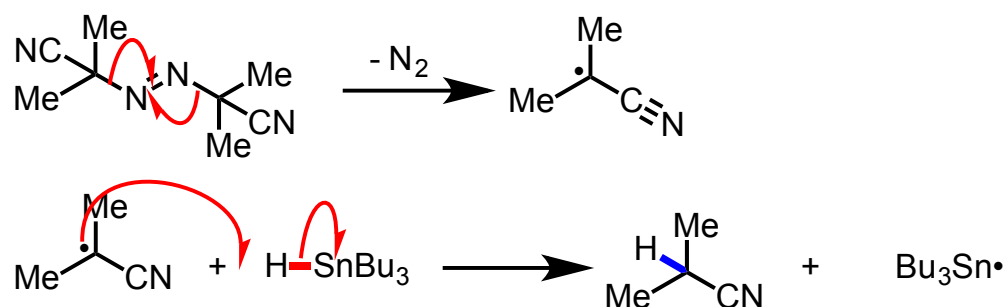
- ■ for an efficient chain process the rate of the propagating steps must out compete the rate of the termination steps - given the vast difference in rate constants for these processes the [R•] must be low – typically 10^{-8} **M**

■ a typical radical chain process

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

Bu_3Sn—H + (cyclohexyl-Br) $\xrightarrow[\text{AIBN}]{\text{(trace)}}$ (cyclohexyl-H) + Bu_3Sn—Br

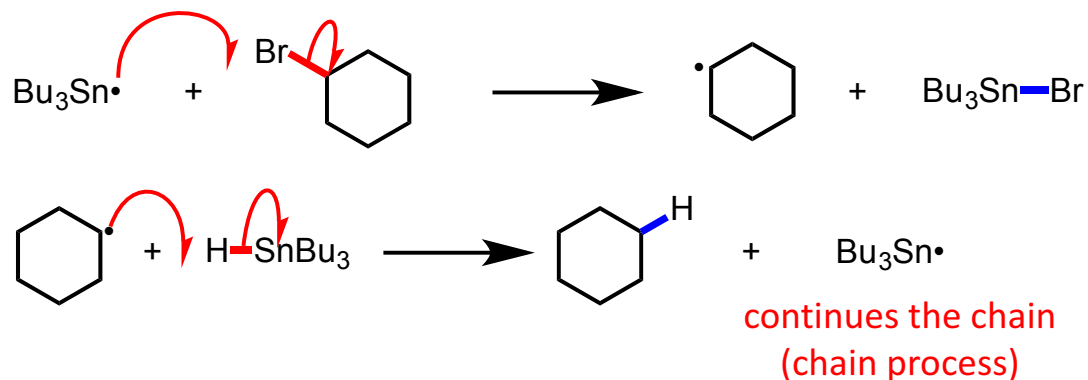■ initiation

$\xrightarrow{- N_2}$

■ overall exothermic reaction
bonds made = **-419 - 332 = -751**
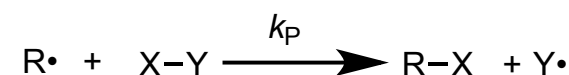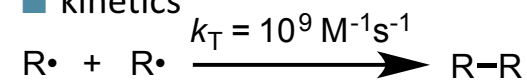bonds broken = **+270 + 267 = +537**
ΔH = -692 + 537 = -214 kJmol^{-1}
very crude analysis due to wide variation in reported bond dissociation energies

■ propagation

$Bu_3Sn•$ + (cyclohexyl-Br) $\longrightarrow$ (cyclohexyl•) + Bu_3Sn—Br

(cyclohexyl•) + H—SnBu$_3$ $\longrightarrow$ (cyclohexyl-H) + $Bu_3Sn•$

continues the chain
(chain process)

■ termination – radical-radical recombination or disproportionation

■ kinetics

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

$R• + X$—$Y \xrightarrow{k_P} R$—$X + Y•$

$\dfrac{d[R-R]}{dt} = k_T[R•]^2 = 10^9 \times (10^{-8})^2 = \mathbf{10^{-7} \text{ Ms}^{-1}}$
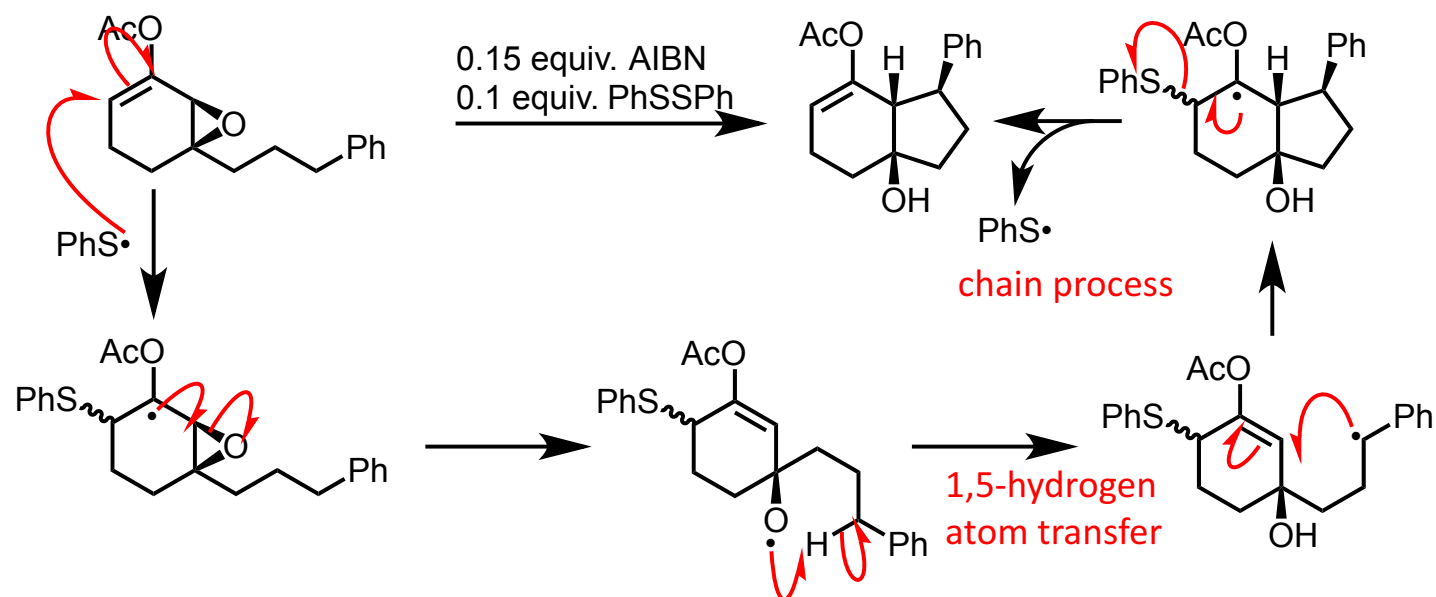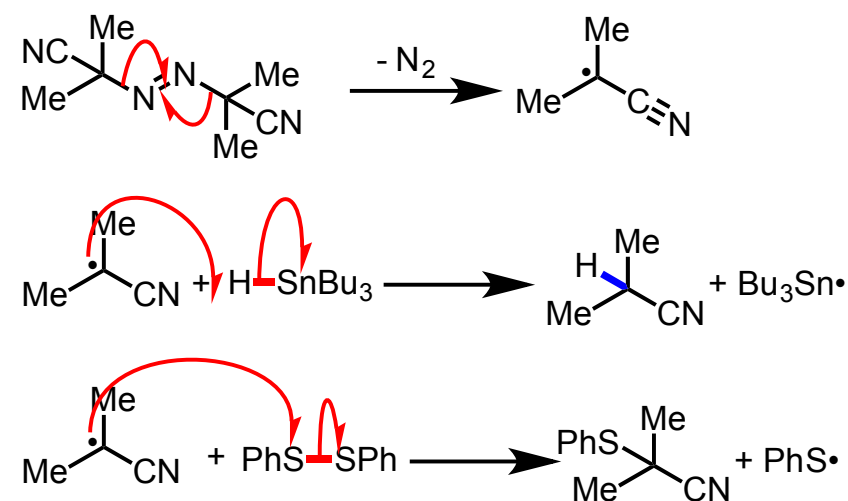
$\dfrac{d[R-X]}{dt} = k_P[R•][X-Y] = 10^{-8} \times 10^0 = \mathbf{k_P 10^{-8} \text{ Ms}^{-1}}$

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

examples

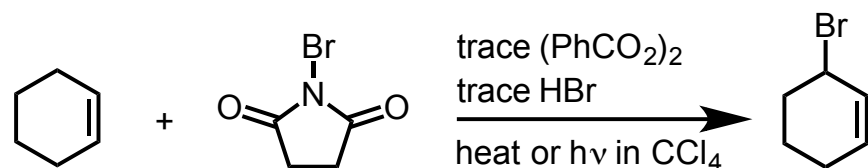AIBN (small amount)
Bu$_3$SnH

chain process

Bu$_3$Sn•

Bu$_3$Sn–H

Bu$_3$Sn•

initiation

– N$_2$

+ Bu$_3$Sn•

+ PhS•

0.15 equiv. AIBN
0.1 equiv. PhSSPh

chain process

PhS•

PhS•
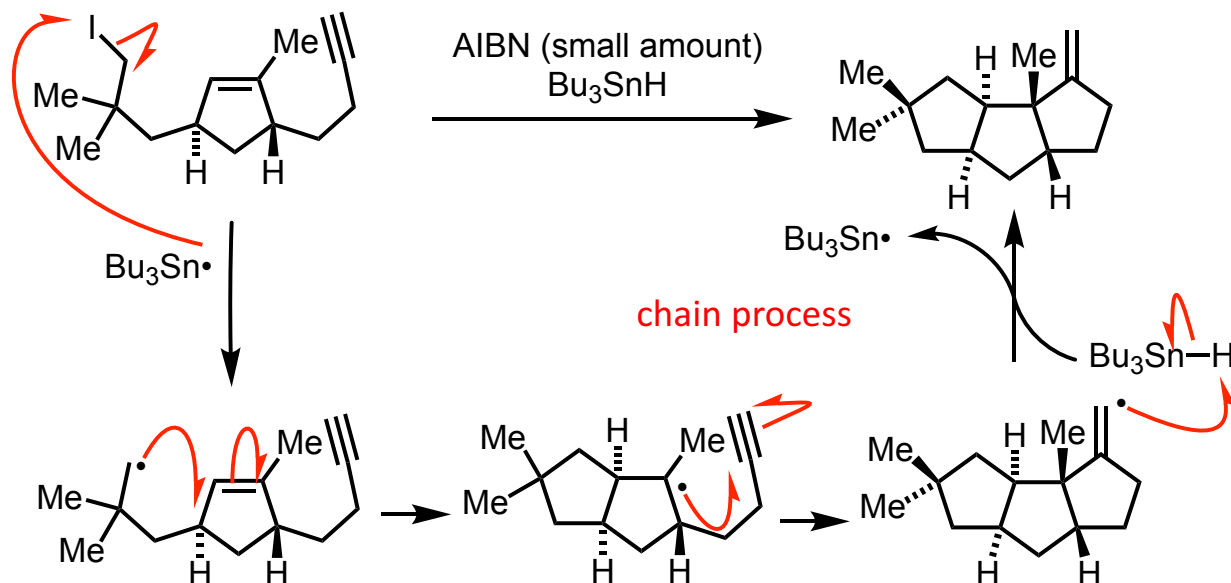
1,5-hydrogen
atom transfer
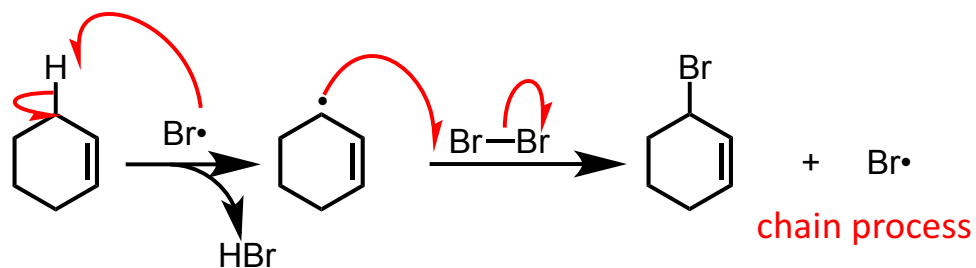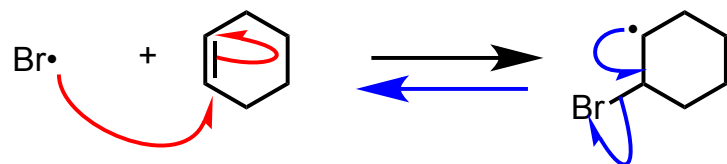
■ Wohl–Ziegler bromination – the Goldfinger mechanism

N-bromosuccinimide, NBS

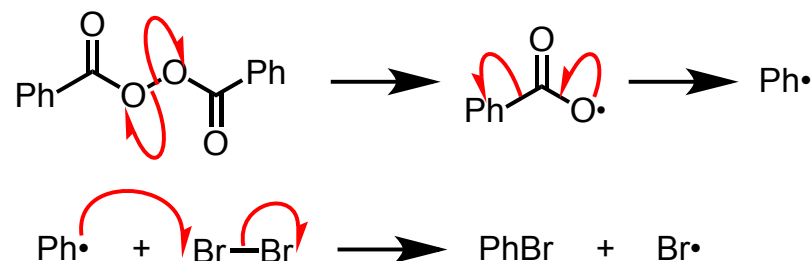trace (PhCO$_2$)$_2$
trace HBr

heat or hν in CCl$_4$

■ plausible initiation

Ph•   +   Br—Br   ⟶   PhBr   +   Br•

chain process

HBr

Br•

HBr   +   ⟶   +   Br$_2$

■ 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

Br•   +   ⟶
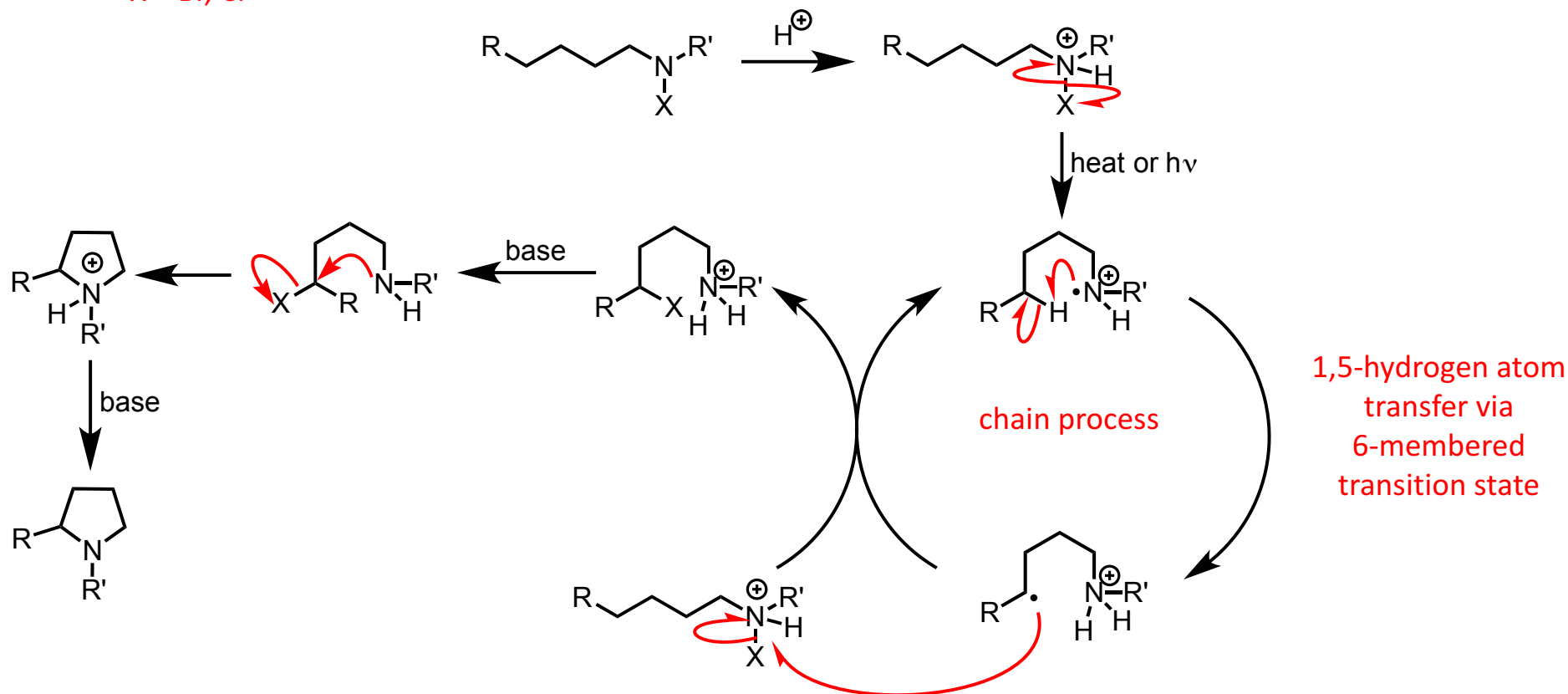
■ addition of Br• to alkene is reversible (nothing to trap the adduct radical)
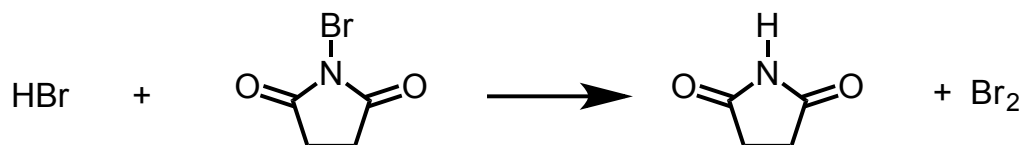
■ with unsymmetrical alkenes Br• abstracts the hydrogen atom so as to give the most stable radical


NBS

trace (PhCO$_2$)$_2$

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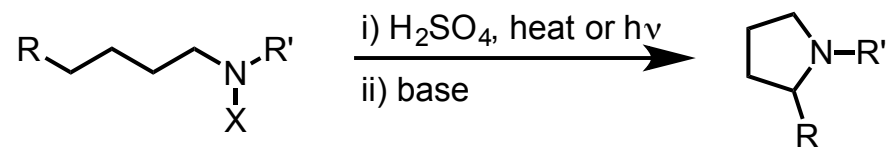
■ both the Wohl-Ziegler bromination and the Hofmann–Löffler–Freytag reaction provide methods for functionalising unactivated C—H bonds

i) H$_2$SO$_4$, heat or hν

ii) base

X = Br, Cl

H$^{\oplus}$

heat or hν

base

base

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
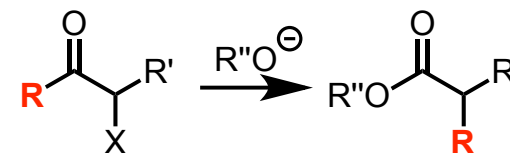

Favorskii rearrangement
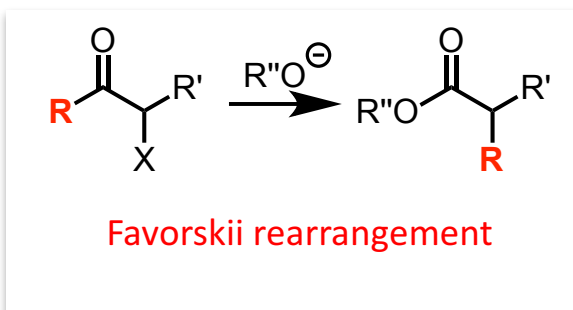
## Case Studies: Elucidating the Mechanisms of Rearrangements

- chemists gather evidence to both support and refute a proposed mechanism

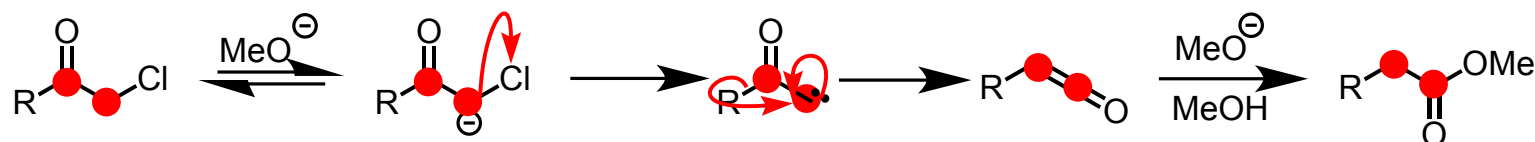- Favorskii rearrangement – previously discussed mechanism
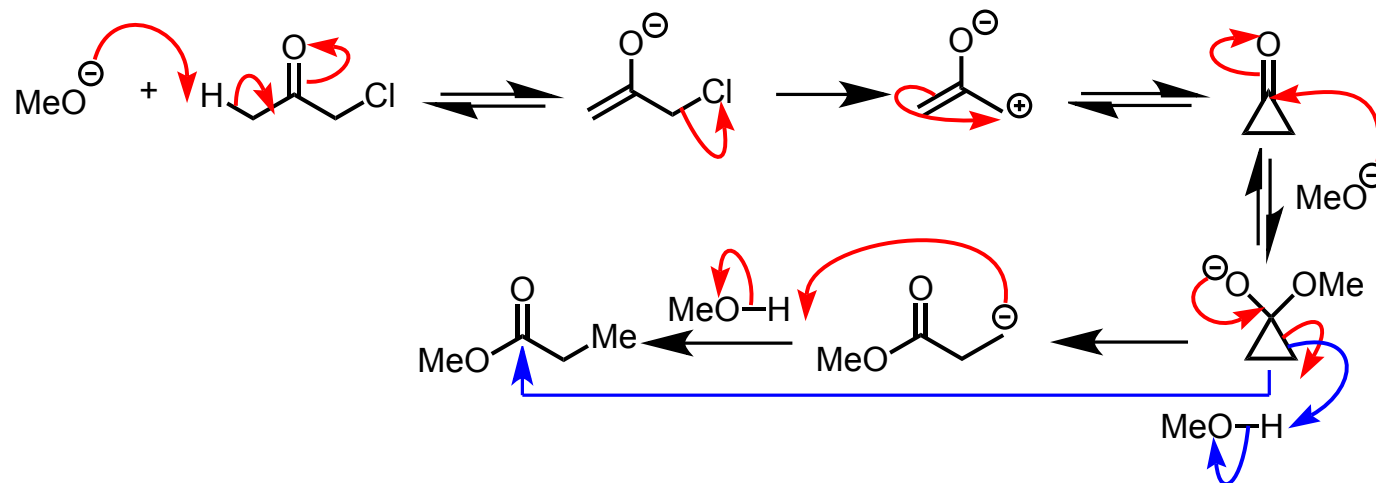
- overall in the Favorskii rearrangement an alkyl group (**R**) moves from one side of the carbonyl group to the other

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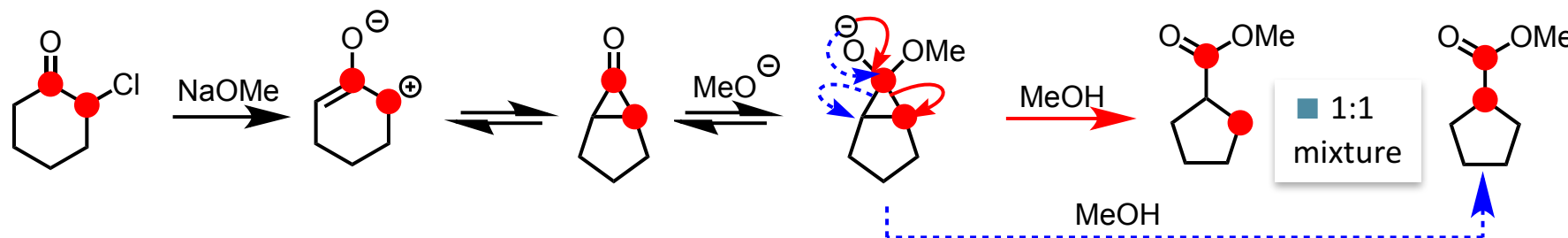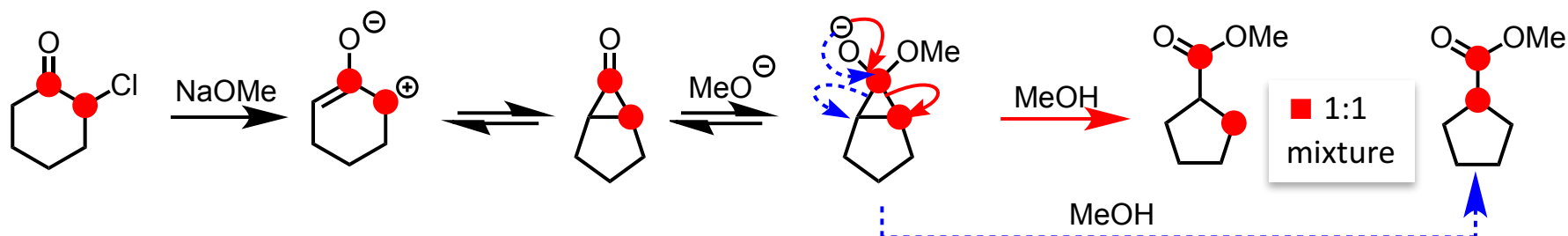

- Loftfield experiment ruled out a number of previously proposed mechanisms such as:


reasonable mechanism ruled out by double labeling experiment

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

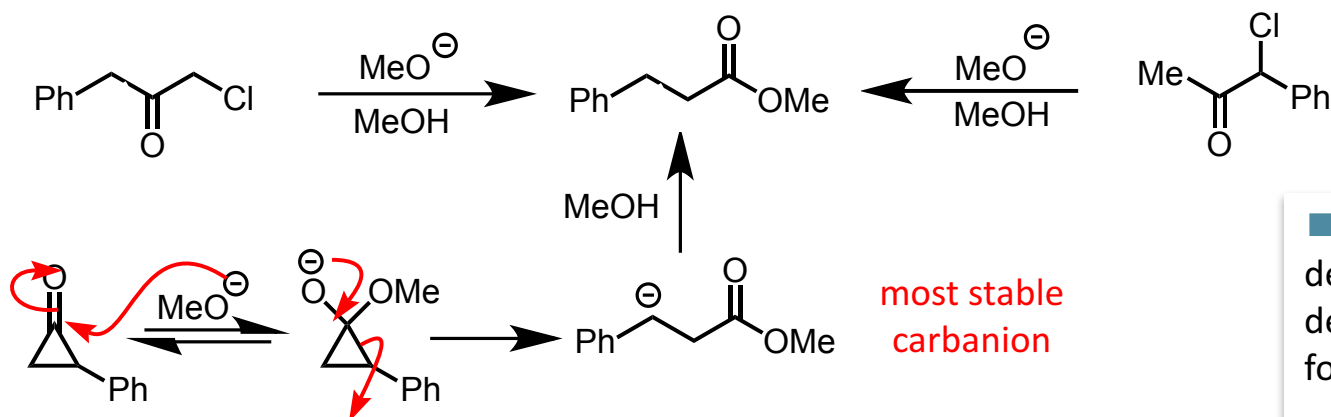■ symmetrical intermediate established by Loftfield with doubly labelled substrate ● = ^{14}C label

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

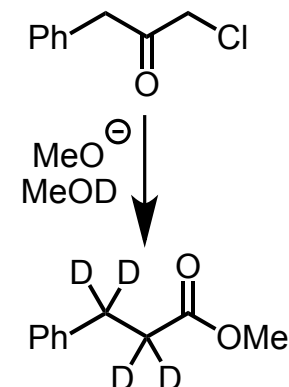chloride isomerisation does not occur
under reaction conditions
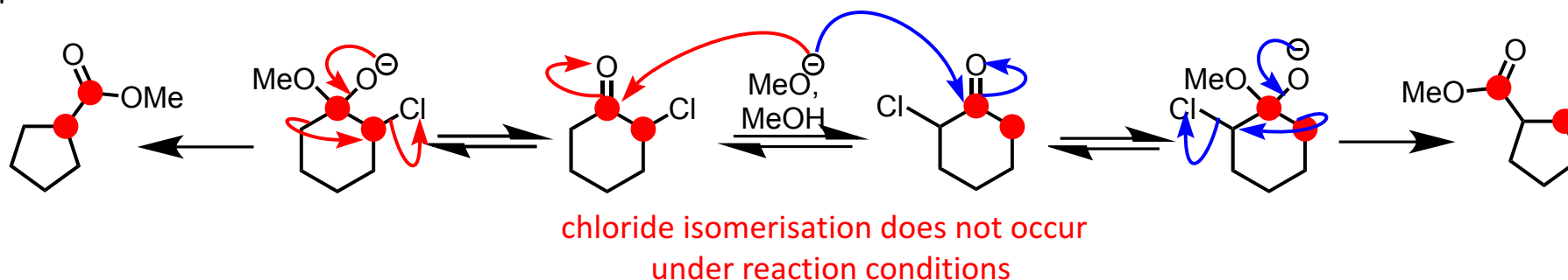
■ Loftfield demonstrated that the isomerisation proposed above **does not** occur under the reaction conditions by halting the reaction prior to completion and reisolating the starting material which had the labelled carbons at their original positions
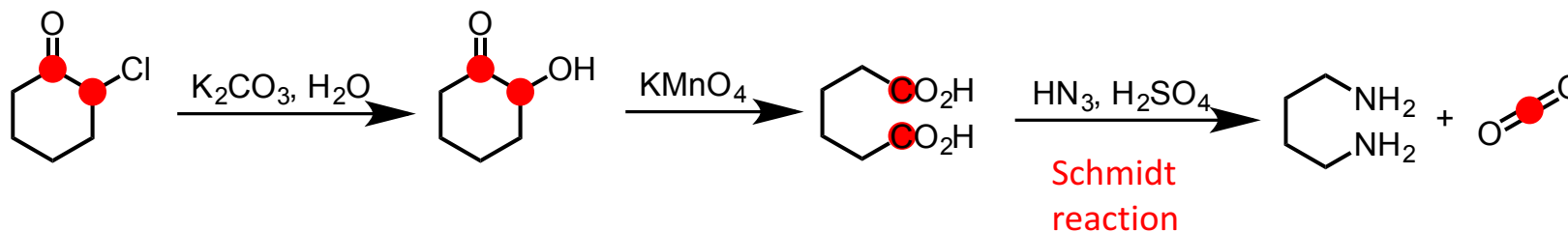
■ further evidence for a cyclopropanone intermediate – isomeric substrates give the same product

most stable carbanion

■ evidence for an oxyallyl intermediate

Favorskii product

cycloaddition

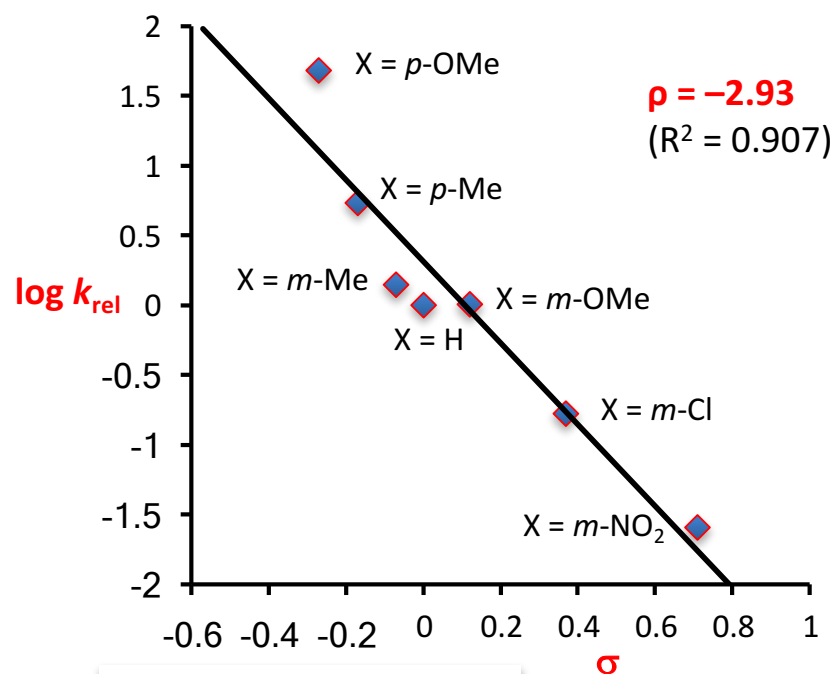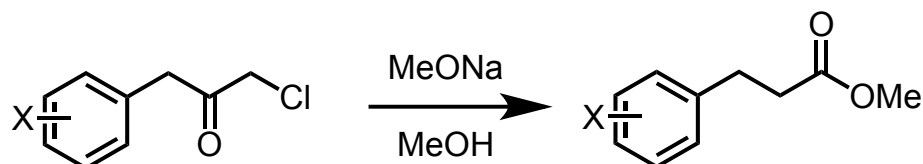■ in the Favorskii reaction deuterium exchange occurs demonstrating that enolates are formed reversibly
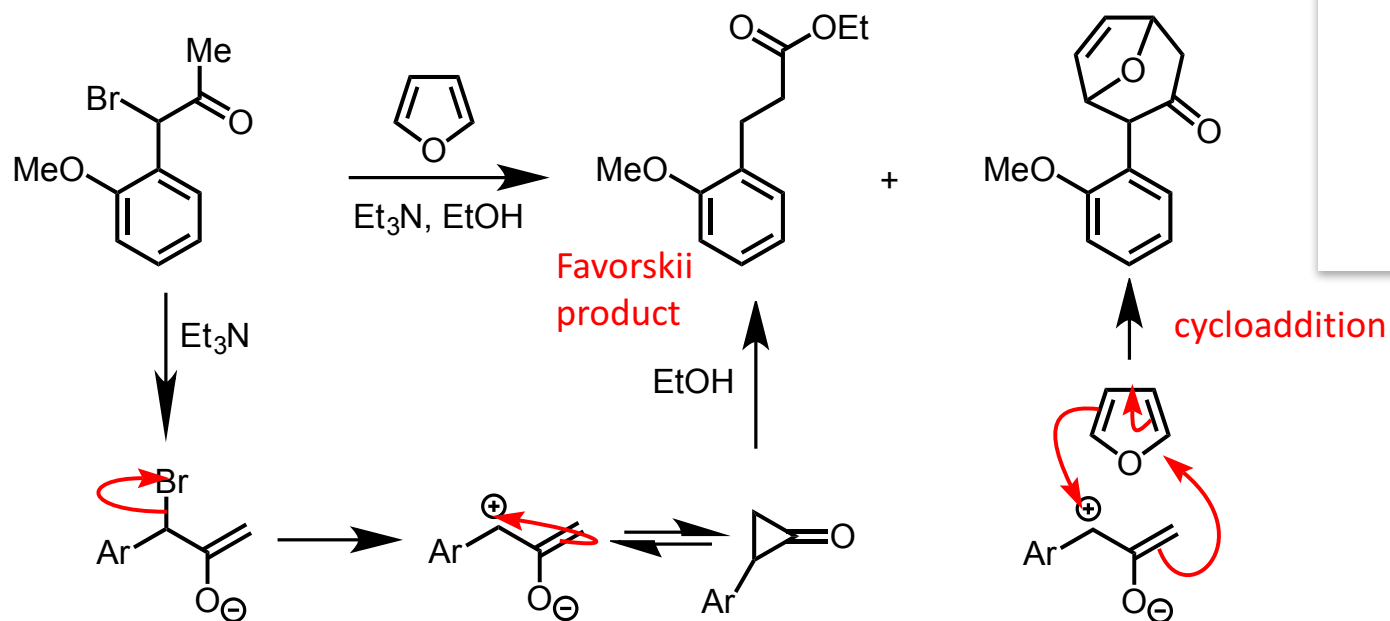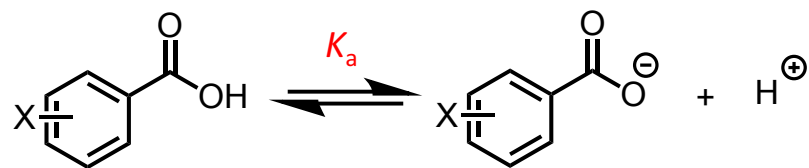
■ deuterium exchange indicates a rapid equilibrium prior to rearrangement

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

$\rho = -2.93$
($R^2 = 0.907$)

■ 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*

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

■ negative ρ value for Favorskii rearrangement needs to be interpreted carefully due to equilibrium prior to rearrangement
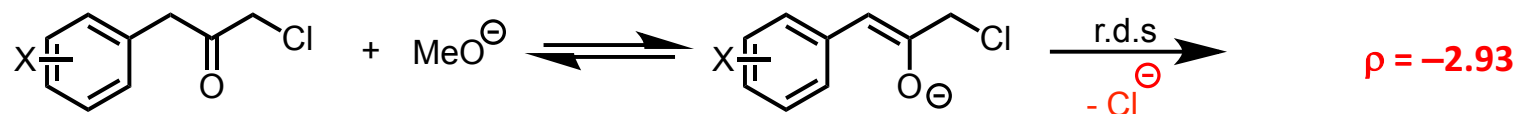
- Hammett ρ value is a combined value for all the steps up to and including the rate determining step

- ρ value for enolisation of arylmethyl phenyl ketones = **+1.73**
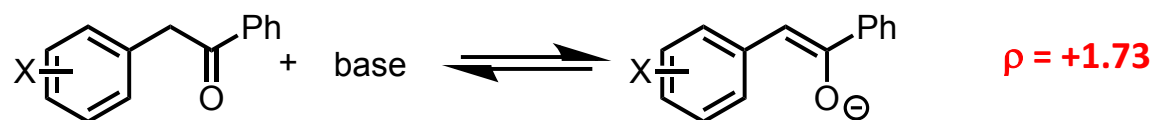
- enolisation in base should be favoured by EWG on aromatic ring $\therefore$ ρ = **+1.73** makes sense

- for Favorskii reaction $\rho_{reaction}$ = **−2.93** which is made up of the enolisation step and the subsequent loss of chloride

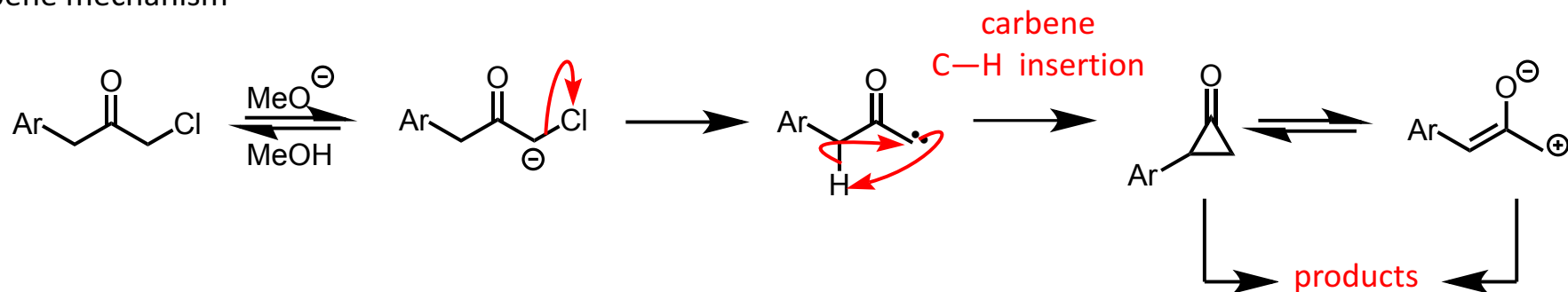- $\rho_{reaction}$ = $\rho_{enolistion}$ + $\rho_{chloride\ loss}$

- $\therefore$ $\rho_{chloride\ loss}$ = **−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

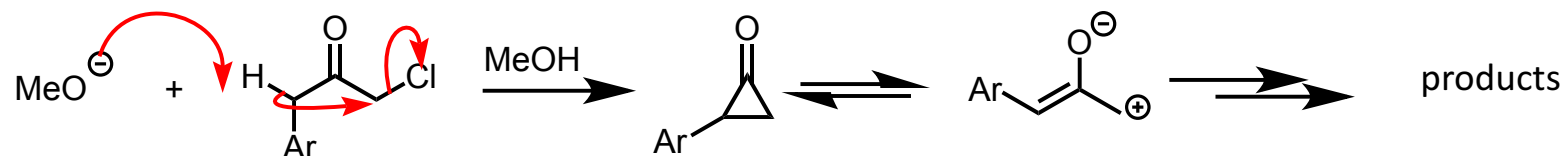ρ = +1.73 ρ = -4.66
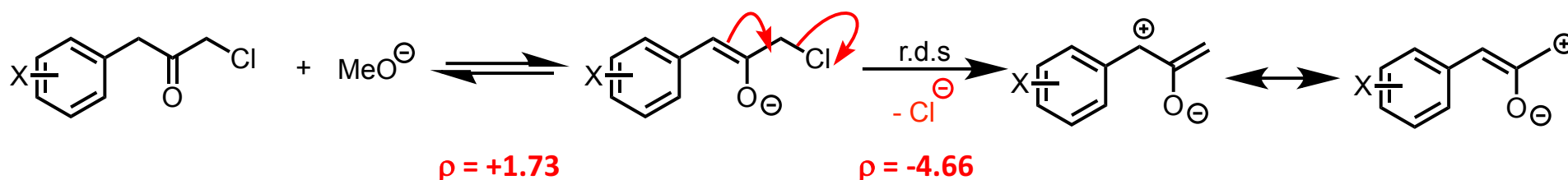
- proposed mechanisms which **do not** fit the data

- 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


$$\rho = +2.61$$
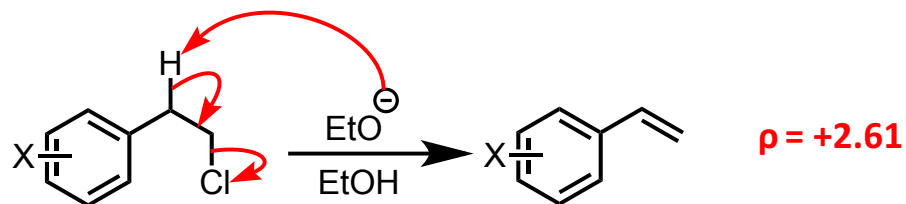
- the concerted 1,3-elimination should have a simliar **ρ** value but as **ρ = –2.93** for the Favorskii rearrangement this allows the concerted mechanism to be discounted in this system

■ 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
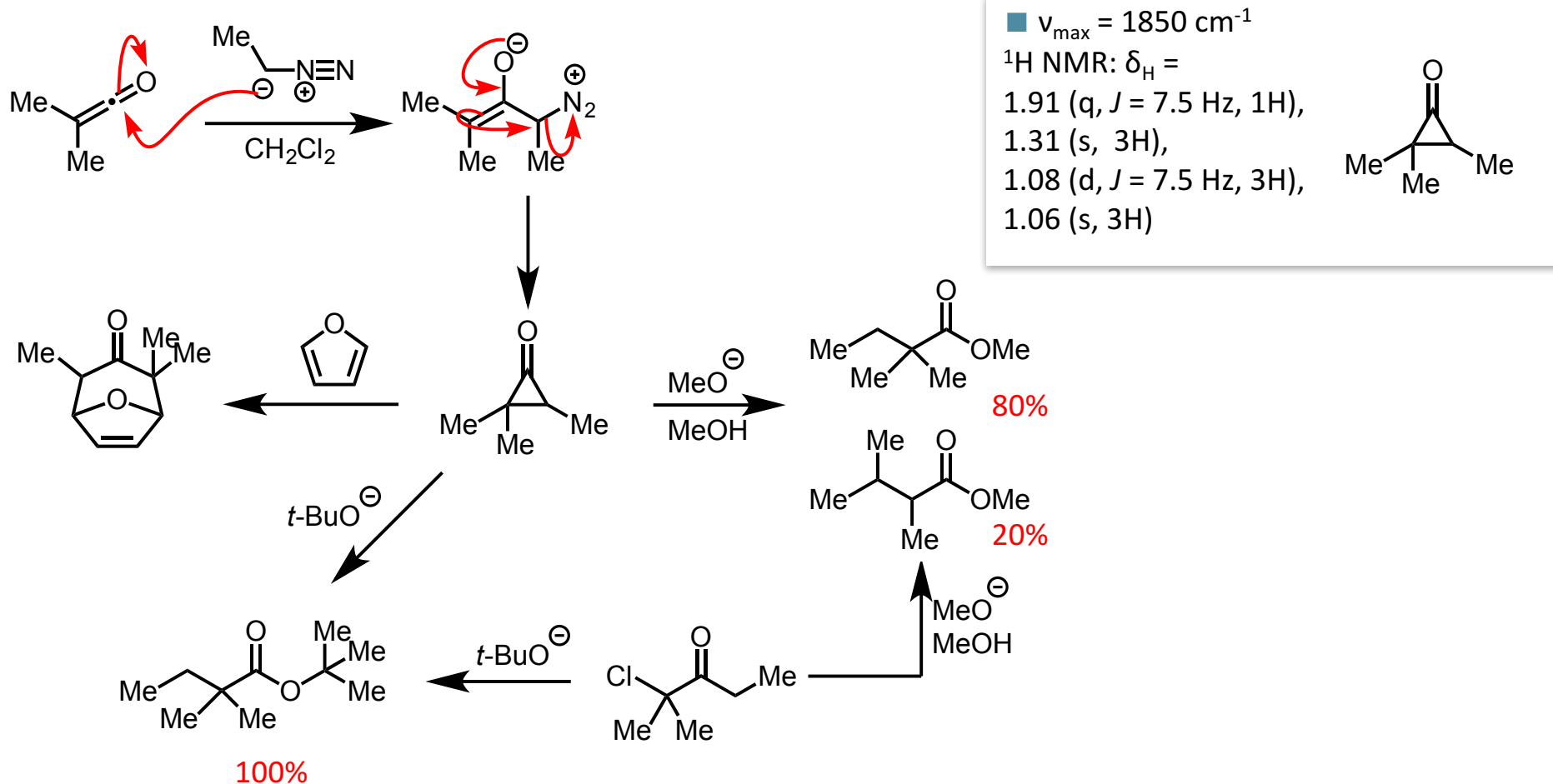

Bn = CH$_2$Ph
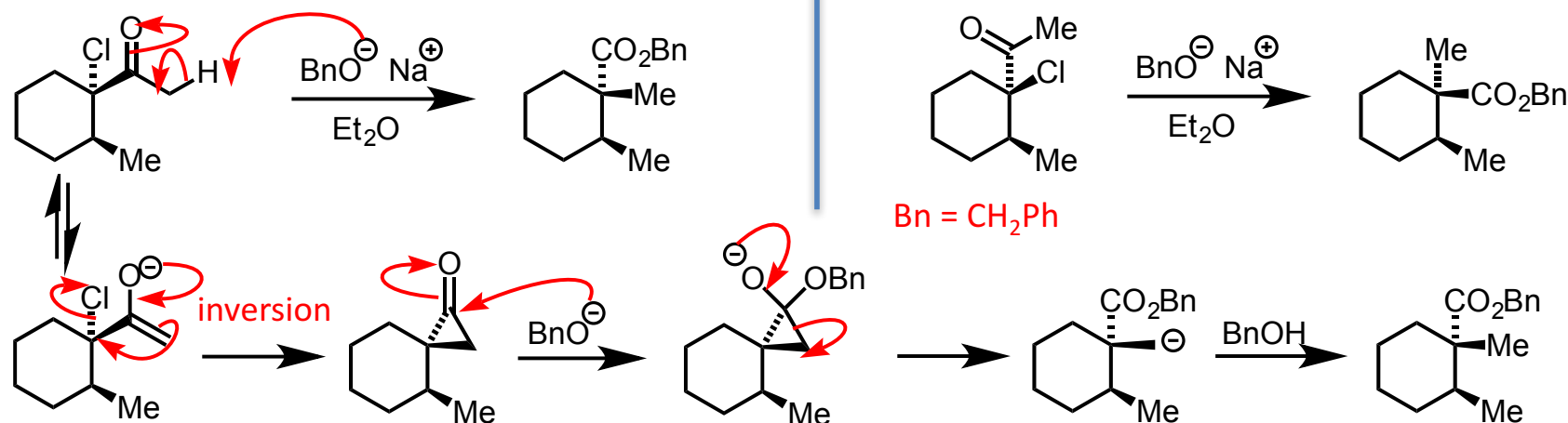
■ in more polar, alcoholic solvent, reaction is no-longer stereospecific


40%   50%
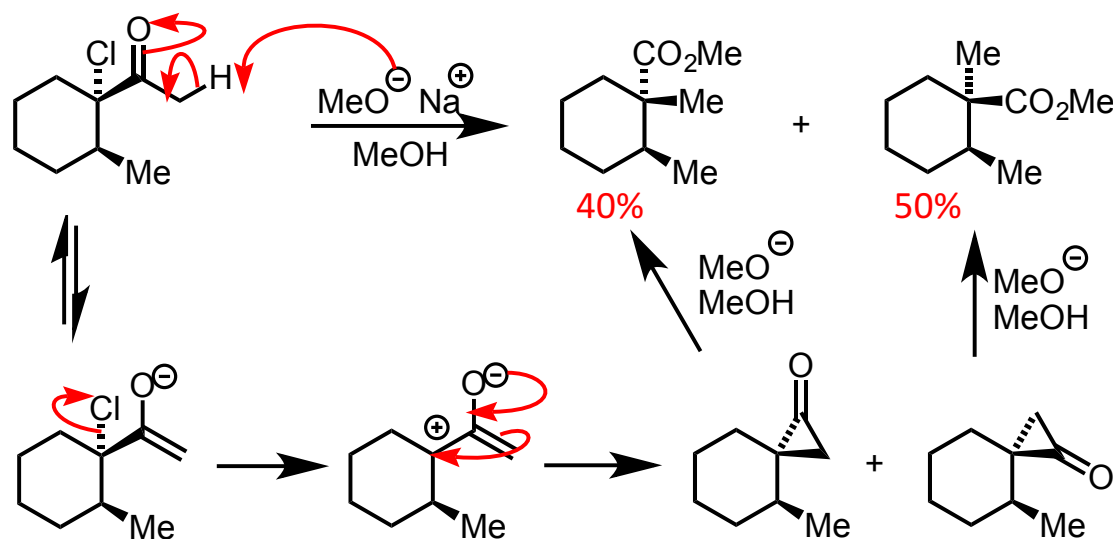
■ use of a non-hydroxylic solvent restores the stereospecificity

95%   trace
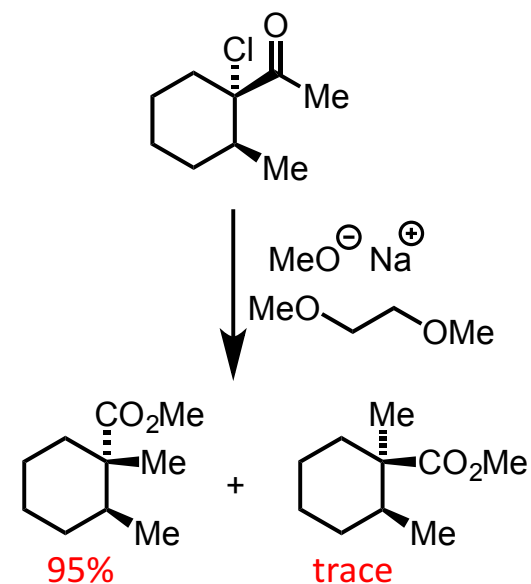
■ further evidence – cyclopropanones can be isolated and they give the same distribution of products as the Favorskii rearrangement of α-haloketones under the same reaction conditions

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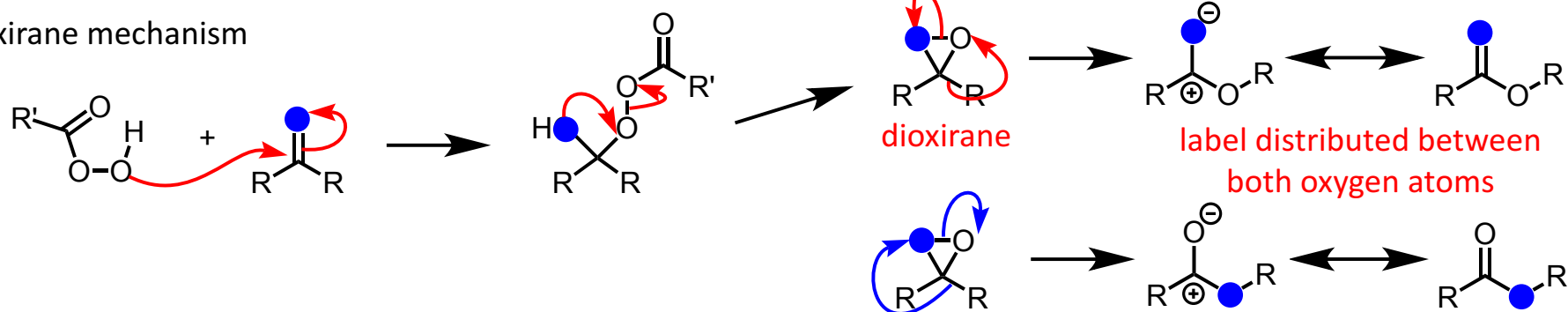1.08 (d, J = 7.5 Hz, 3H),
1.06 (s, 3H)

■ cyclopropanones can also be isolated under Favorskii rearrangement conditions
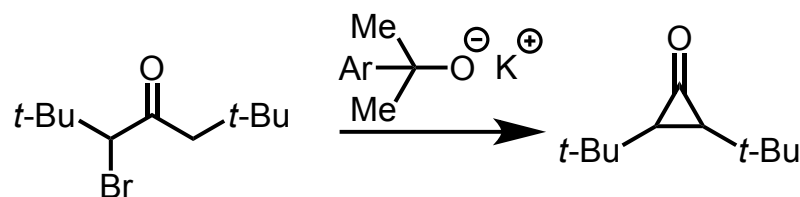
- Baeyer-Villiger oxidation - the group which best supports a positive charge migrates
- accepted mechanism (Criegee mechanism)

label in carbonyl oxygen
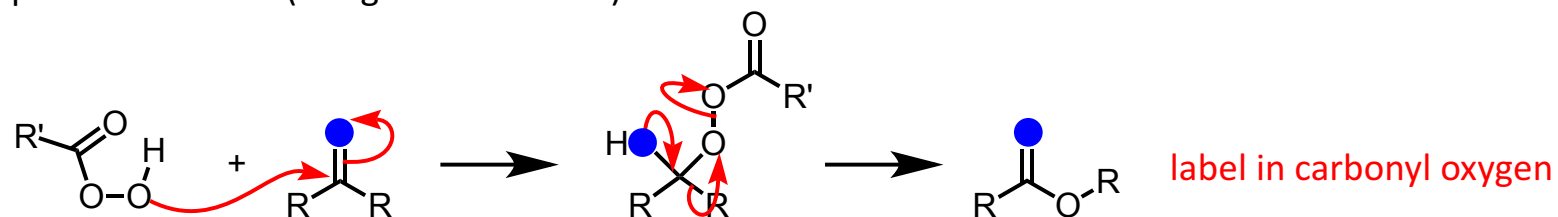
- some other reasonable mechanisms were originally proposed
- dioxirane mechanism

dioxirane

label distributed between both oxygen atoms
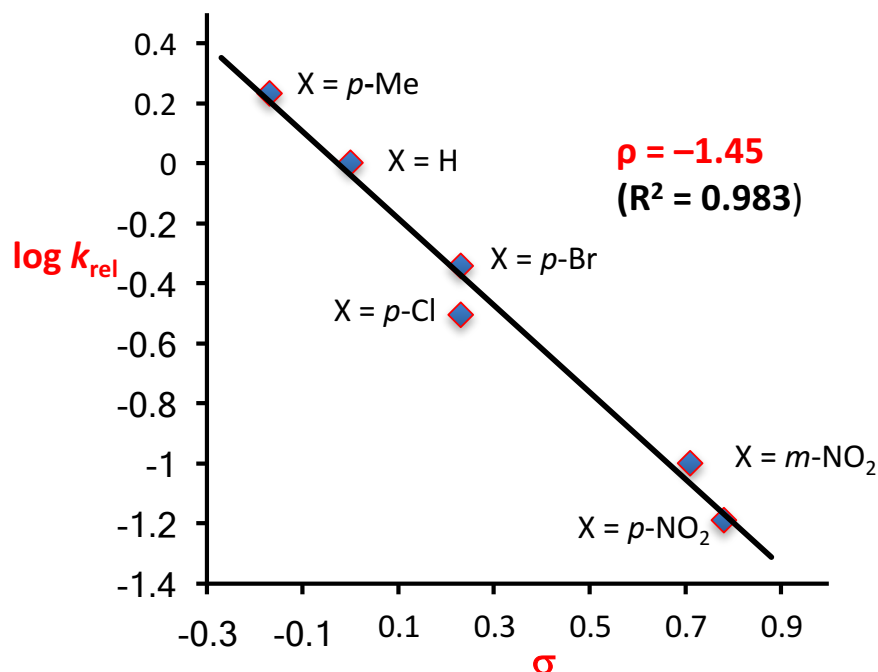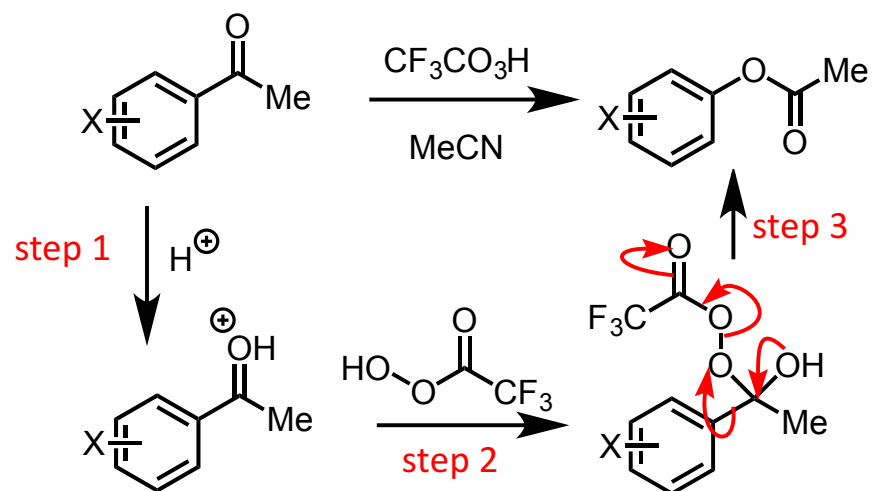
- peroxide mechanism

peroxide

label in non-carbonyl oxygen
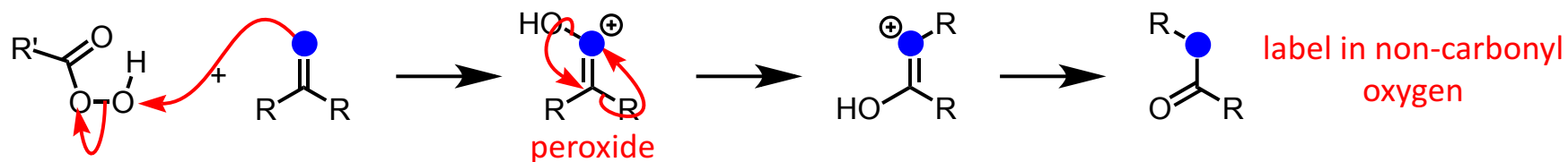
- isotope labeling studies are only consistent with the Criegee mechanism ($\bullet$ = ^{18}O)
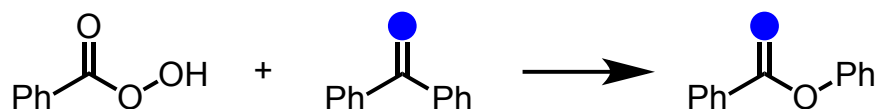
■ Baeyer-Villiger oxidation – nature of the rate determining step

■ 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$_3$O	0.998
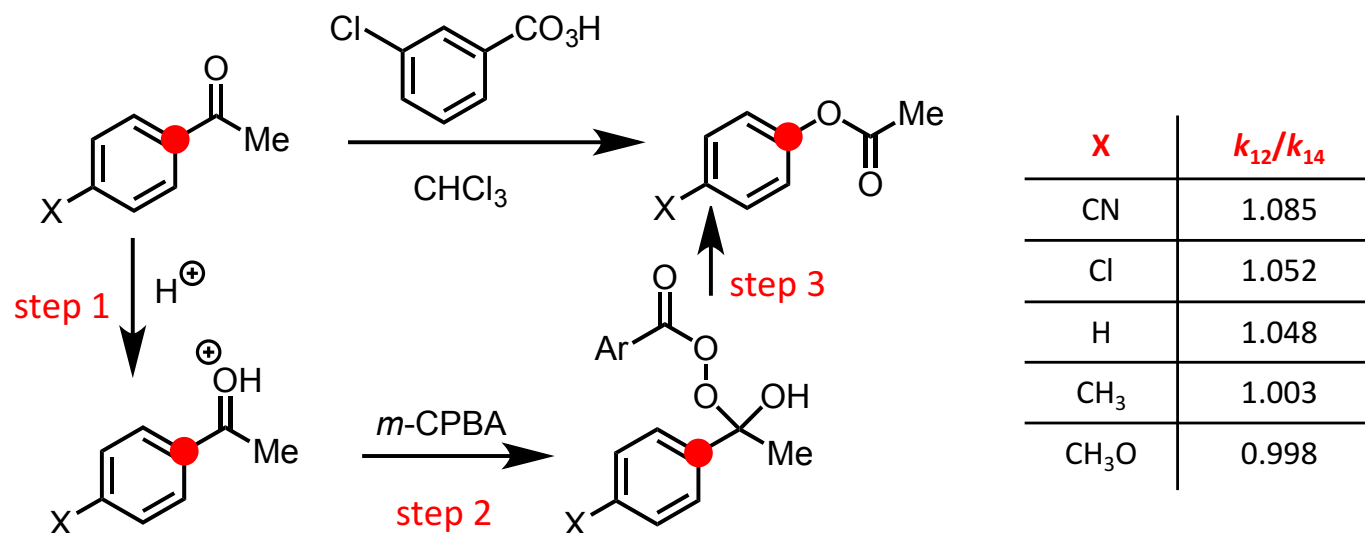
■ kinetic isotope effect demonstrates that rate determining step is **step 3** for all the substituents except **X = OCH$_3$** i.e. there is significant alteration in the bonding to the labelled carbon in the rate determining step giving rise to the observed kinetic isotope effect

■ 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