CHEM95002:
Orbitals in Organic Chemistry - Stereoelectronics

LECTURE 4 *Neighbouring Group Participation (NGP), Rearrangements & Fragmentations*

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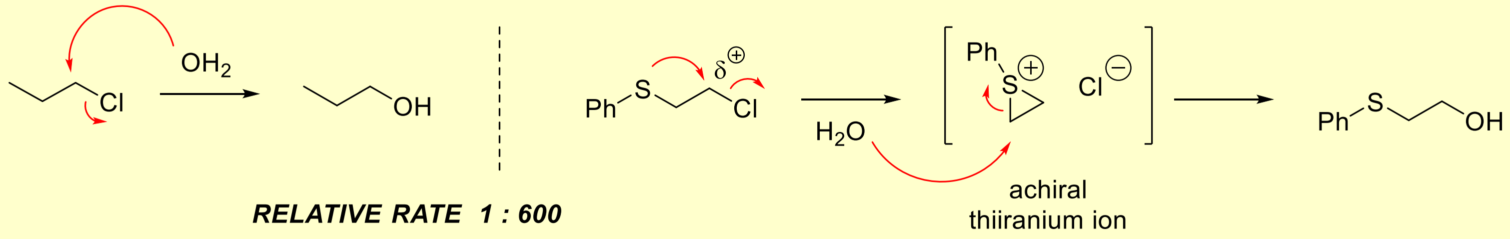
Format & scope of lecture 4

- ***N*eighbouring *G*roup *P*articipation (NGP)**
- ***Non-classical carbocations***
- ***1,2-rearrangements/shifts/migrations***
  - Wagner-Meerwein methyl and hydride shifts
  - Pinacol & semi-pinacol
  - Baeyer-Villiger reaction
  - Beckmann rearrangement
- ***Fragmentations***
  - Grob
  - Eschenmoser ring expansion

Neighboring group participation (NGP)

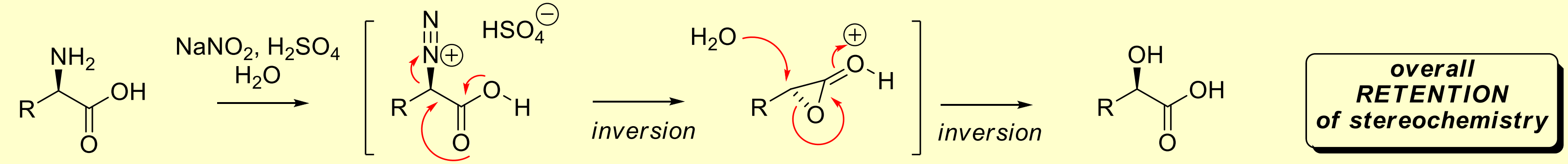
- *Groups remote from a reaction centre can participate in substitution reactions –* ***Neighboring Group Participation*** *(NGP) (or* ***anchimeric assistance****):*
  - *lone pairs of electrons, typically on N, O, S or Hal atoms interact with* **electron deficient/cationic centres**
  - *NGP is characterised by:*
    - *rate acceleration*



RELATIVE RATE 1 : 600

achiral
thiiranium ion

-
    - *retention of stereochemistry (via double inversion):*



α-amino acid

α-lactone

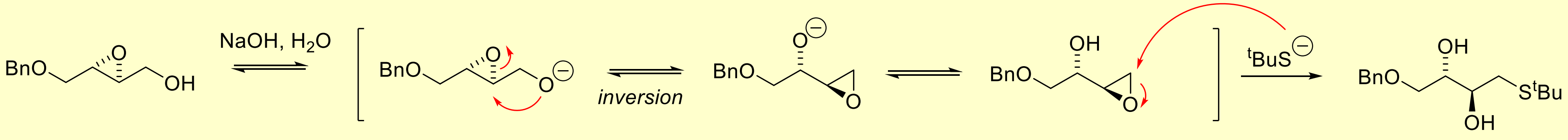
α-hydroxy acid

overall RETENTION of stereochemistry

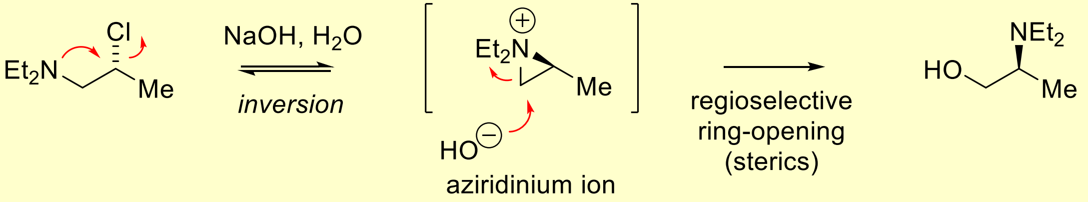
  - ***Rearrangements*** *occur when the participating group ends up bonded to a different atom...*

NGP with rearrangement

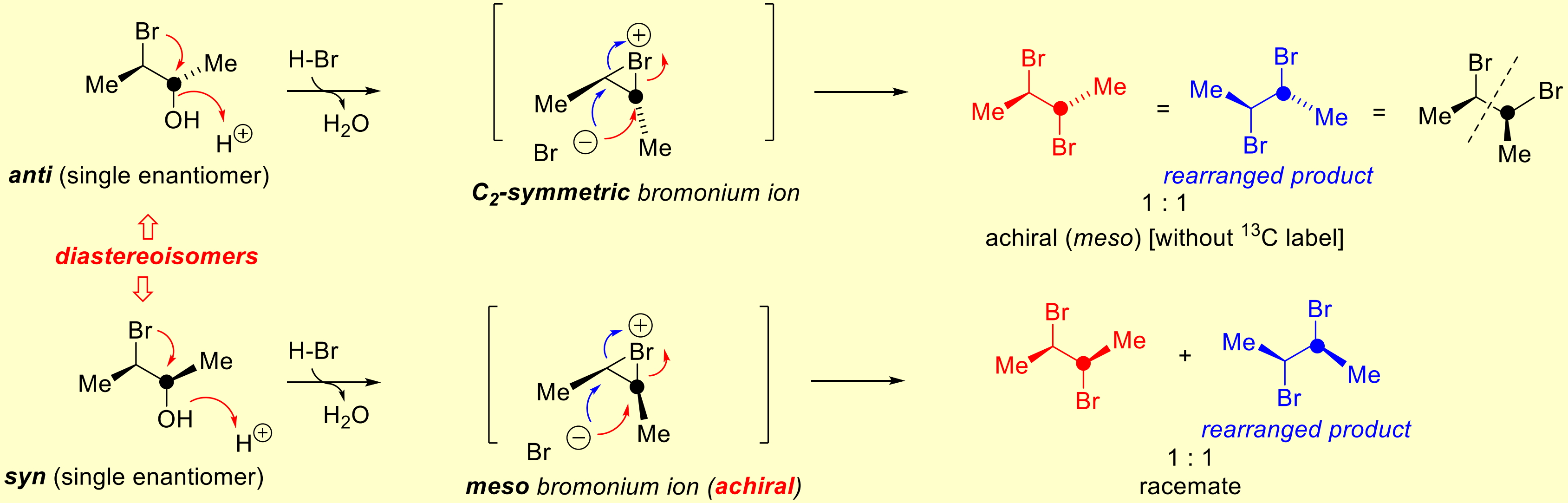
- ***Payne** rearrangements:*



- ***aza-Payne** rearrangements:*



- ***Bromonium ion** rearrangements:*



anti (single enantiomer)

***C_2*-symmetric** *bromonium ion*

rearranged product

1 : 1

achiral (*meso*) [without ^{13}C label]

syn (single enantiomer)

meso *bromonium ion (**achiral**)*

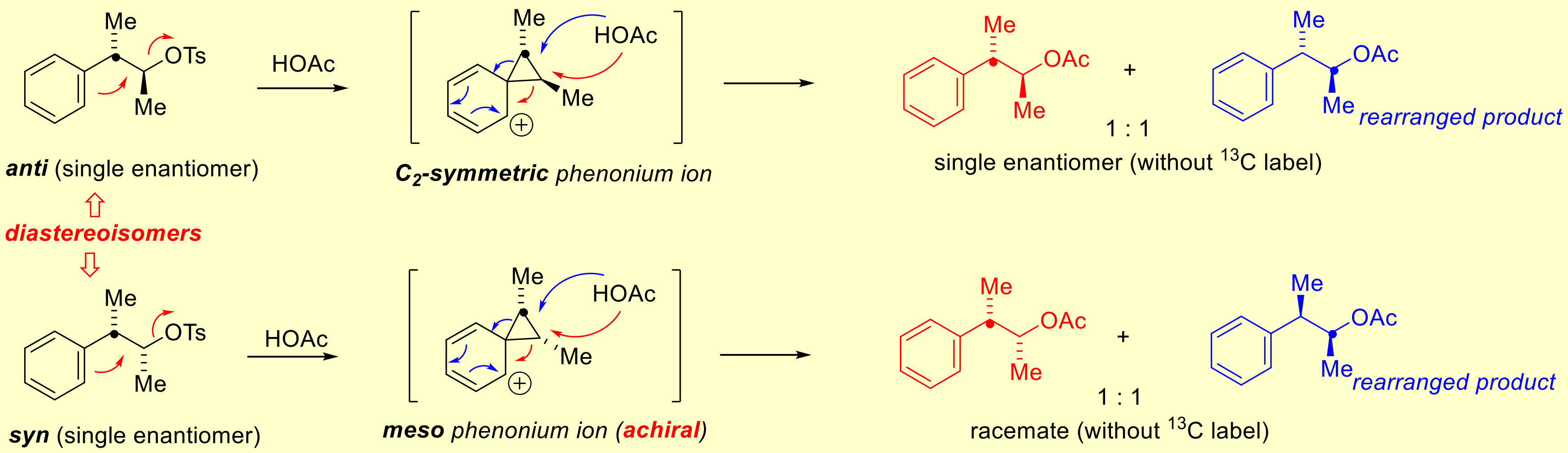
rearranged product

1 : 1

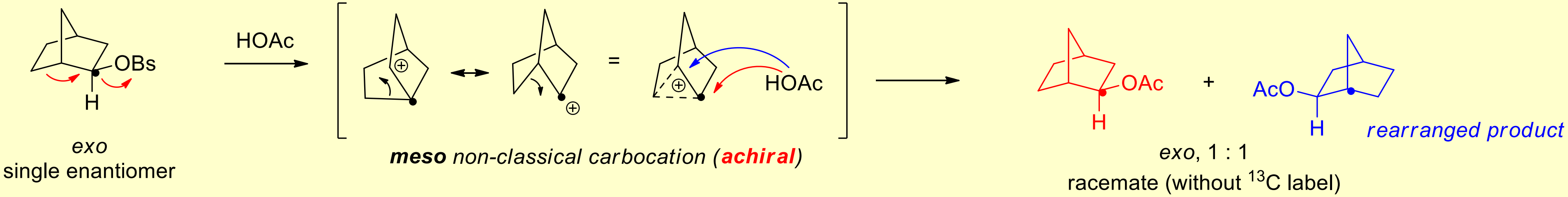
racemate

NGP with rearrangement – *involvement of π & σ bonds*

- *NGP by **aryl groups** (& **alkenes**) results in related rearrangements via **phenonium/arenium ions:***



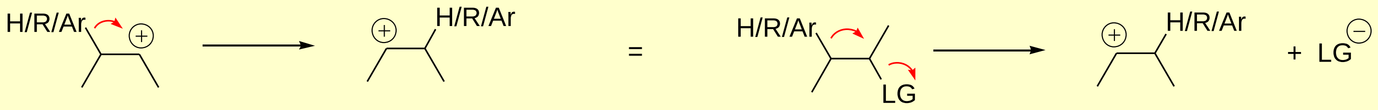
- *NGP by **alkyl groups** can also proceed via **non-classical cations:***
  - Crystal structure of this carbocation finally obtained in 2013! See: Scholz *Science*, **2013**, *341*, 62 [**DOI**]



- *The rearranged products of the above "NGP" processes can also be regarded as having undergone **rearrangements/shifts/migrations...***

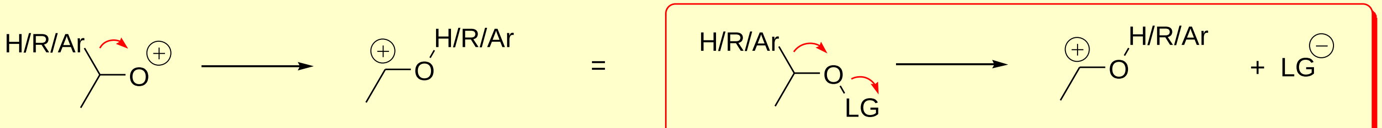
1,2-Rearrangements/Shifts/Migrations

- ***1,2-Rearrangements/shifts/migrations*** *take place when an* ***electron deficient/cationic centre*** *is formed adjacent to a group capable of migration using a lone or bonding pair of electrons*
  - *Participation of bonding electrons of aryl, alkyl and hydride groups are of particular importance:*
  - ***1,2-Aryl-, alkyl-*** *&* ***hydride shifts*** *towards* ***carbenium ions/electron deficient carbon:***



a range of mechanistic cases from true carbenium ion-mediated to fully concerted rearrangements

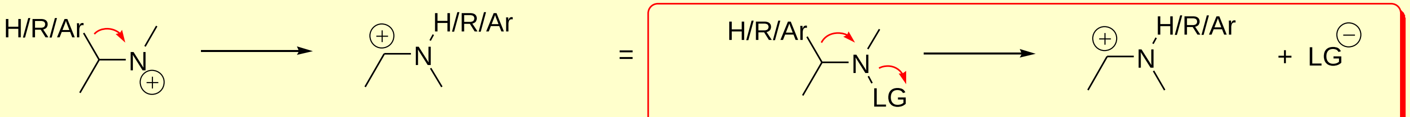
  - ***1,2-Aryl-, alkyl-*** *&* ***hydride shifts*** *towards* ***electron deficient oxygen:***



oxenium ion
too high in energy to exist

group exhibiting
oxenium ion character

  - ***1,2-Aryl-, alkyl-*** *&* ***hydride shifts*** *towards* ***electron deficient nitrogen:***

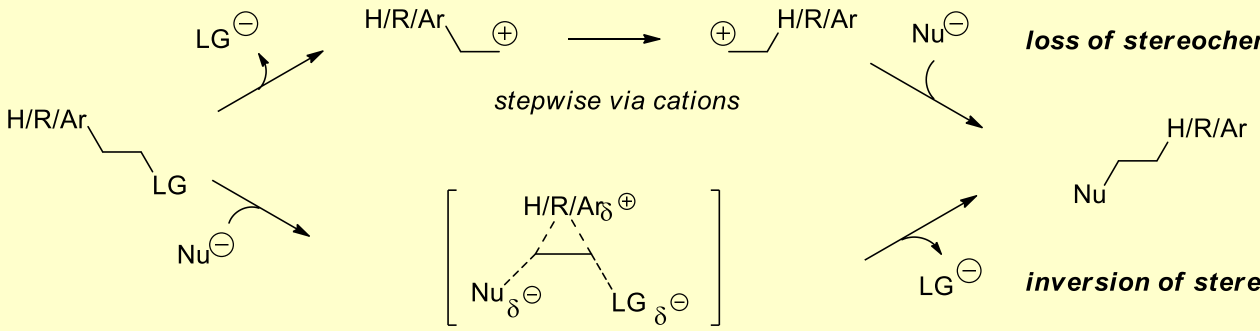


nitrenium ion
too high in energy to exist

group exhibiting
nitrenium ion character

Mechanistic variations

- *The overall mechanisms of 1,2-migrations vary from **stepwise** to **concerted** (cf. $S_N1 \leftrightarrow S_N2$) wrt the adjacent centres from and to which the migrating group moves:*



stepwise via cations

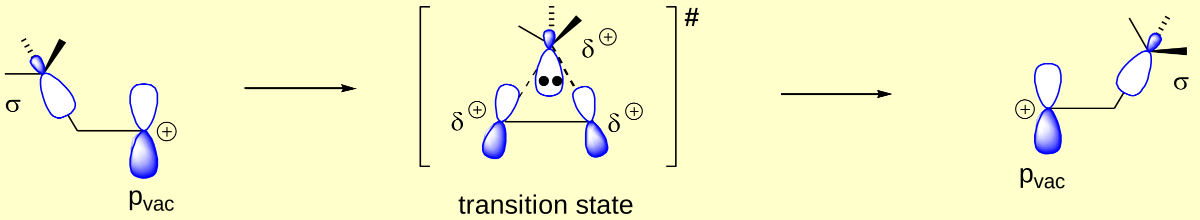
loss of stereochemical integrity at cationic centres

inversion of stereochemistry at migration origin and/or terminus

non-classical ion intermediate
or
transition state

'onium ions' are usually *intermediates* for heteroatom migrations & Ar
but usually *transition states* for R & H

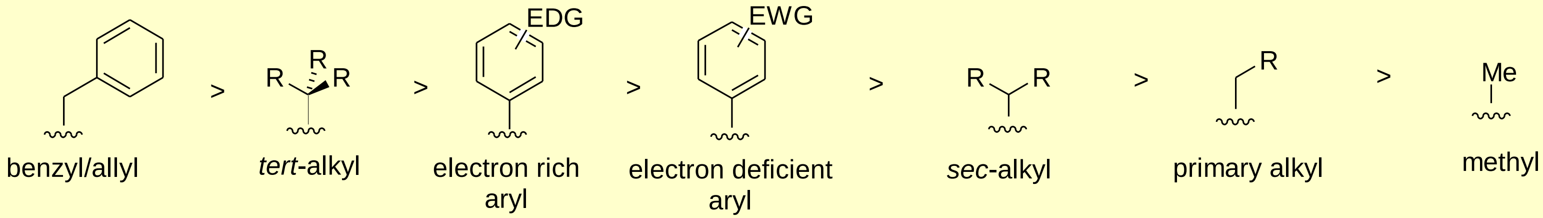
- *The **migrating centre** however **always retains* its configuration** during the actual migration step*
  - This process is necessarily concerted and can be considered a [1,2]-sigmatropic shift (see Pericyclic lectures)
  - The migrating centre retains an octet of electrons, e.g. consider the case of a 1,2-alkyl shift:



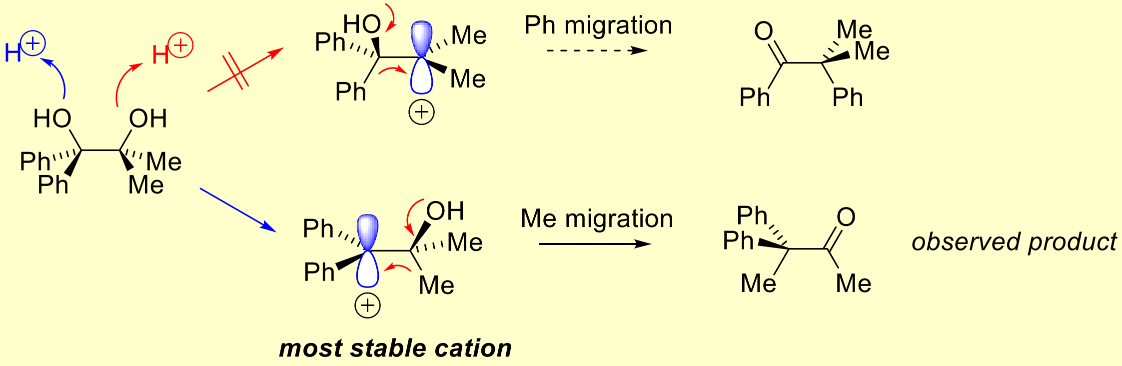
  - **Inversion* of configuration at the migrating centre is possible for [1,3]- and higher sigmatropic rearrangements, but loss of stereochemical integrity at this centre is never observed (see Pericyclic lectures).

Migratory Aptitudes

- *The ease with which carbon-based groups migrate* ***vary according to the particular reaction*** *& the* ***conditions***
- *However, an approximate ranking is possible:*
  - Data has been accrued from relative rate data and from competition experiments on various rearrangements
  - In general, the group best able to stabilise positive charge (in the transition state/intermediate) migrates:



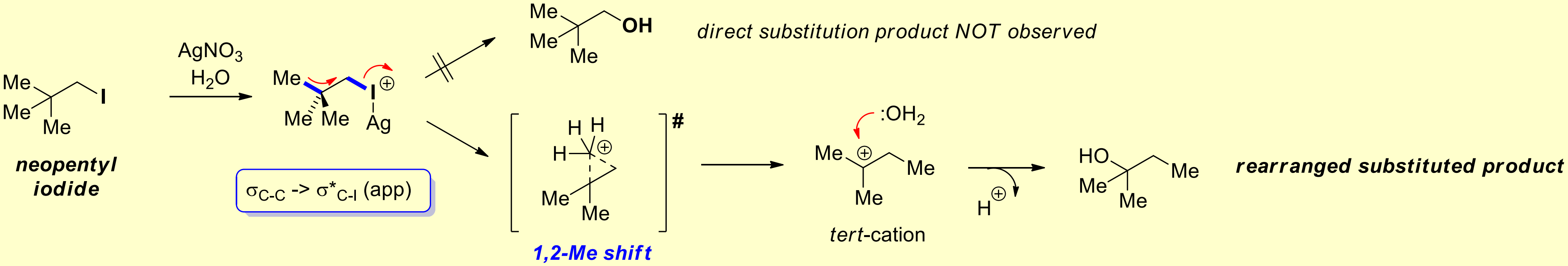
  - The position of ***HYDRIDE*** in this series is highly unpredictable – often migrates very readily!
  - Care is required in interpreting results as other factors may dominate:
    - *e.g.* a pinacol rearrangement where cation stability is the determining factor:



  - However, ***CORRECT ORBITAL OVERLAP IS CRUCIAL*** in the transition state and so (by Hammond's postulate) the orbital alignment in the substrate must be appropriate for migration...

1,2-Shifts to C^+ - *Wagner-Meerwein rearrangements*

- ***1,2-Rearrangements/shifts/migrations** of **hydride** & **alkyl groups** towards **carbenium ions** are referred to as **Wagner-Meerwein shifts** (a **Me group 1,2-shift** is specifically known as a **Nametkin rearrangement**)*
  - *e.g. rearrangement during substitution at a neopentyl centre:*



neopentyl iodide

$\sigma_{C\text{-}C}$ -> $\sigma^*_{C\text{-}I}$ (app)

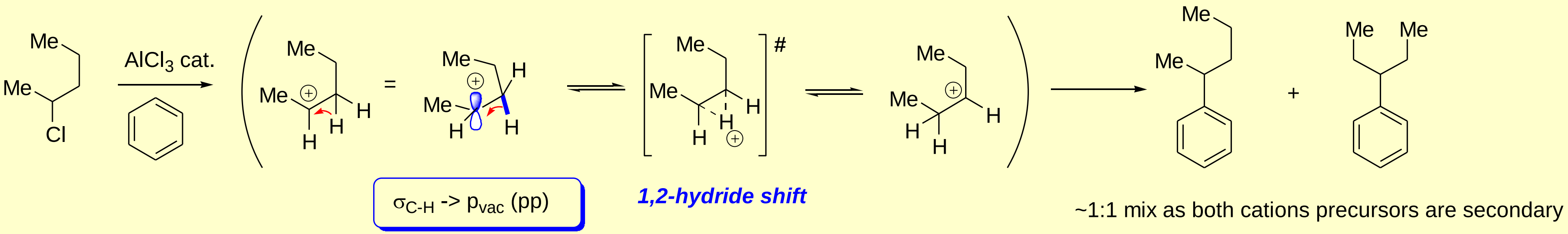
direct substitution product NOT observed

1,2-Me shift

tert-cation

rearranged substituted product

  - *e.g. rearrangement during Friedel-Crafts alkylation:*



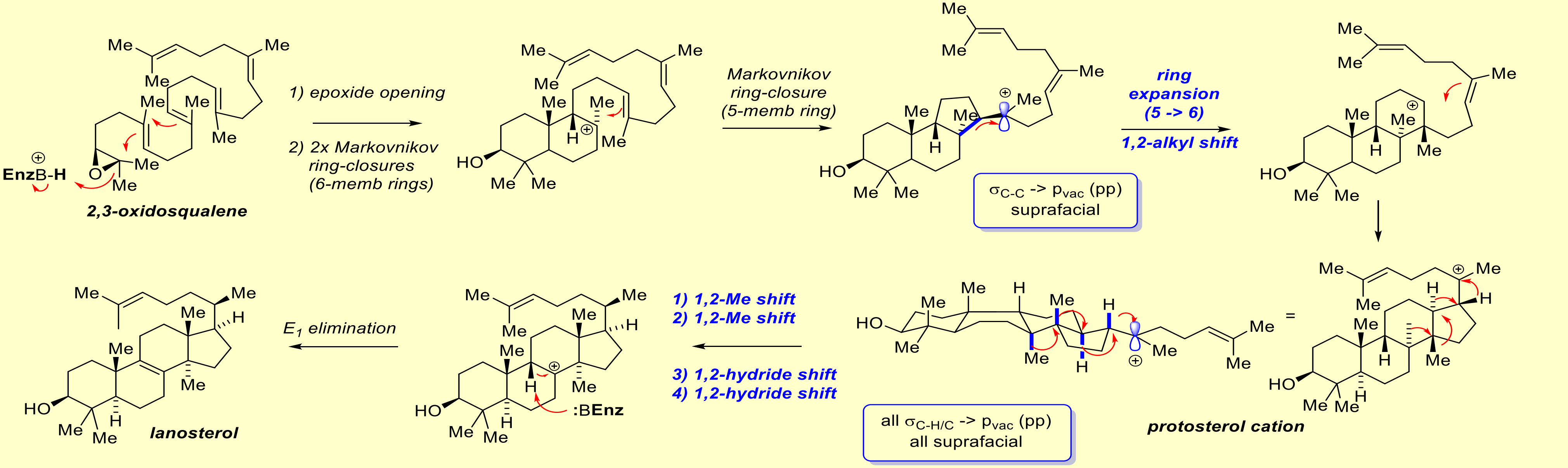
$\sigma_{C\text{-}H}$ -> p_{vac} (pp)

1,2-hydride shift

~1:1 mix as both cations precursors are secondary

Wagner-Meerwein rearrangements - *biosynthesis*

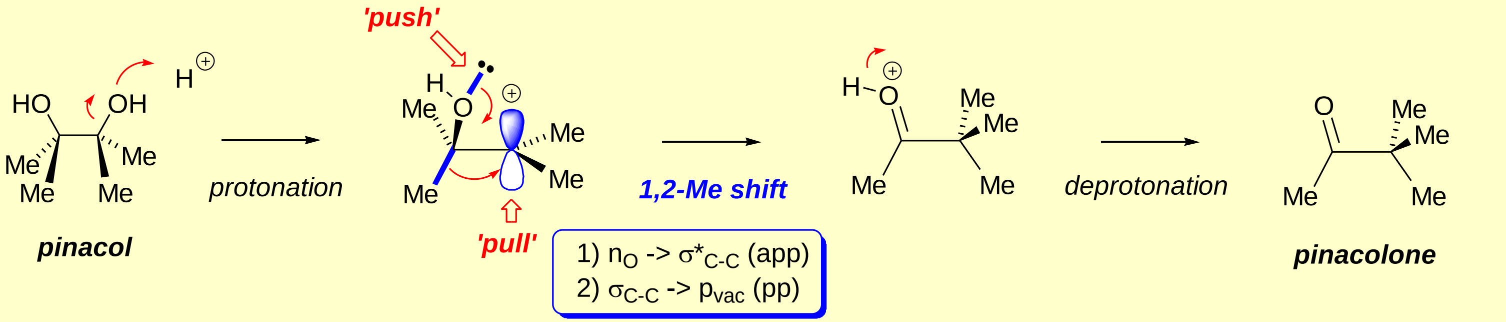
- ***Wagner-Meerwein rearrangements** are prevalent in the **biosyntheis of terpenoids such as lanosterol** (precursor to **cholesterol** & the human sex hormones)*
  - ***lanosterol*** is formed by the polycyclisation of 2,3-oxidosqualene by the enzyme ***OxidoSqualene Cyclase*** *(OSC)*
  - the ***conformation*** enforced by the enzyme is ***~ chair-boat-chair***, the process is ***NOT concerted***, discrete ***cationic intermediates*** are involved ***& stereoelectronics dictate*** the ***regio- & stereoselectivity***



  - *"The enzyme's role is most likely to shield intermediate carbocations… thereby allowing the hydride and methyl group migrations to proceed down a thermodynamically favorable and kinetically facile cascade"*
    - Wendt *Angew. Chem. Int. Ed.* **2000**, *39*, 2812 [DOI]

1,2-Shifts to C$^+$ – *pinacol rearrangements*

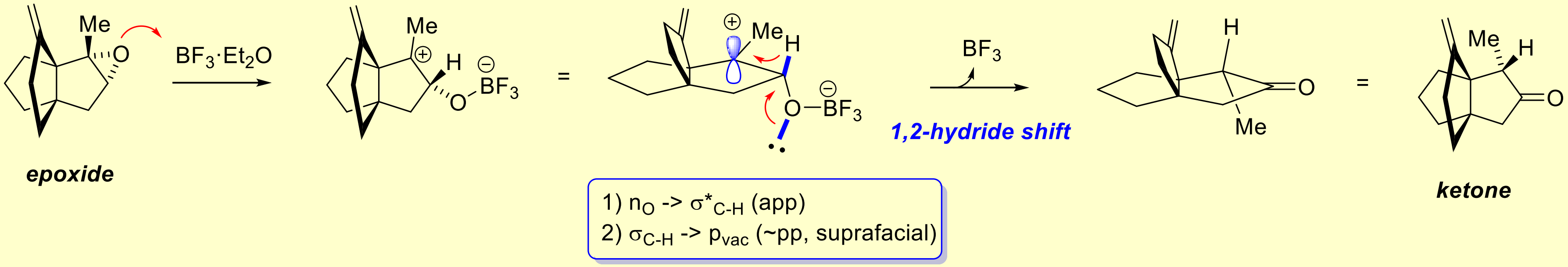
- *Treatment of the 1,2-diol '**pinacol**' with acid results in a 1,2-rearrangement to give a ketone '**pinacolone**':*
  - Review: Song *et al. Chem. Rev*. **2011**, *111*, 7523 [DOI]



1) n_{O} -> $\sigma^{*}_{C\text{-}C}$ (app)
2) $\sigma_{C\text{-}C}$ -> p_{vac} (pp)

  - *the 'push' of the lone pair and the 'pull' of the carbenium ion provide a low energy kinetic pathway*
  - *the exothermicity of C=O bond formation provides a thermodynamic driving force*

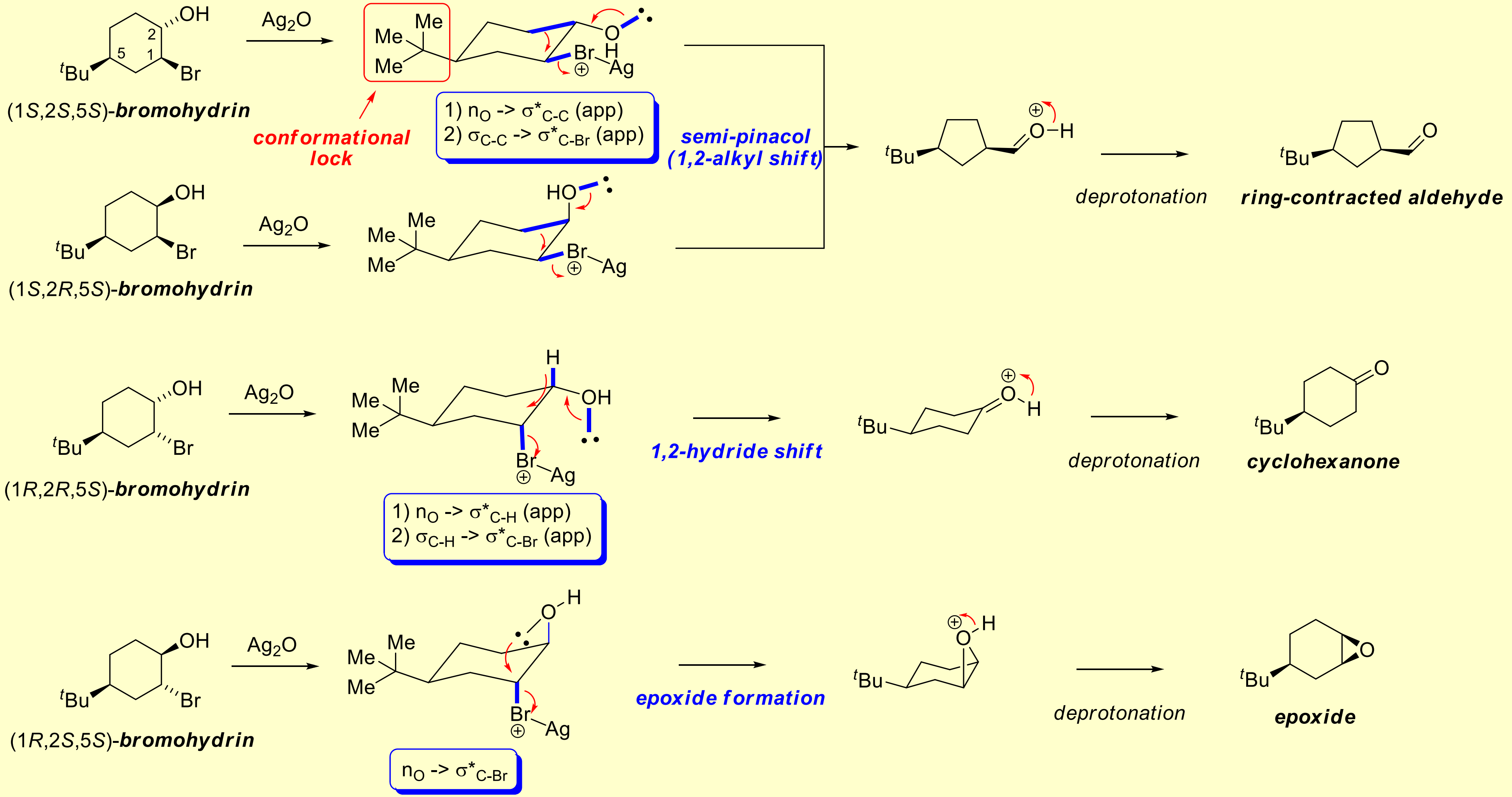
- *More generally, any functionality giving rise to a carbenium ion adjacent to an oxygenated carbon can undergo a **semi-pinacol rearrangement**...*
  - Treatment of epoxides with Lewis acids results in semi-pinacol rearrangements:



1) n_{O} -> $\sigma^{*}_{C\text{-}H}$ (app)
2) $\sigma_{C\text{-}H}$ -> p_{vac} (~pp, suprafacial)

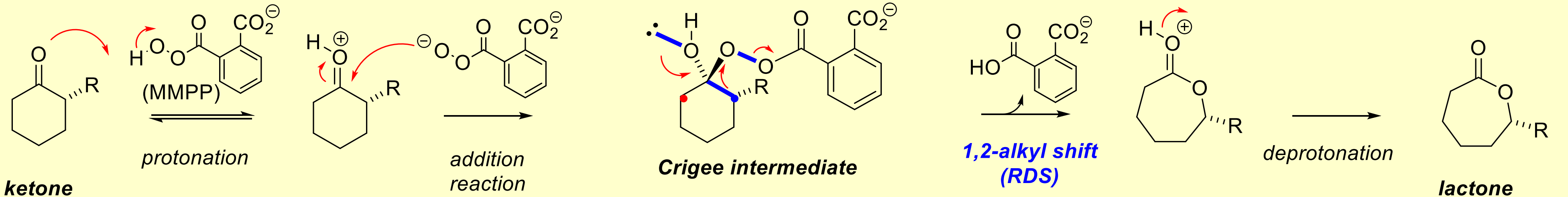
Semi-pinacol rearrangement - *stereochemistry*

- *The importance of **correct orbital alignment** for 1,2-shifts is illustrated by subjecting all four isomers of the following bromohydrin to identical conditions:*



1,2-Shifts to O$^+$ – *Baeyer-Villiger reaction*

- *Treatment of **ketones** & **aldehydes** with **peracids** induces a **Baeyer-Villiger reaction:***

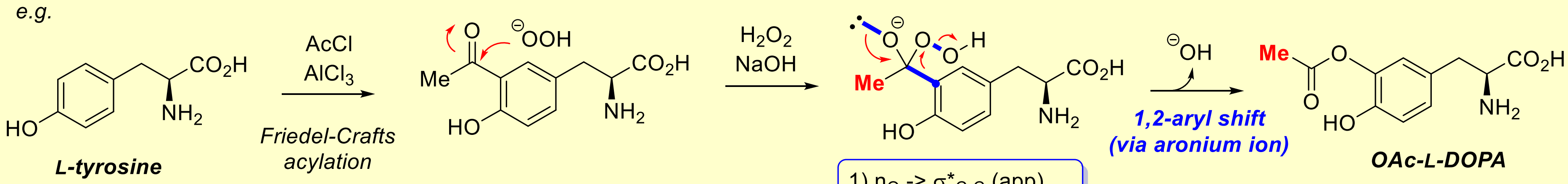


1) $n_O \rightarrow \sigma^*_{C\text{-}C}$ (app)
2) $\sigma_{C\text{-}C} \rightarrow \sigma^*_{O\text{-}O}$ (app)

blue centre migrates not ***red*** one because it can better accomodate positive charge: 2° *vs.* 1°

  - *use of **basic hydrogen peroxide** on an electron rich **aryl ketone/aldehyde** is called the **Dakin reaction***

e.g.



1) $n_O \rightarrow \sigma^*_{C\text{-}C}$ (app)
2) $\sigma_{C\text{-}C} \rightarrow \sigma^*_{O\text{-}O}$ (app)

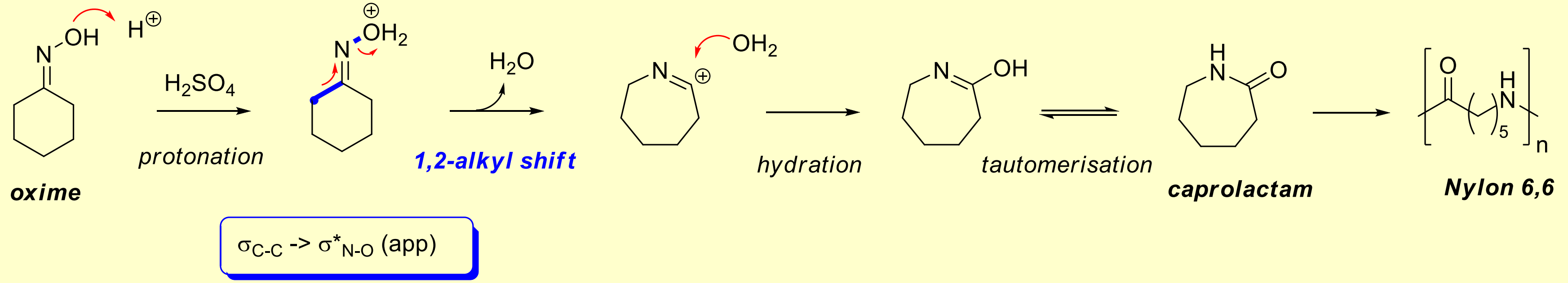
  - the driving force is the exothermicity of cleavage of a weak O-O bond and formation of a C=O bond
  - order of migration generally follows migratory aptitude series presented earlier:

oxidation occurs at indicated position
i.e. ***blue*** group migrates

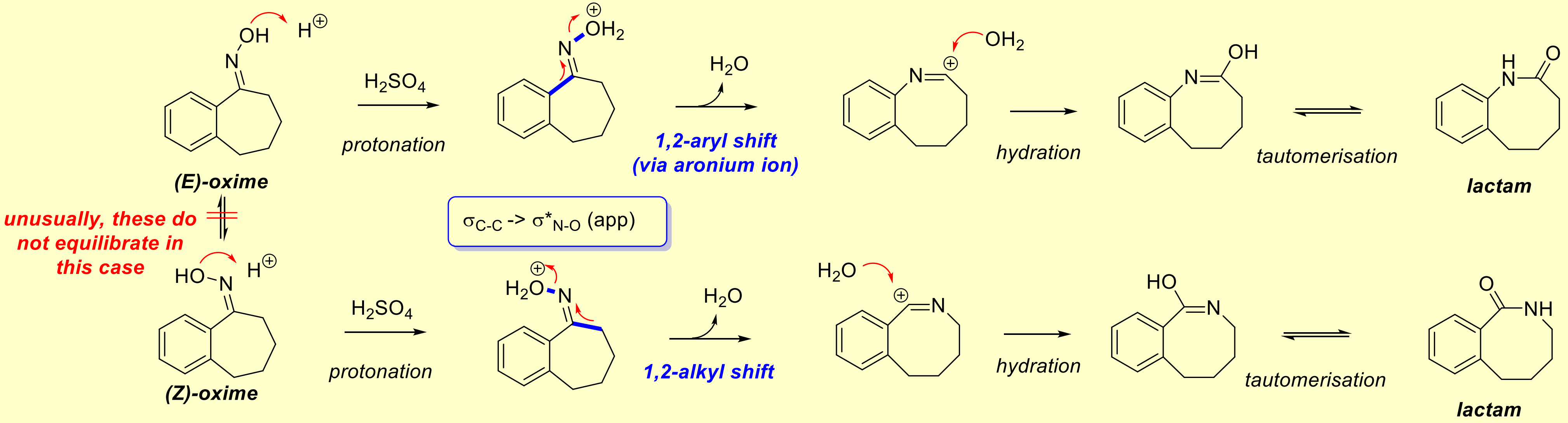
1,2-Shifts to N$^+$ – *Beckmann rearrangement*

- ***Hydride**, **alkyl** & **aryl groups** also migrate towards **electron deficient nitrogen centres***
  - ***NB. nitrenium ions** themselves are too high in energy to exist (cf. **carbenium ions**)*

- ***Oximes** undergo useful **1,2-rearrangements** in **acidic media** – the **Beckmann rearrangement:***



- *the group **app** to the N-O bond migrates irrespective of migratory aptitude BUT **beware oxime E/Z isomerisation***

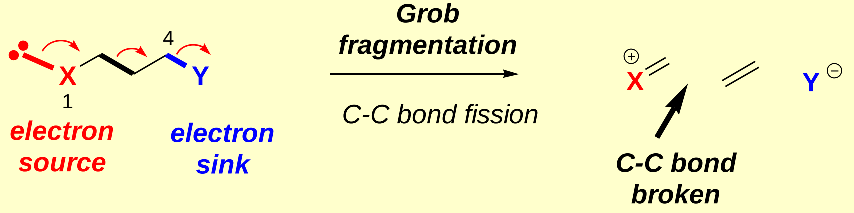


Ionic fragmentations – *characteristics*

- ***Ionic fragmentation reactions** are reactions in which a molecule breaks into 3 (or more) fragments.*
- *Typically, at least one **C-C bonds is broken** in a **heterolytic fashion***
- *They are relatively rare **NOT because C-C bonds are particularly strong:***
  - ***cf.* Bond Dissociation Energies:**

C-C	339kJmol^{-1}	***weakest***
C-O	351 kJmol^{-1}	
C-H	418 kJmol^{-1}	
O-H	460 kJmol^{-1}	***strongest***

- ***BUT because C-C bonds are NOT generally highly polarised/polarisable***
- ***It follows that fragmentations occur for polarised/polarisable C-C bonds***
  - *the most common scenario involves an **electron source** at one end and an **electron sink** at the other:*



electron source

electron sink

Grob fragmentation

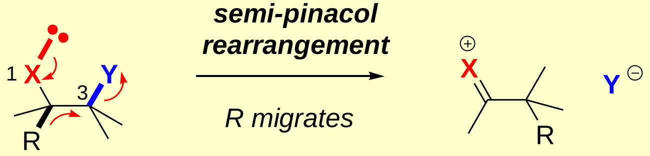
C-C bond fission

C-C bond broken

1) n_X -> σ^*_{C-C} (app)
2) σ_{C-C} -> σ^*_{C-Y} (app)

NB. the molecule breaks into three fragments

cf.



semi-pinacol rearrangement

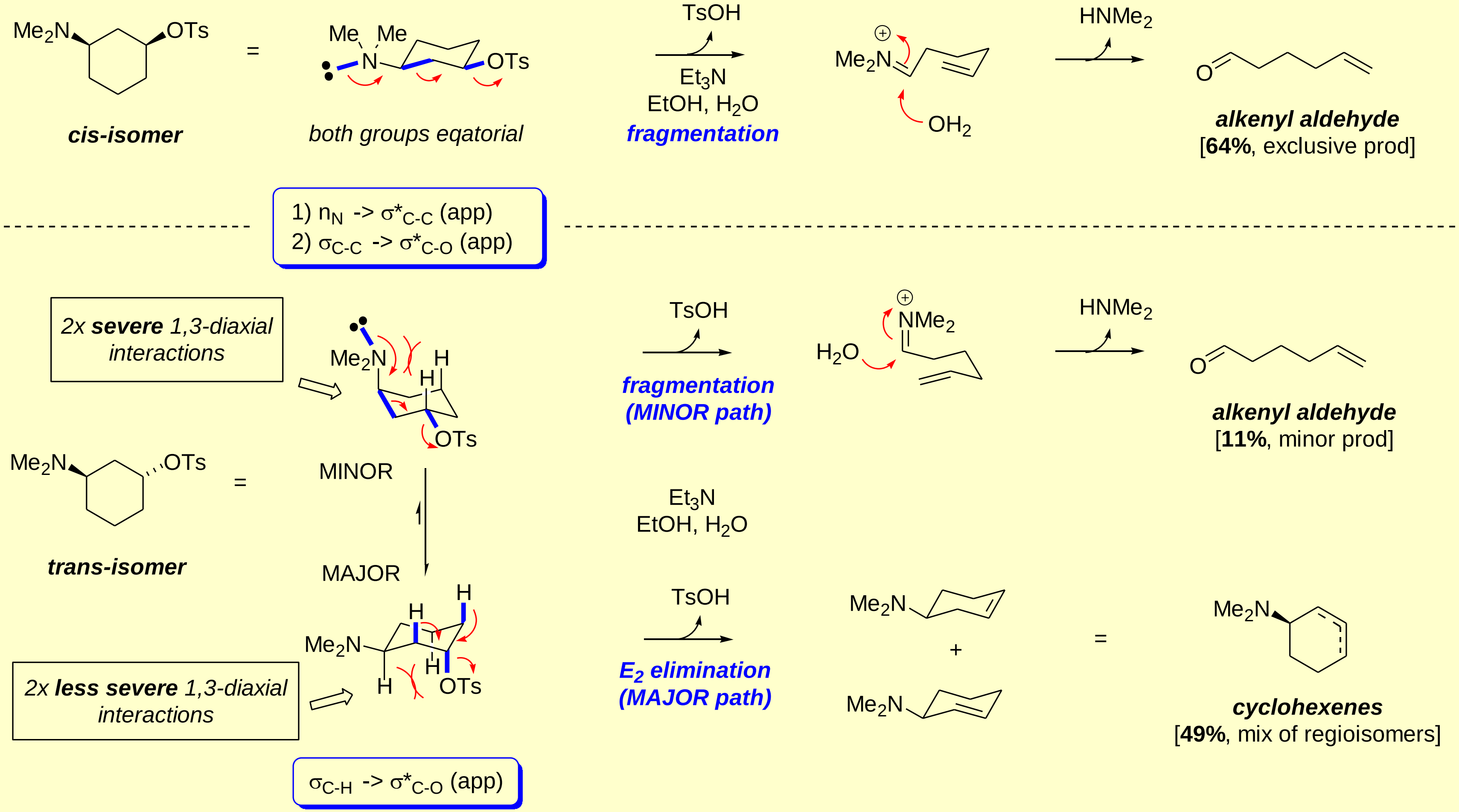
R migrates

1) n_X -> σ^*_{C-C} (app)
2) σ_{C-C} -> σ^*_{C-Y} (app)

  - *This type of fragmentation is sometimes referred to as a **Grob fragmentation** (=homologous pinacol)*
  - *As with 1,2-rearrangements **CORRECT ORBITAL OVERLAP IS CRUCIAL...***

Grob-type fragmentations

- *There are numerous variants of the* ***Grob fragmentation – in all cases correct conformation*** *&* ***stereoelectronics*** *are* ***crucial for success***
  - *Contrast the behaviour of two isomeric tosylates:*



***cis*-isomer**

both groups eqatorial

fragmentation

alkenyl aldehyde
[**64%**, exclusive prod]

1) n_N -> $\sigma^*_{C\text{-}C}$ (app)
2) $\sigma_{C\text{-}C}$ -> $\sigma^*_{C\text{-}O}$ (app)

2x ***severe*** *1,3-diaxial interactions*

fragmentation (MINOR path)

alkenyl aldehyde
[**11%**, minor prod]

***trans*-isomer**

2x ***less severe*** *1,3-diaxial interactions*

E_2 elimination (MAJOR path)

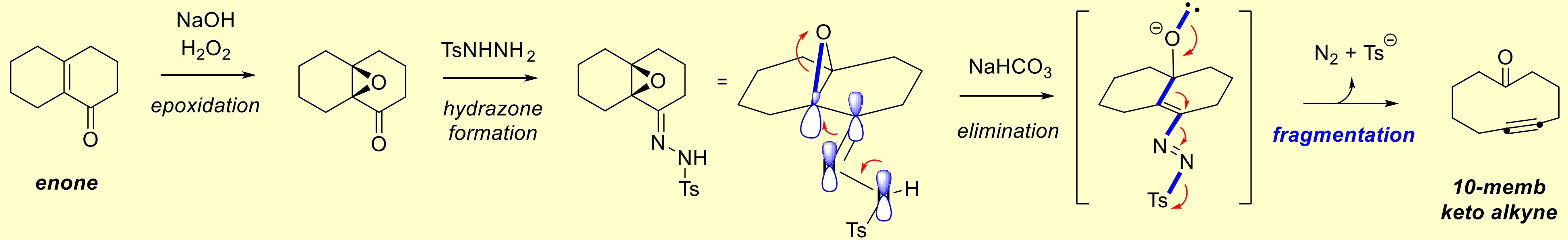
cyclohexenes
[**49%**, mix of regioisomers]

$\sigma_{C\text{-}H}$ -> $\sigma^*_{C\text{-}O}$ (app)

- *NB.* NMe_2 group is ‘bigger’ than OTs group (*i.e*. has greater A-value) so occupies equatorial position preferentially

The Eschenmoser fragmentation

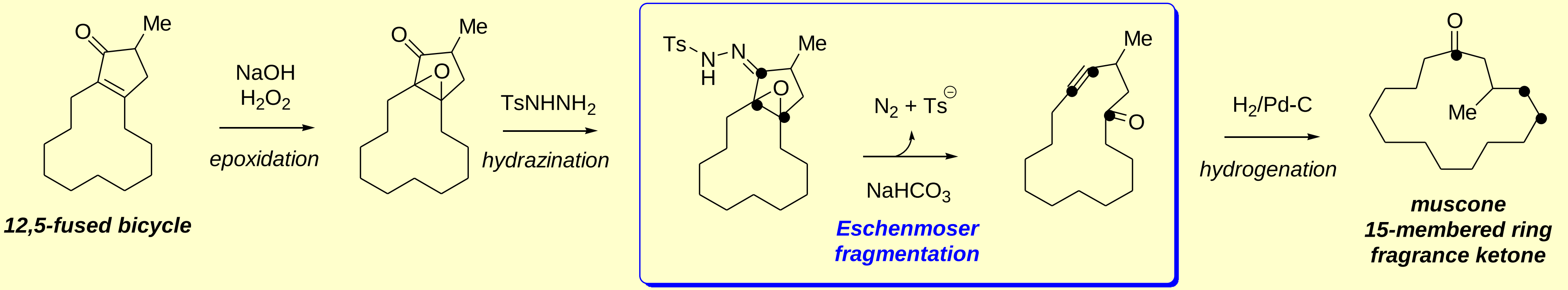
- *A particularly spectacular type of fragmentation for ring-expansion was developed in the late 1960s by the Swiss chemist Albert Eschenmoser – the **Eschenmoser fragmantation***



1) n_N -> $\pi^*_{N\text{-}C}$ (pp)
2) $\pi_{N\text{-}C}$ -> $\sigma^*_{C\text{-}O}$ (~pp)

1) n_O -> $\sigma^*_{C\text{-}C}$ (app)
2) $\sigma_{C\text{-}C}$ -> $\sigma^*_{C\text{-}N}$ (app)
3) $\sigma_{C\text{-}N}$ -> $\sigma^*_{N\text{-}S}$ (app)

  - *the driving force for the fragmentation is enthalpic (formation of toluene sulfinate) & entropic [formation of N_2 (g)]*



  - *For a minireview on fragmentation for the synthesis of medium-rings, see: Clarke Chem. Sci. **2020**, 11, 2876* [DOI]