

***CHEM60001:
An Introduction to Reaction Stereoelectronics***

***LECTURE 5 Neighbouring Group Participation,
Non-classical Carbocations
& Wagner-Meerwein 1,2-Shifts***

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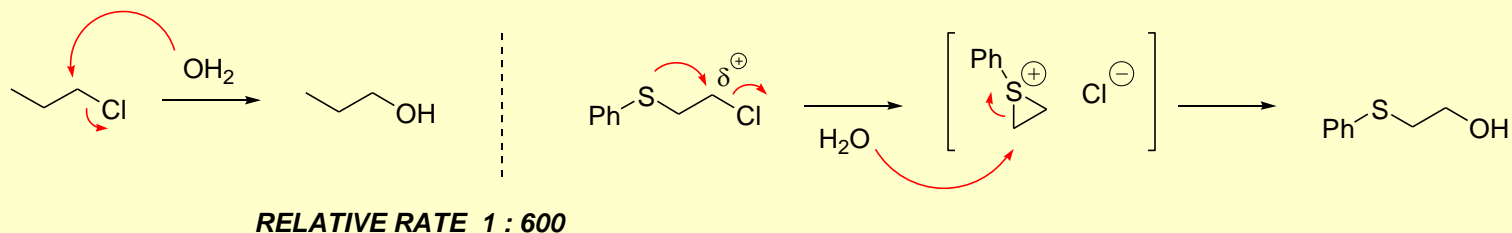
Format & scope of lecture 5

- ***Neighbouring Group Participation (NGP)***
- ***Non-classical carbocations***
- ***Ionic 1,2-rearrangements, part 1***
 - Wagner-Meerwein methyl and hydride shifts

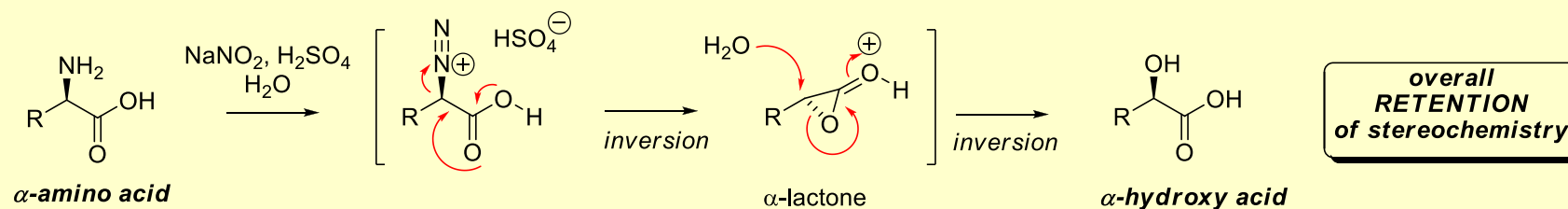
Neighboring group participation (NGP)

- 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



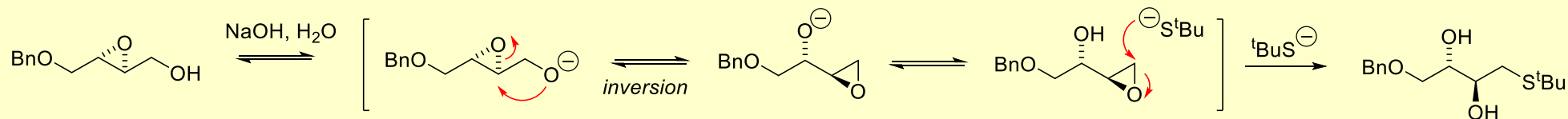
- retention of stereochemistry (via double inversion):



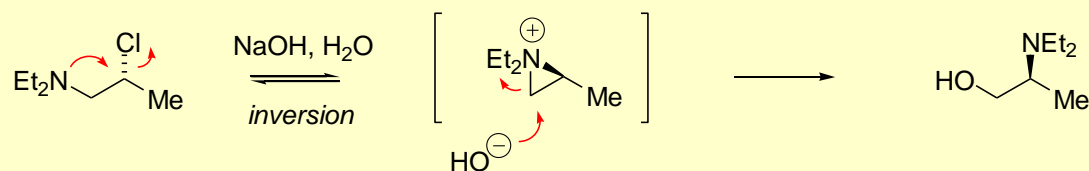
- **Rearrangements** occur when the participating group ends up bonded to a different atom...

NGP with rearrangement

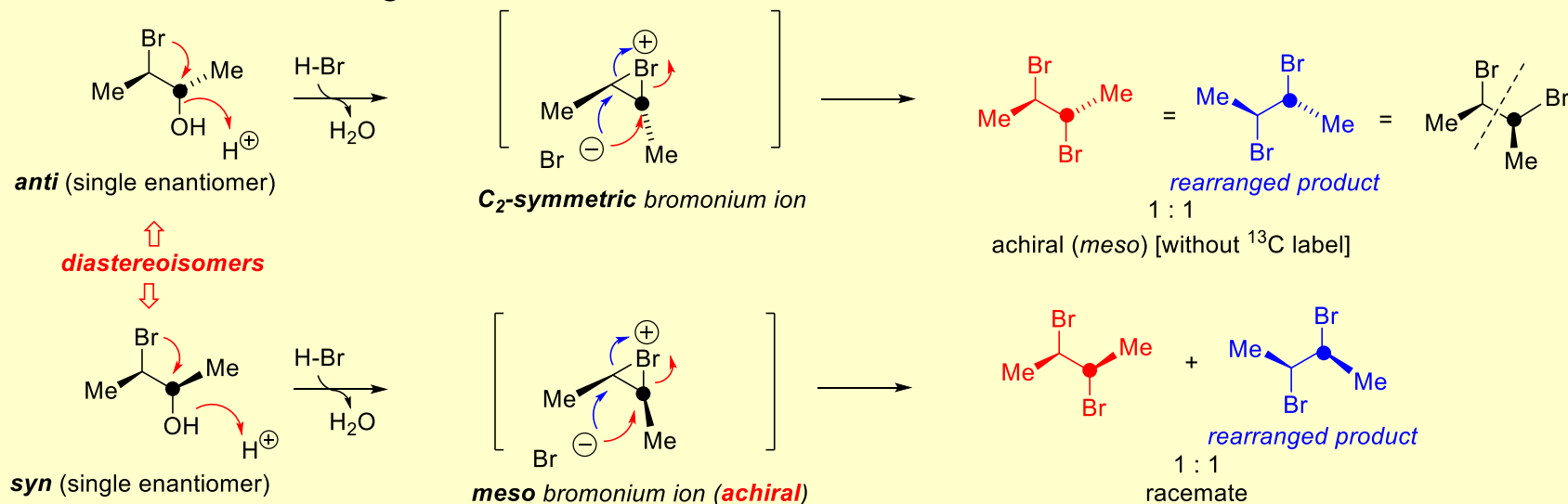
- Payne rearrangements:**



- aza-Payne rearrangements:**

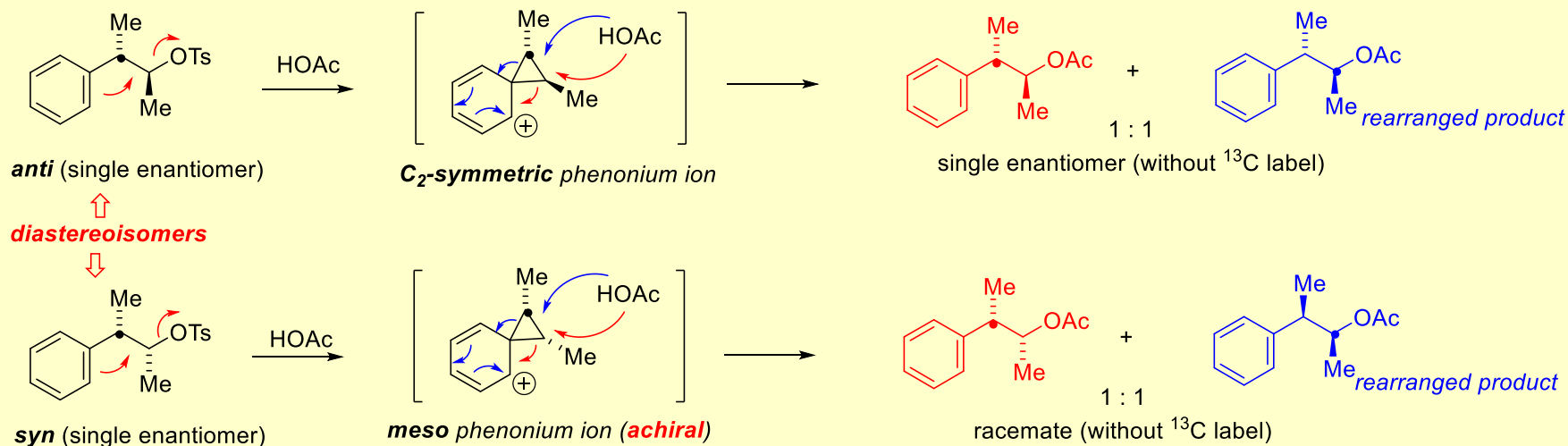


- Bromonium ion rearrangements:**



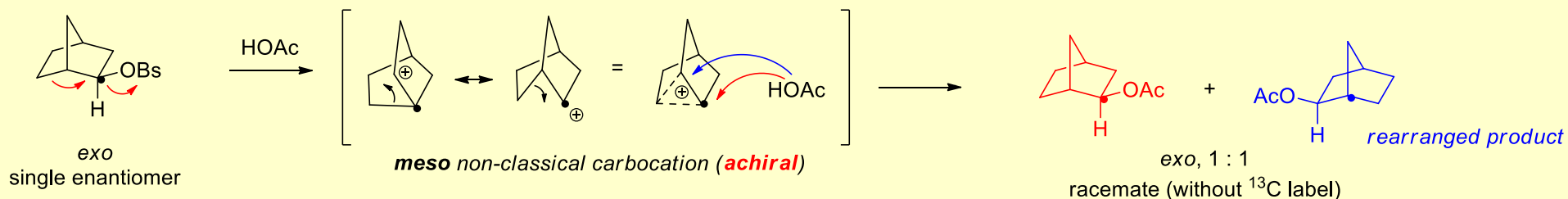
NGP with rearrangement – involvement of π & σ bonds⁵

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



- NGP by **alkyl groups** can also proceed via **non-classical cations**:

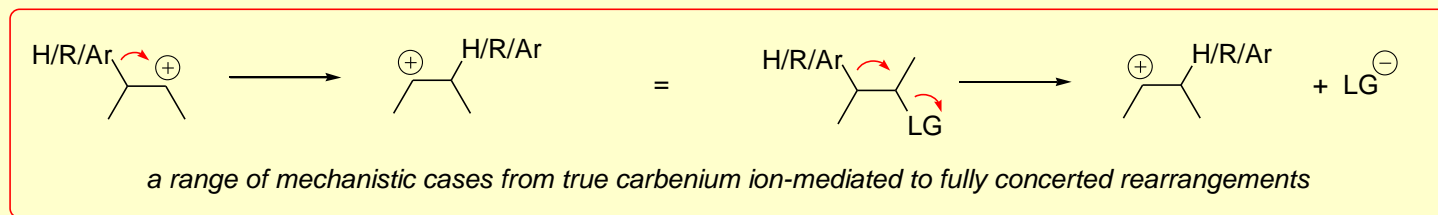
– Crystal structure of this carbocation finally obtained in 2013! See: Scholz *Science*, **2013**, 341, 62 [\[DOI\]](#)



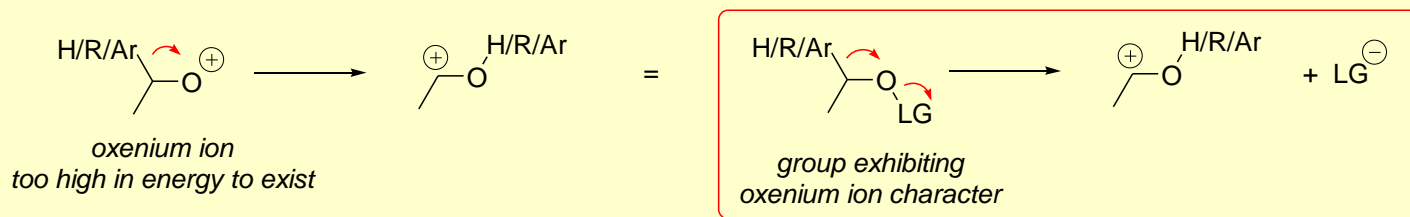
- The rearranged products of the above “NGP” processes can also be regarded as having undergone **[1,2]-sigmatropic rearrangements...**

[1,2]-Sigmatropic rearrangements

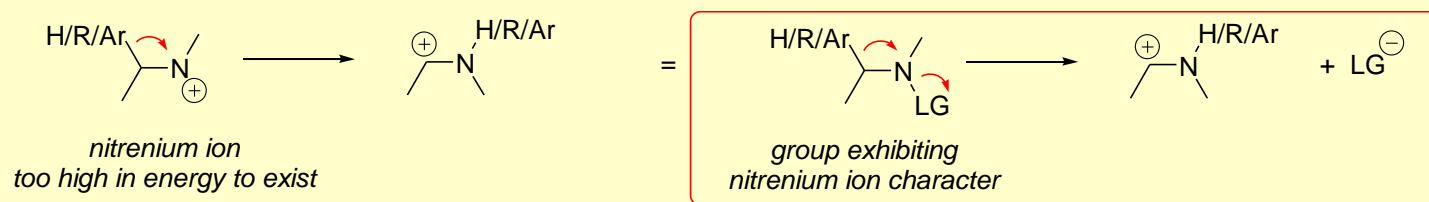
- **[1,2]-Sigmatropic rearrangements** take place when an **electron deficient/cationic centre** is formed adjacent to a group capable of migration using a lone or bonding pair of electrons
 - Participation of bonding electrons of aryl, alkyl and hydride groups are of particular importance:
 - **1,2-Aryl-,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



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

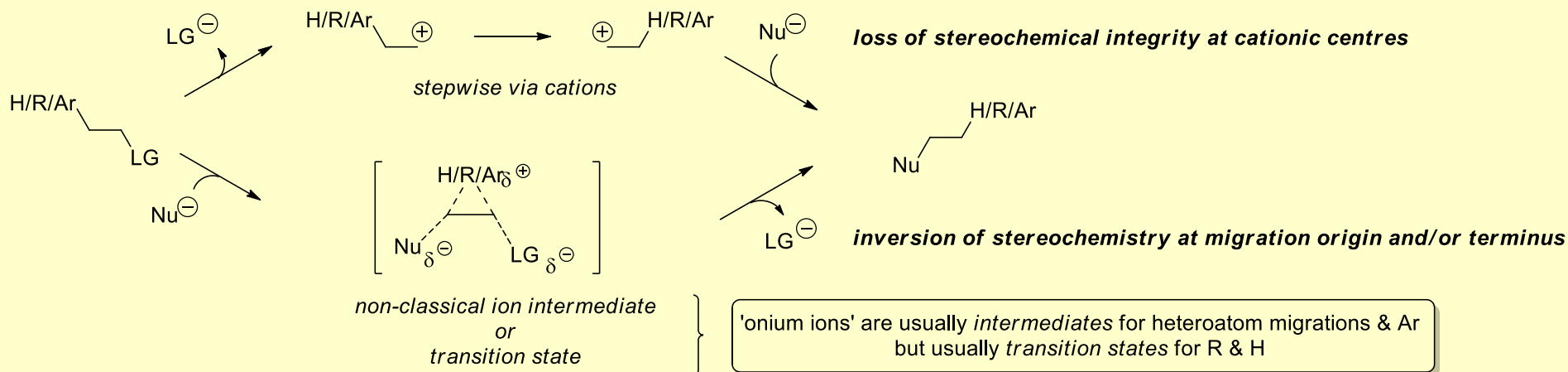


- **1,2-Aryl-, alkyl- & hydride shifts** towards **electron deficient nitrogen**:



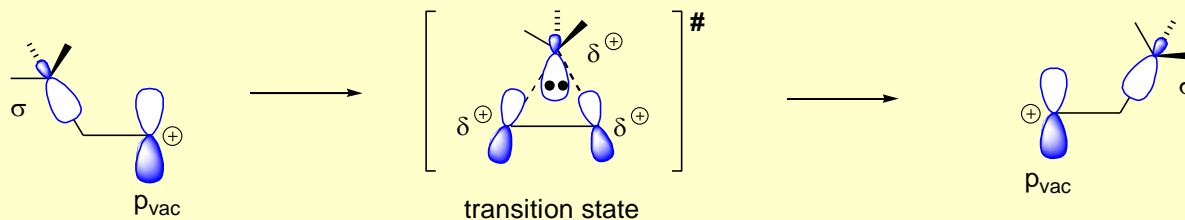
Mechanistic variations

- The mechanism of 1,2-migrations vary from **stepwise** to **concerted** (cf. $S_N1 \leftrightarrow S_N2$):



- The **migrating centre** however **always retains* its configuration** as it retains an **octet of electrons**:

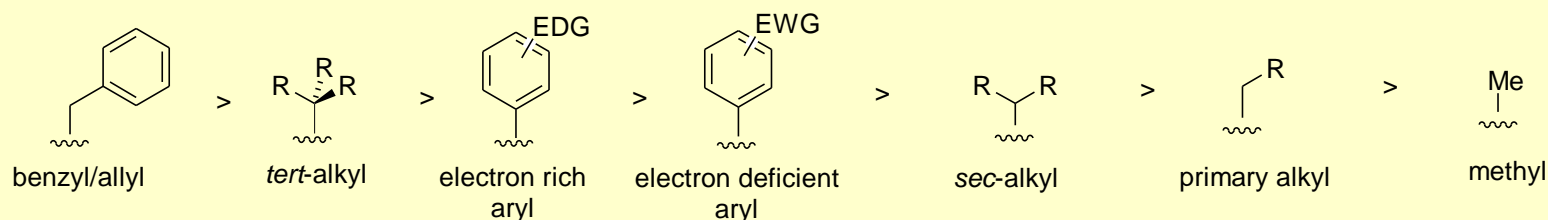
- Consider the case of a 1,2-alkyl shift:



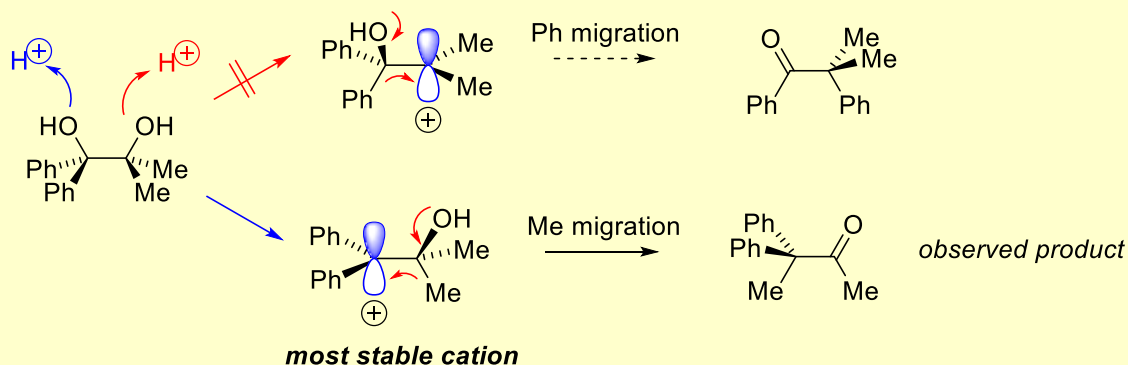
- Inversion* of configuration at the migrating centre is possible for 1,3 and higher sigmatropic rearrangements (see 'Pericyclic reactions' lectures), but loss of stereochemical integrity at this centre is never observed

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:

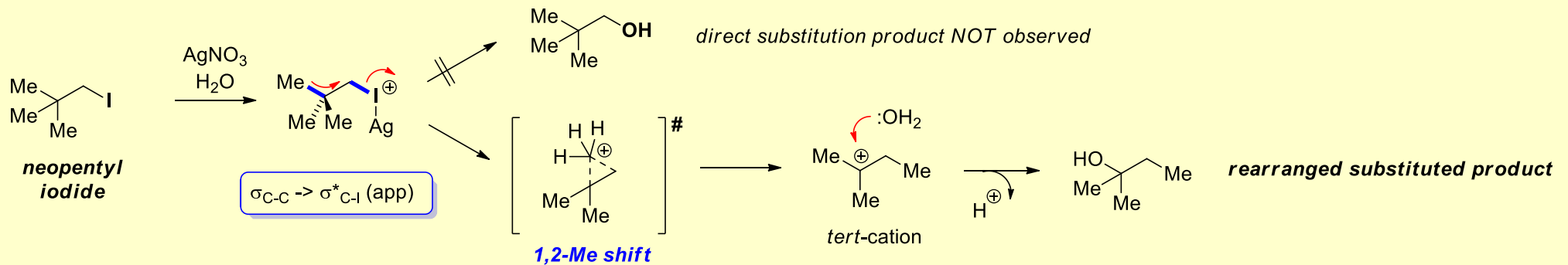


- However, **CORRECT ORBITAL OVERLAP IS CRUCIAL** in the transition state and so (by Hammond's postulate) the orbital alignment in the substrate must be appropriate for migration...

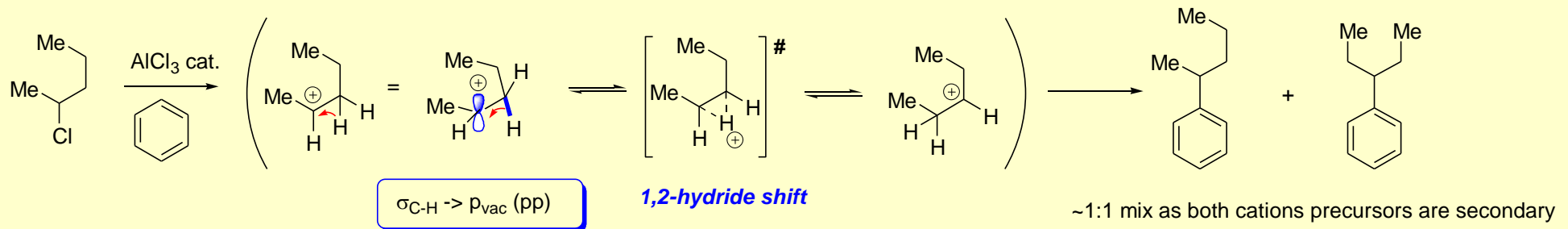
1,2-Shifts to C⁺ - Wagner-Meerwein rearrangements⁹

- **[1,2]-Sigmatropic shifts 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:



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

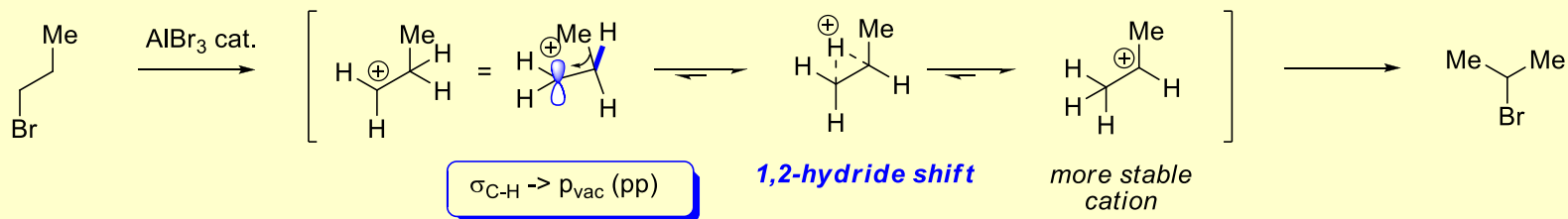


Wagner-Meerwein rearrangements - *isomerisations*

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- Synthetically useful **Wagner-Meerwein rearrangements**

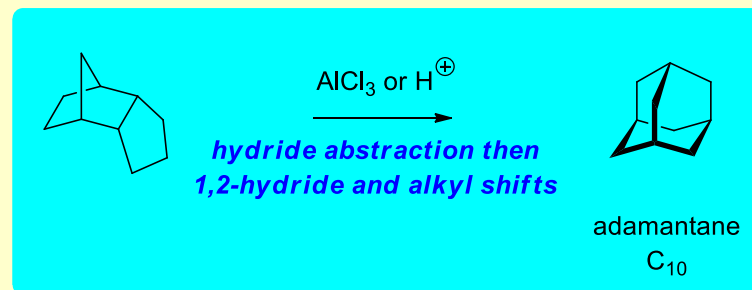
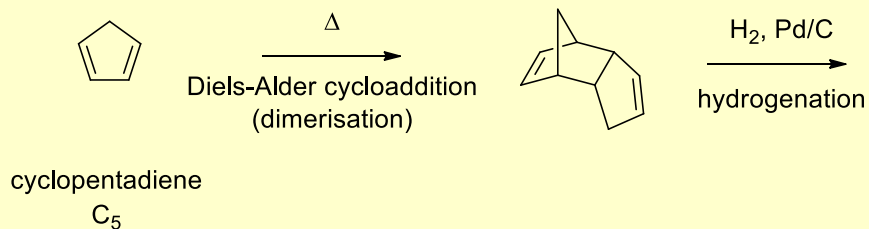
- e.g. isomerisation of alkyl halides:



- A remarkable synthesis of adamantane ($\text{C}_{10}\text{H}_{16}$):

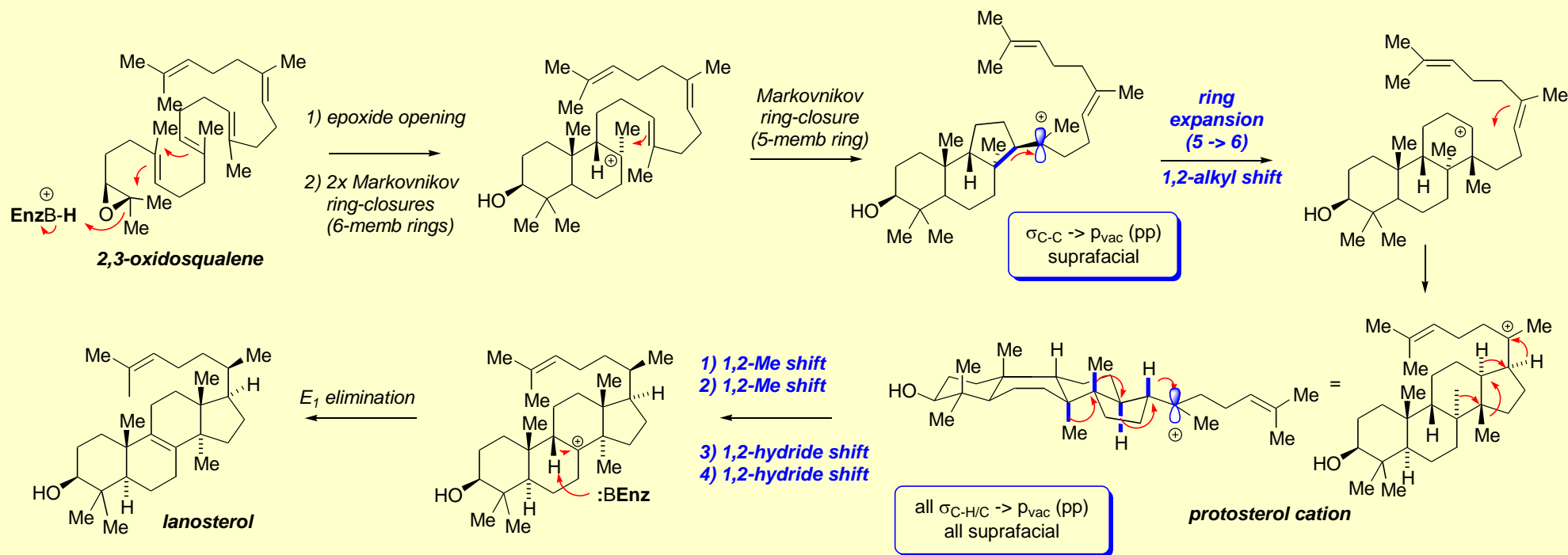
- Schleyer *J. Am. Chem. Soc.* **1960**, 82, 4645 [\[DOI\]](#)

- Whitlock *J. Am. Chem. Soc.* **1968**, 90, 4929 (**2897 possible pathways!**) [\[DOI\]](#)



Wagner-Meerwein rearrangements - *biosynthesis*

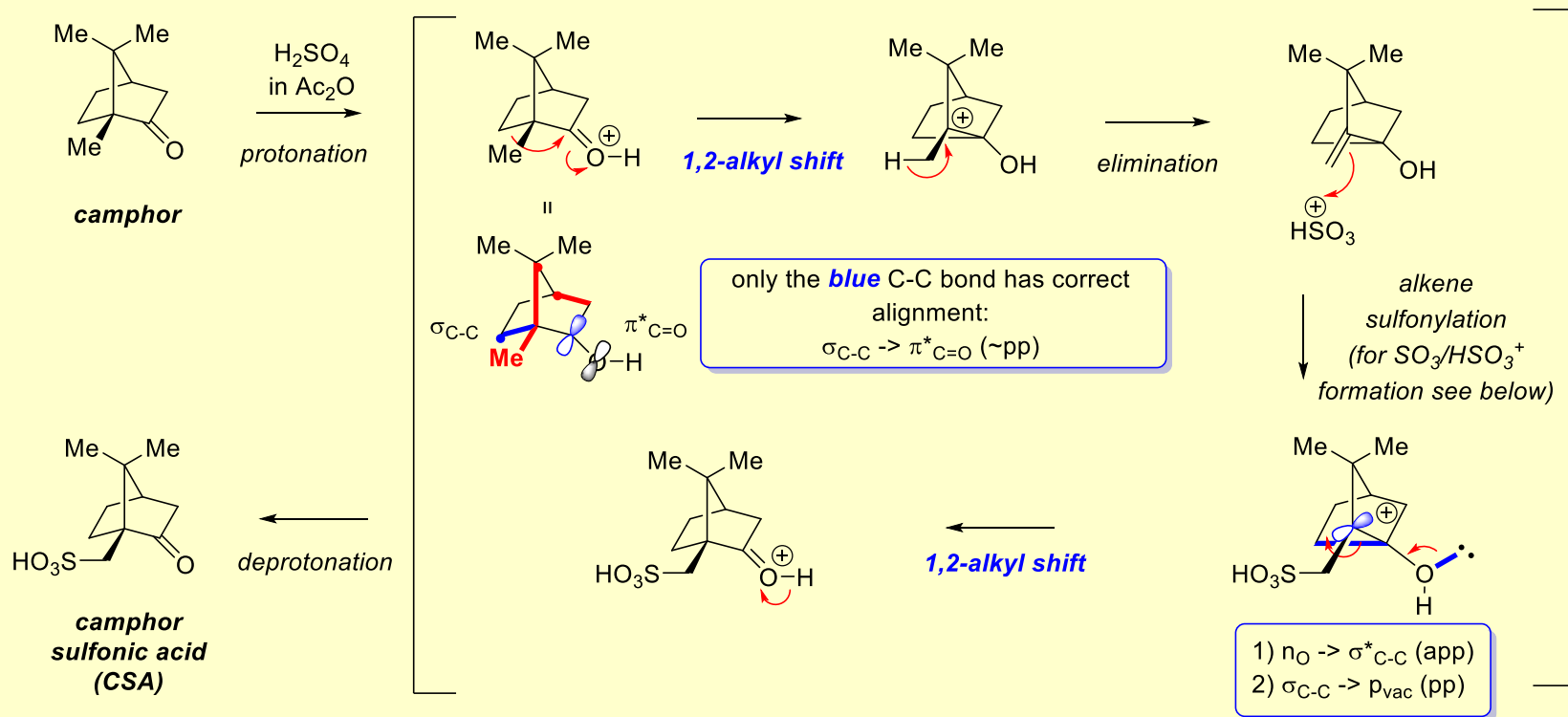
- **Wagner-Meerwein rearrangements** are prevalent in the **biosynthesis** of terpenoids such as **lanosterol** (precursor to **cholesterol** & the human sex hormones)
 - **lanosterol** is formed by the polycyclisation of 2,3-oxidosqualene by the enzyme **OxidoSqualene Cyclase (OSC)**
 - the **conformation** 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](#)]

Wagner-Meerwein rearrangements - *monoterpenes*

- **Wagner-Meerwein rearrangements** occur widely during the biosynthesis of terpenes (isoprenoids) and are also synthetically useful for the functionalisation of these metabolites:
 - e.g. synthesis of camphor sulfonic acid from camphor:



- NB. $\text{H}_2\text{SO}_4/\text{Ac}_2\text{O}$ is a weak sulfonating mixture (cf. oleum) for $\text{S}_{\text{E}}\text{Ar}$:

