

CHEM60001:
An Introduction to Reaction Stereoelectronics

LECTURE 6 1,2-Rearrangements &
Fragmantations

Alan C. Spivey
a.c.spivey@imperial.ac.uk

Imperial College
London

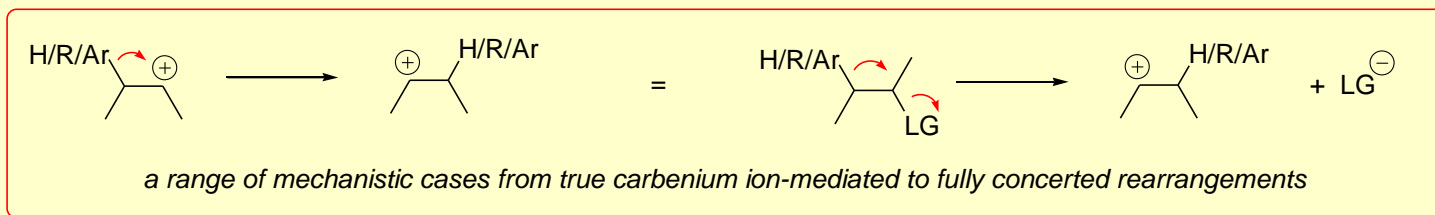
Nov 2016

Format & scope of lecture 6

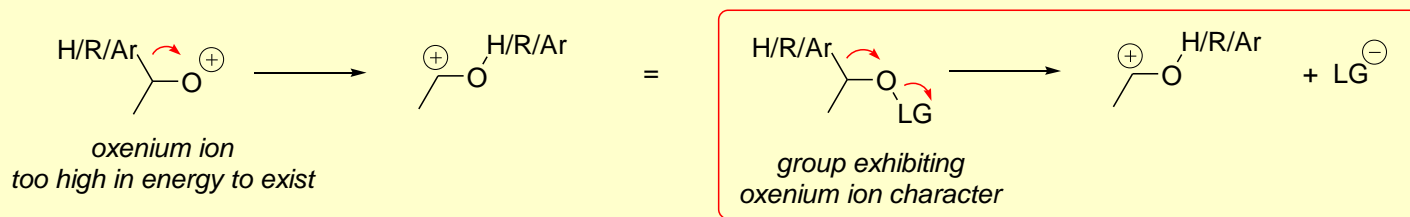
- ***Ionic 1,2-rearrangements, part 2***
 - Pinacol & semi-pinacol
 - Baeyer-Villiger reaction
 - Beckmann rearrangement
- ***Ionic fragmentations***
 - Grob
 - Eschenmoser ring expansion
- ***Reflection on Importance of Reaction Stereoelectronics***

[1,2]-Sigmatropic rearrangements

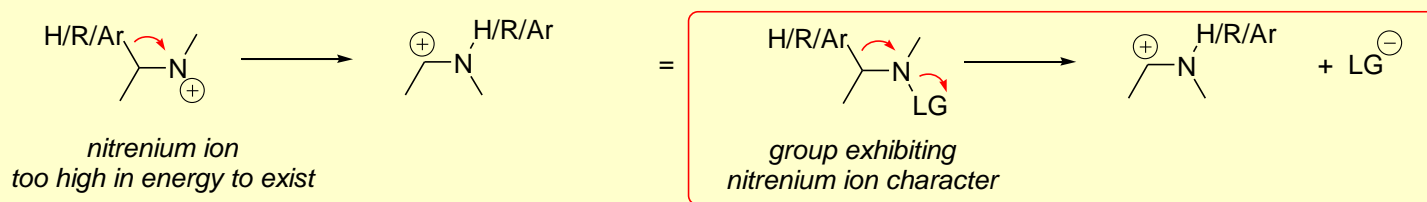
- **[1,2]-Sigmatropic rearrangements** take place when an **electron deficient/cationic centre** is formed adjacent to a group capable of migration using a lone or bonding pair of electrons
 - Participation of bonding electrons of aryl, alkyl and hydride groups are of particular importance:
 - **1,2-Aryl-,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



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

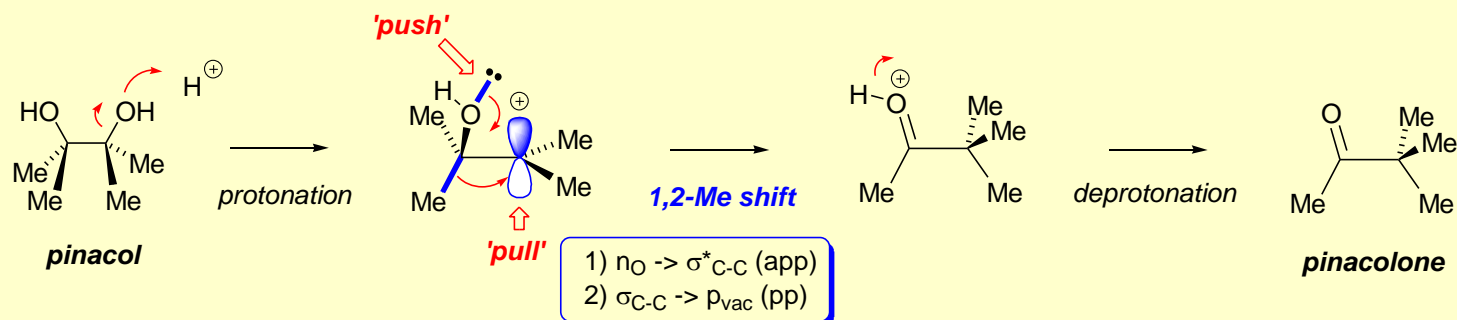


- **1,2-Aryl-, alkyl- & hydride shifts** towards **electron deficient nitrogen**:



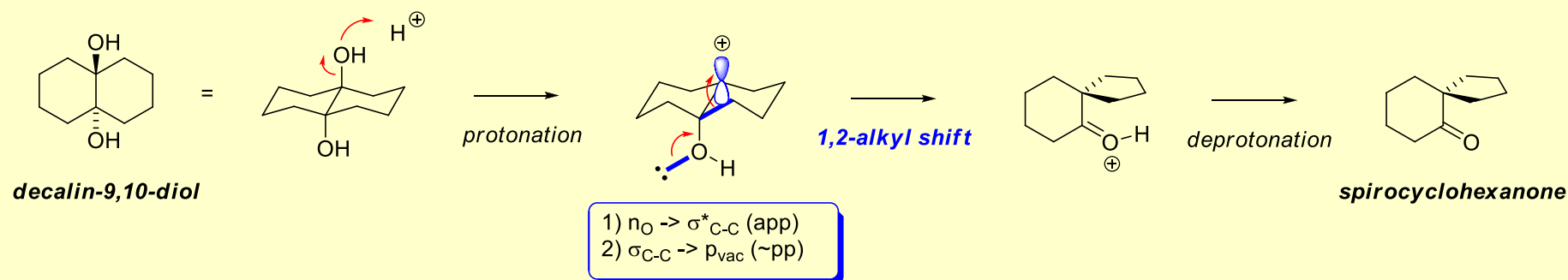
1,2-Shifts to C⁺ – *pinacol rearrangements*

- 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]



- 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

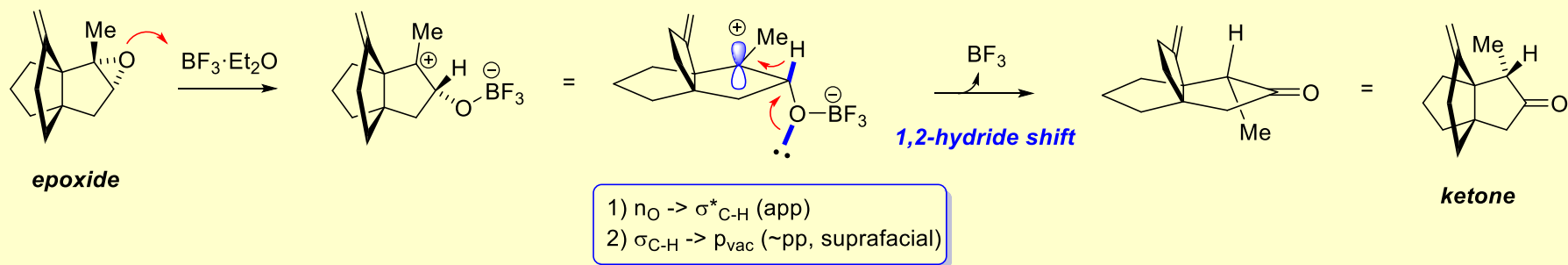
- The reaction is a useful method of preparing **spirocyclic compounds**:



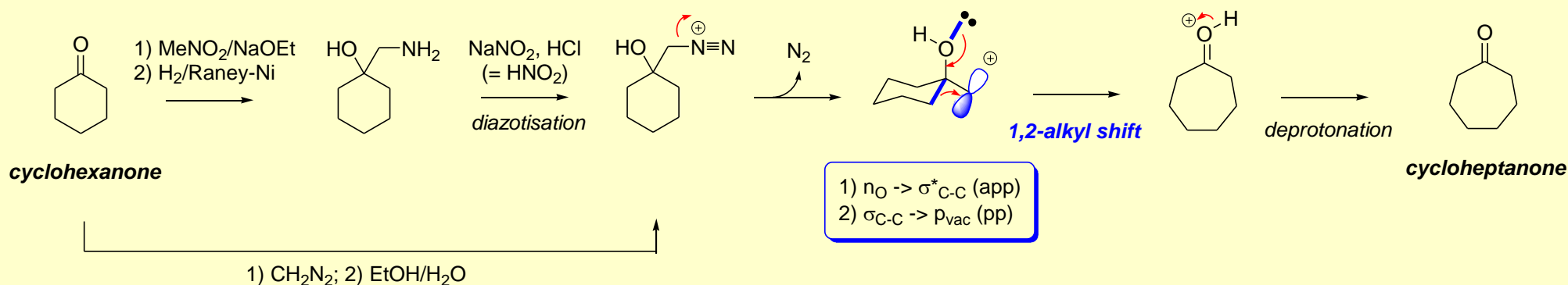
- More generally, any functionality giving rise to a carbenium ion adjacent to an oxygenated carbon can undergo a **semi-pinacol rearrangement**...

1,2-Shifts to C⁺ – semi-pinacol rearrangements

- Treatment of **epoxides** with **Lewis acids** results in **semi-pinacol rearrangements**:

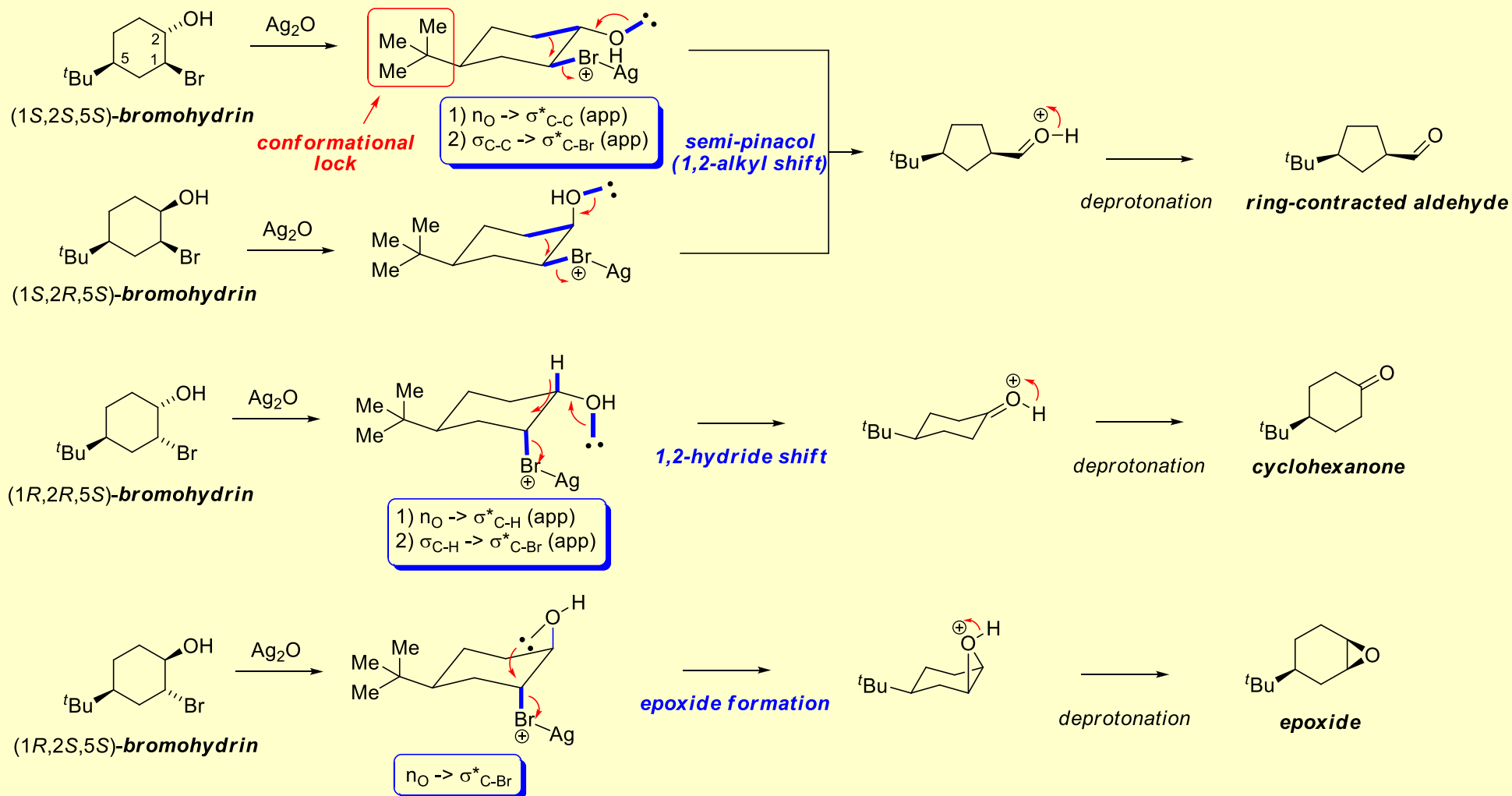


- Diazotisation of β -amino alcohols** results in **semi-pinacol rearrangements (Tiffeneau-Demyanov)**:



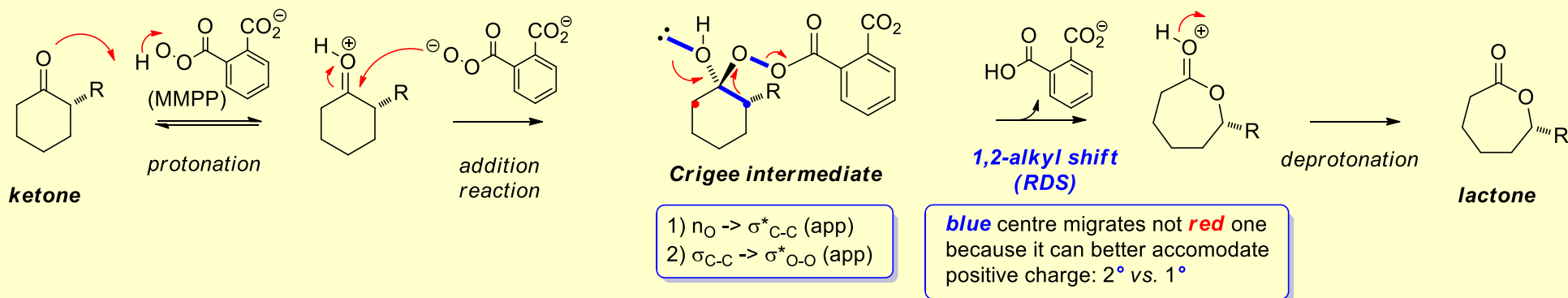
Semi-pinacol rearrangement - stereochemistry

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

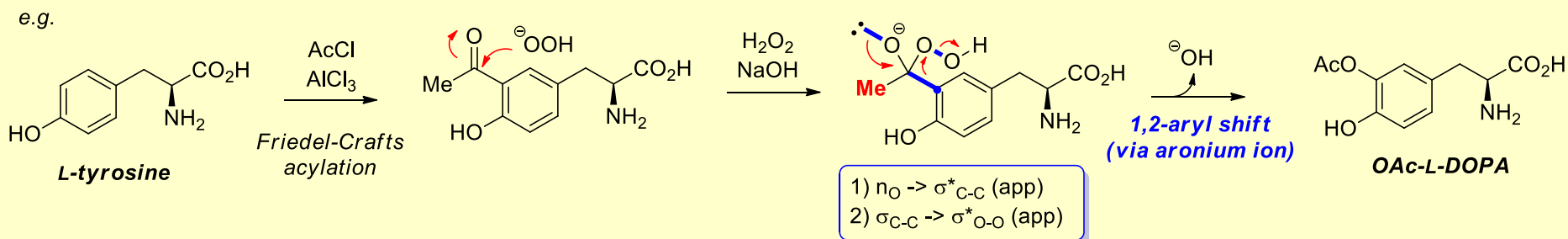


1,2-Shifts to O⁺ – Baeyer-Villiger reaction

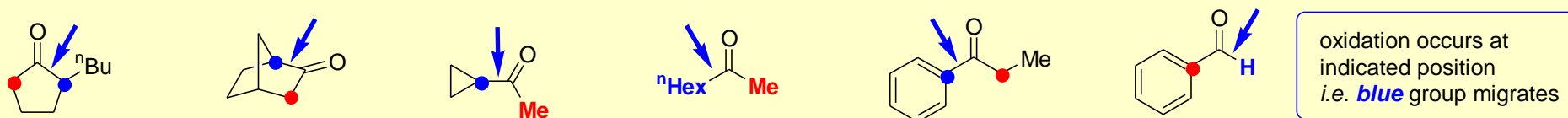
- Treatment of **ketones & aldehydes** with **peracids** induces a **Baeyer-Villiger reaction**:



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

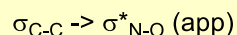
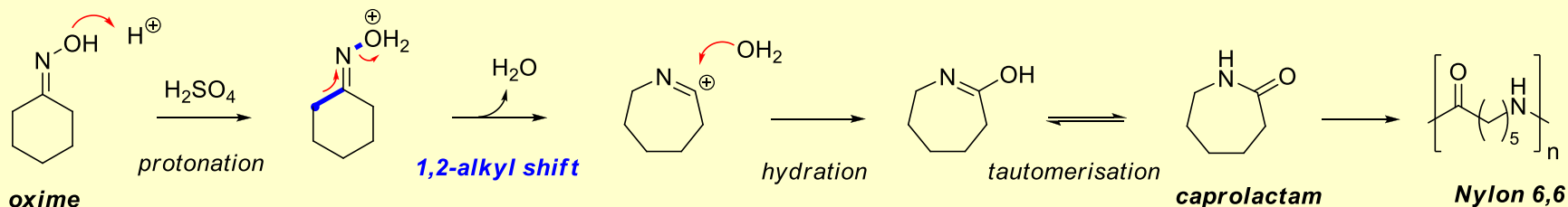


- the driving force is the exothermicity of cleavage of a weak O-O bond and formation of a C=O bond
- order of migration generally follows migratory aptitude series presented earlier:

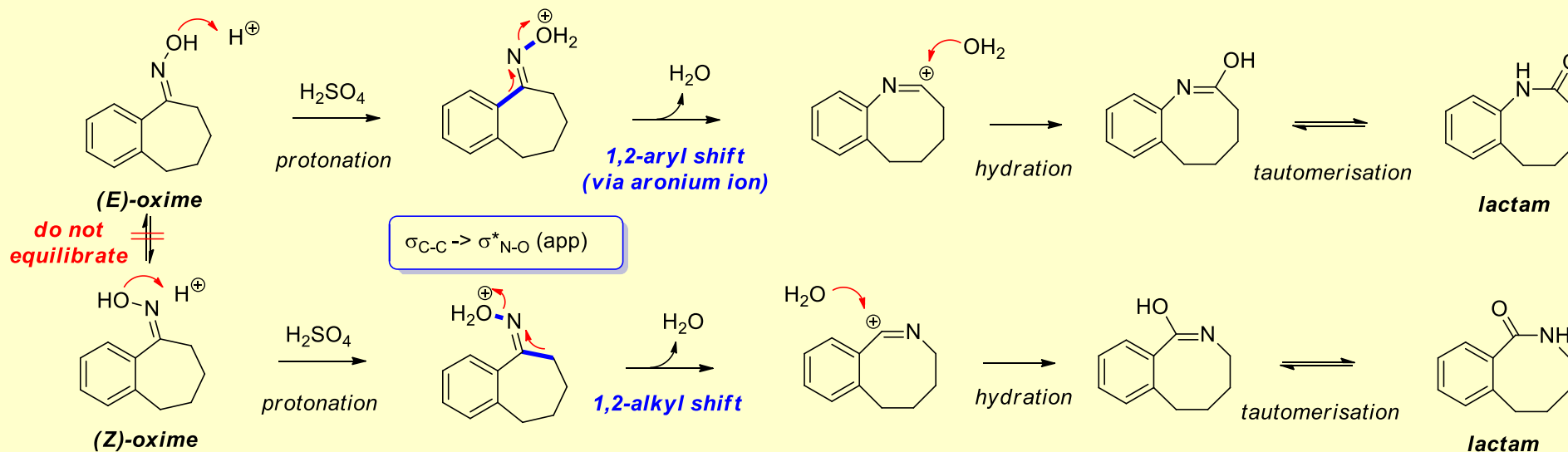


1,2-Shifts to N⁺ – Beckmann rearrangement

- 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**

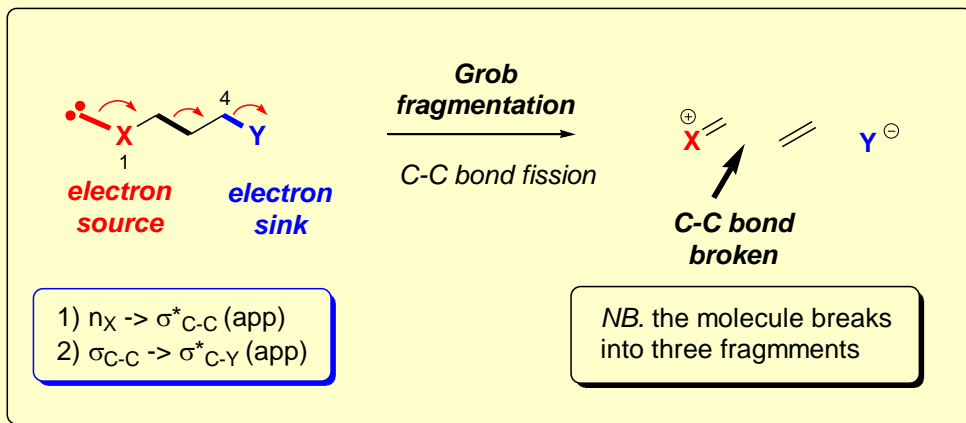


Ionic fragmentations – *characteristics*

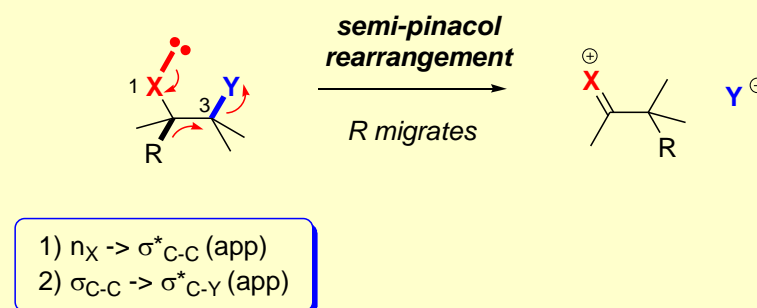
- **Ionic fragmentation reactions are reactions in which C-C bonds are broken in a heterolytic fashion**
- They are relatively rare **NOT** because **C-C bonds are particularly strong**:
 - cf. Bond Dissociation Energies:

C-C	339 kJmol ⁻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:



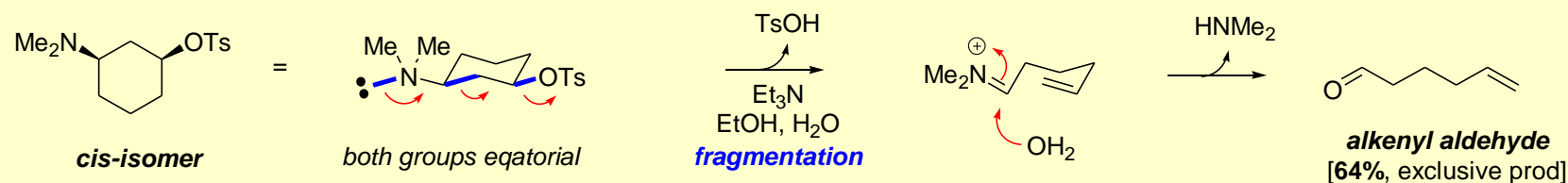
cf.



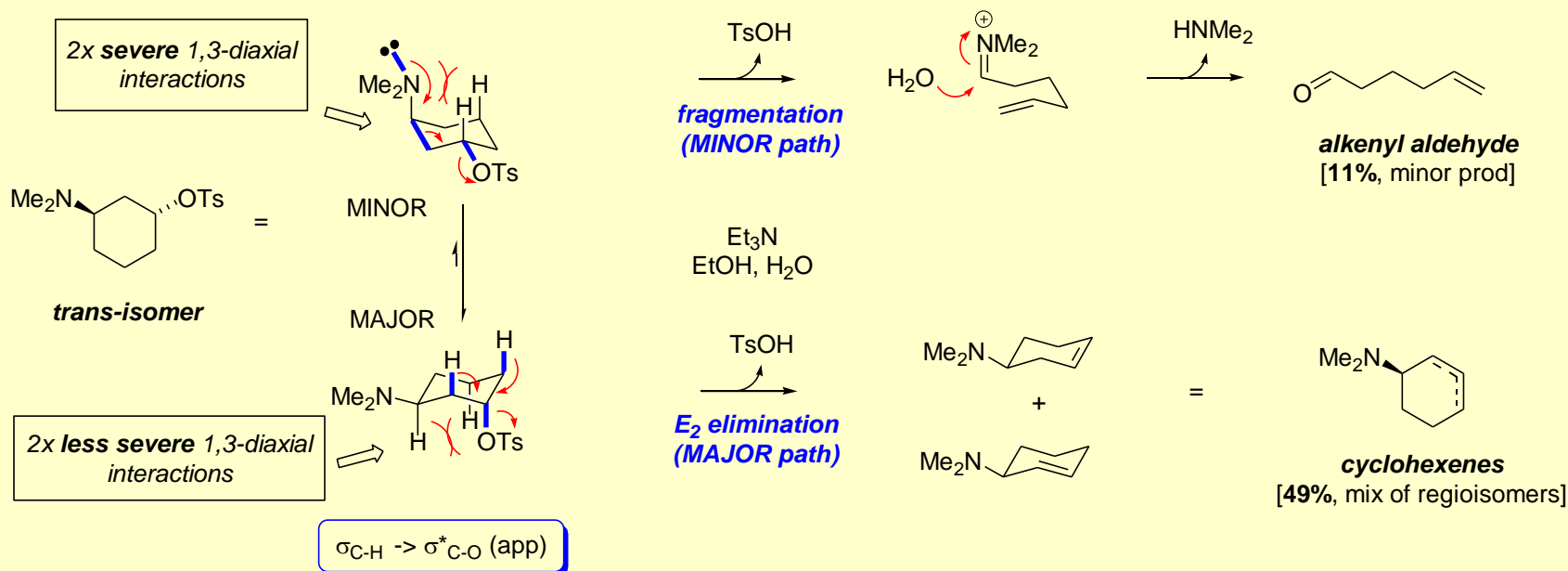
- This type of fragmentation is sometimes referred to as a **Grob fragmentation** (=homologous pinacol)
- As with 1,2-rearrangements **CORRECT ORBITAL OVERLAP IS CRUCIAL...**

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:

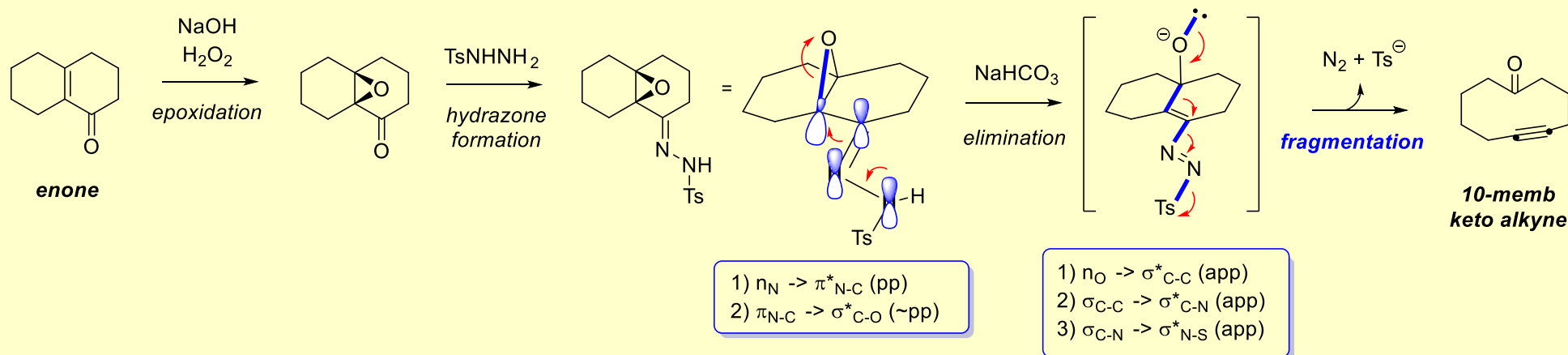


1) $n_{\text{N}} \rightarrow \sigma^*_{\text{C-C}}$ (app)
 2) $\sigma_{\text{C-C}} \rightarrow \sigma^*_{\text{C-O}}$ (app)

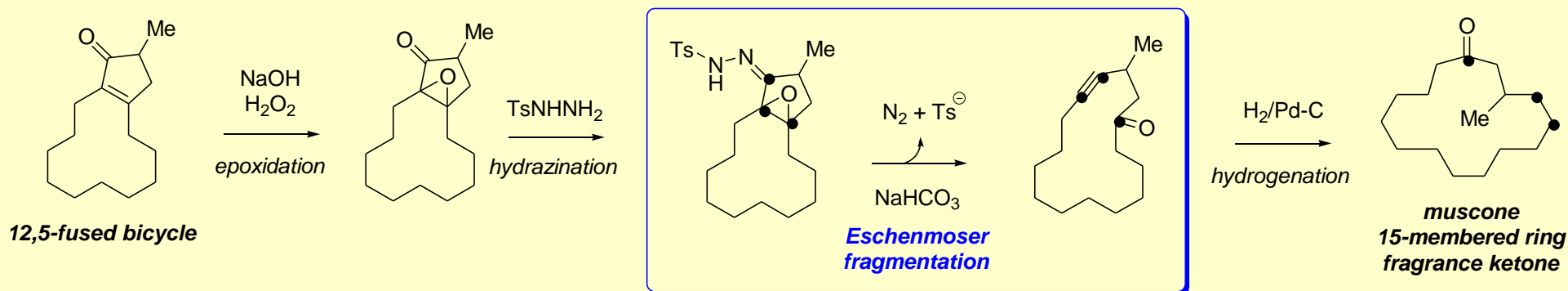


The Eschenmoser fragmentation

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



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



Stereoelectronics - *A panacea for rationalisation of conformation & reactivity?*

- ***NO!...stereoelectronic analysis is constrained by the limitations of:***
 - APPROXIMATIONS INVOLVED IN CONSIDERING ONLY LOCALISED MOLECULAR ORBITALS (e.g. NBOs)
 - PERTURBATION THEORY (i.e. the Klopman-Salem expression)
 - FRONTIER ORBITAL THEORY
- ***Moreover, stereoelectronic analysis must, as we have seen, be augmented by consideration of many additional factors which influence chemical reactivity:***
 - STRAIN: Compressive/tensile: Bayer (=angle)/Pitzer (=torsional)/Prelog (=transannular). All van der Waals in origin
 - STERIC EFFECTS: van der Waals in origin (e.g. hydrocarbon conformations; Lennard-Jones potential)
 - ENTROPY EFFECTS: Statistics! [e.g. possibly of significance in the 'Thorpe-Ingold effect']
 - SOLVENT EFFECTS: electrostatic and dipole interactions with the reaction medium
 - ELECTROSTATIC/DIPOLE EFFECTS: [e.g. a factor in the anomeric effect, significant factor in carbonyl addition reactions cf. Felkin-Anh]