

CHEM60001:
Advanced Chemistry Topics 1 – Pericyclic
Reactions

LECTURE 7
Sigmatropic Rearrangements

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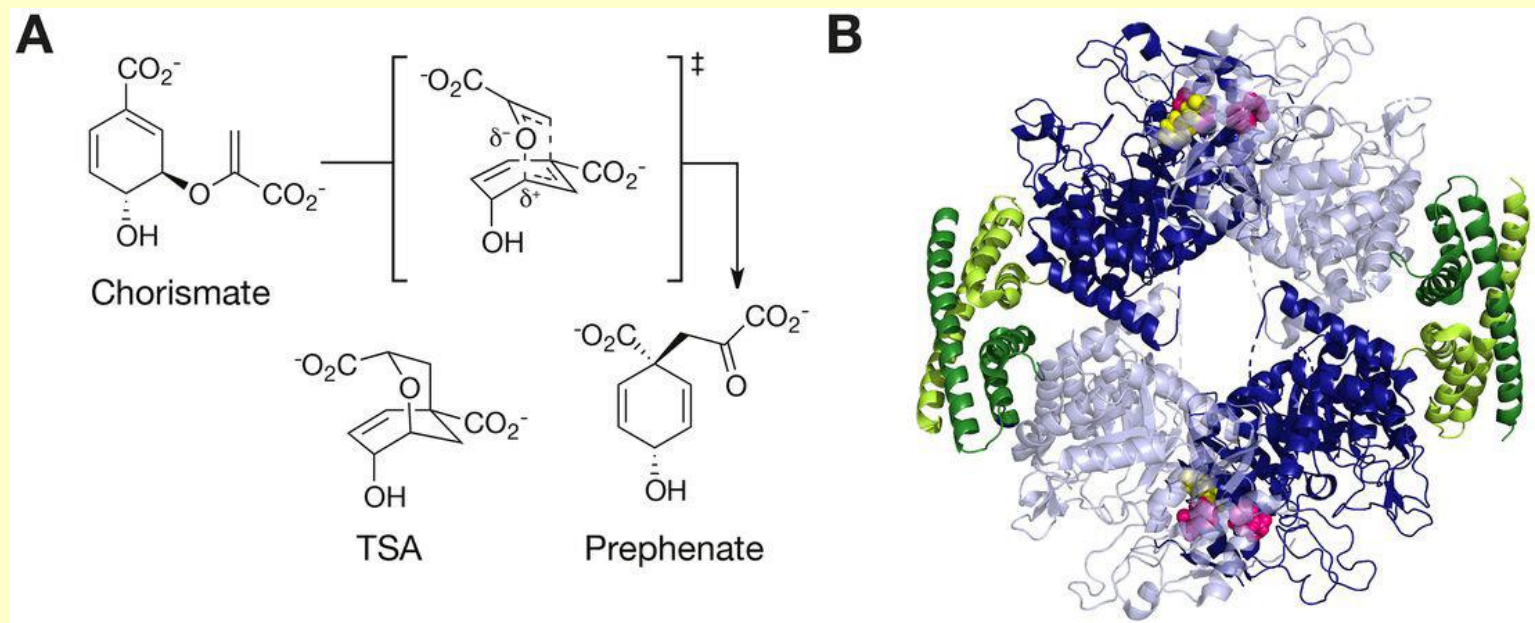
Format & scope of lecture 7

- ***[3,3]-sigmatropic rearrangements***
 - Cope & oxy-Cope
 - Claisen & variants
- ***[1,n]-hydride and alkyl shifts***
 - 1,2-shifts
 - 1,3-shifts
 - 1,5-shifts
- ***[2,3]-sigmatropic rearrangements***
 - Wittig
 - Sommelet-Hauser
 - Mislow-Evans

Key further reading:

- **BOOK:** Clayden, Greeves & Warren, *Organic Chemistry*, 2nd Ed.,
 - ***Chapter 35*** – pericyclic reactions 2 – sigmatropic and electrocyclic reactions
- **WEB:** Pericyclic Reactions - https://www.stereoelectronics.org/webPR/PR_home.html
 - ***Chapter 6*** – Sigmatropic rearrangements

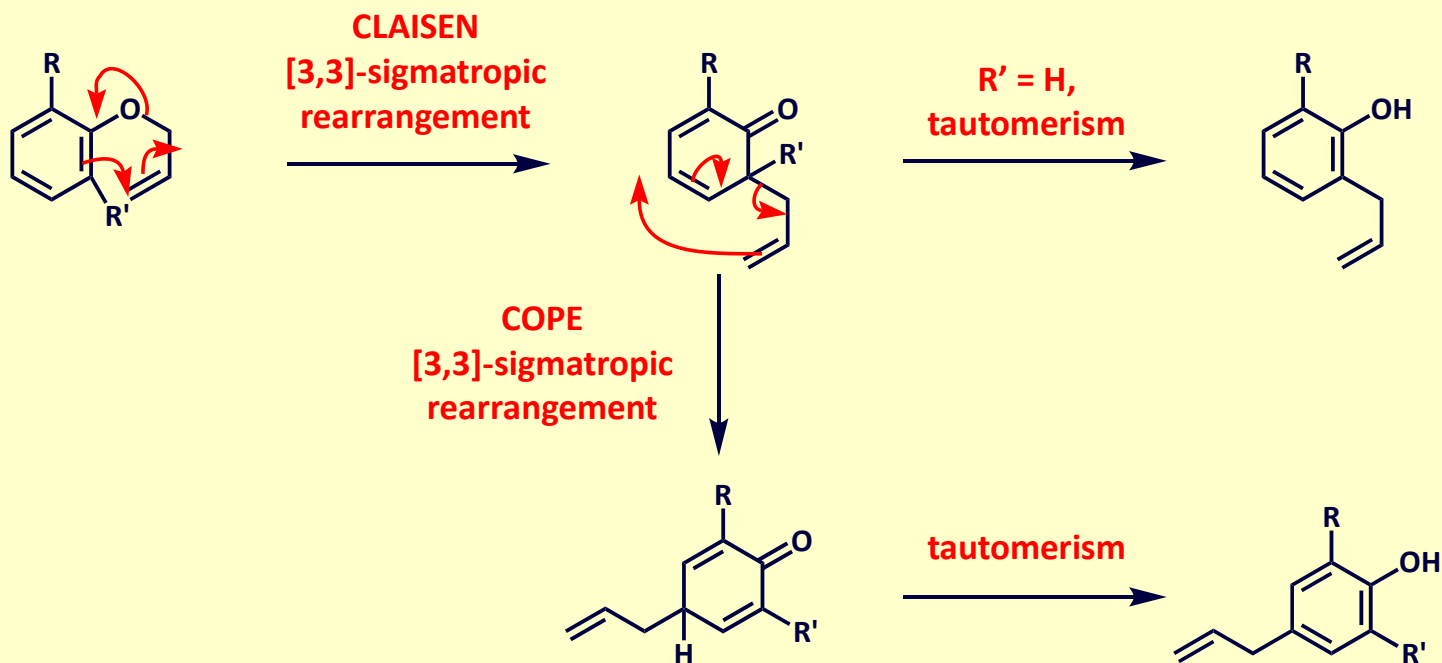
[3,3]-Sigmatropic rearrangements



Chorismate mutase (PDB: [5CKX](#)) catalyses a [3,3]-Claisen rearrangement *en route* from chorismite to prephenate in the shikimate biosynthetic pathway to the aromatic amino acids phenylalanine, tyrosine and tryptophan. This biosynthetic pathways only operates in plants and this enzyme is the only known “Claisen rearrangementase”...

[3,3]-Sigmatropic rearrangements

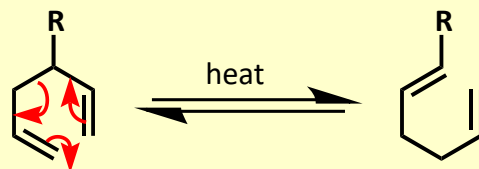
- **Synthetically, the most important sigmatropic rearrangements are the Cope and Claisen rearrangements.**
 - They are both [3,3]-sigmatropic rearrangements.
 - They can proceed *via* chair or boat transition states – the chair transition state is strongly favoured unless there are steric constraints that force a boat transition state.
 - Where possible, substituents generally adopt equatorial sites in the chair transition state.



The Cope and Oxy-Cope rearrangements

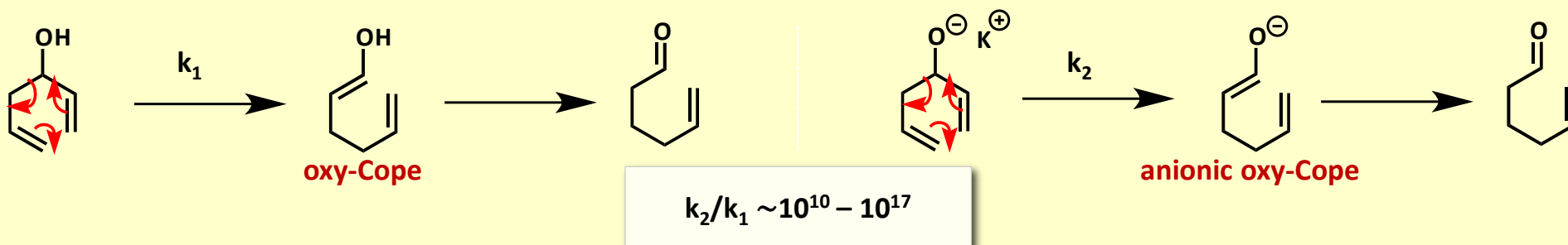
- **The Cope rearrangement**

- High temperatures generally required (>200 °C)

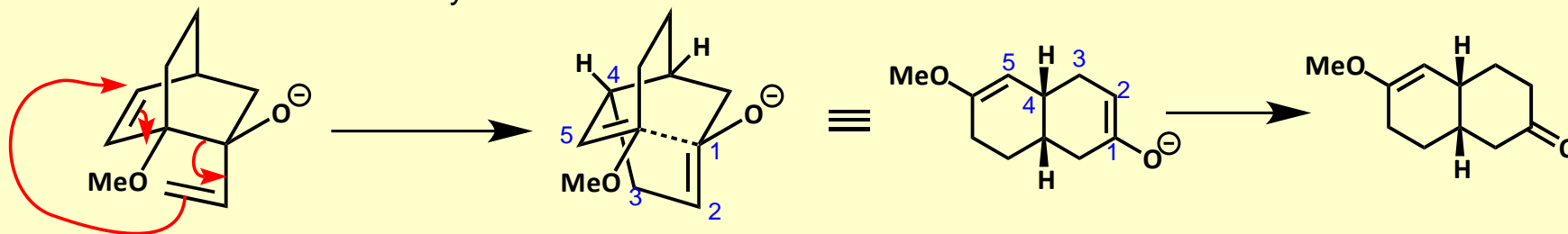


- **The anionic oxy-Cope rearrangement.**

- can be conducted at low temperature (0 °C).
- *retro*-synthetic 'signature' is a δ,ϵ -unsaturated carbonyl



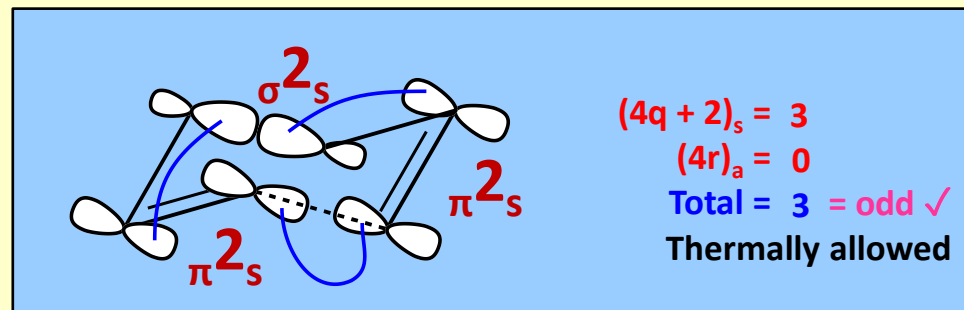
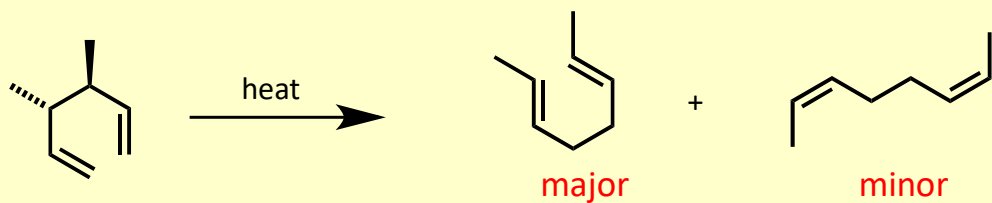
- a useful method for the synthesis of *cis*-decalins from norbornene derivatives...



The Cope rearrangement

- **[3,3]-Sigmatropic rearrangement**

- Thermally allowed



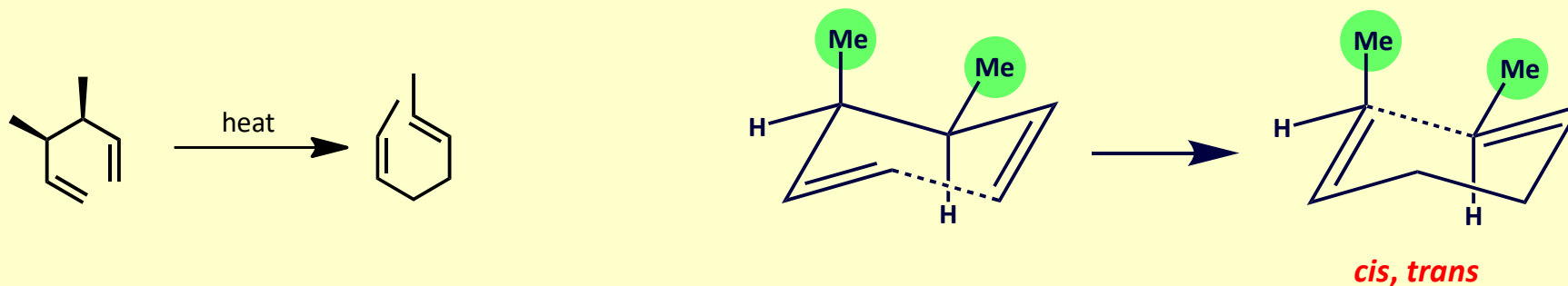
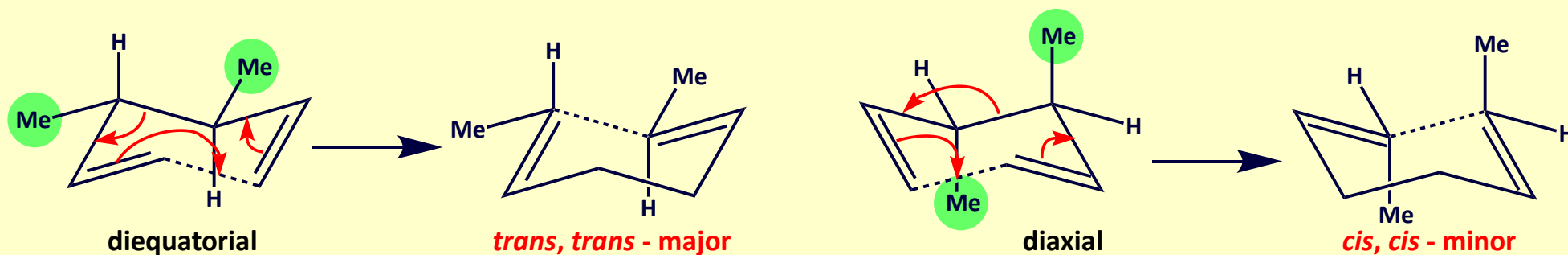
$$(4q + 2)_s = 3$$

$$(4r)_a = 0$$

$$\text{Total} = 3 = \text{odd} \checkmark$$

Thermally allowed

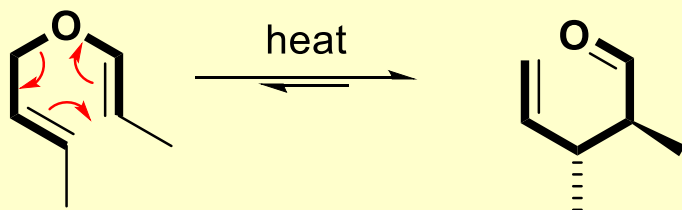
W-H approach



The Claisen rearrangement and variants

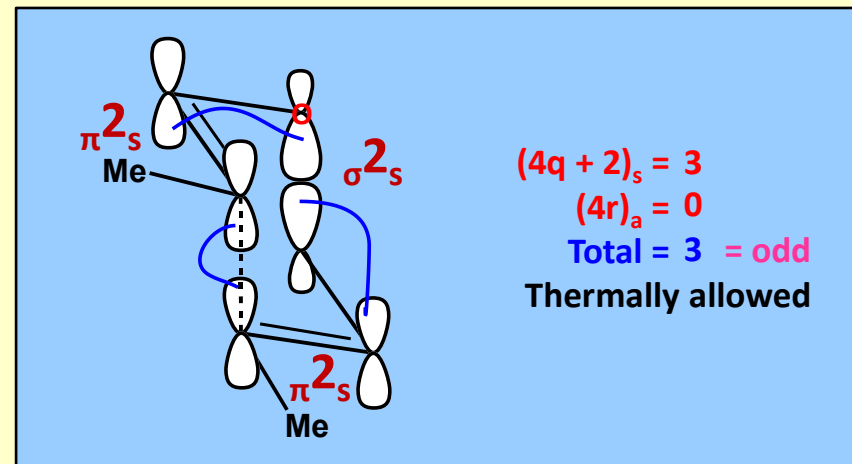
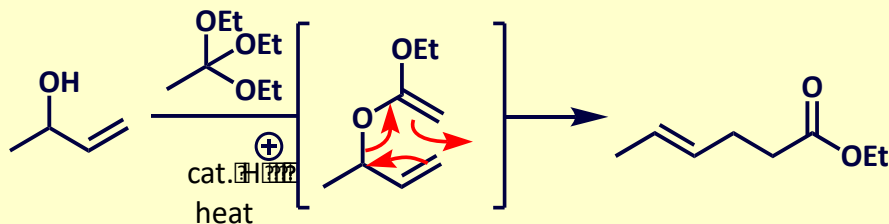
- **The Claisen rearrangement:**

- allyl vinyl ether to γ,δ -unsaturated carbonyl derivative
- driven by formation of C=O bond.



- **The Johnson-Claisen rearrangement**

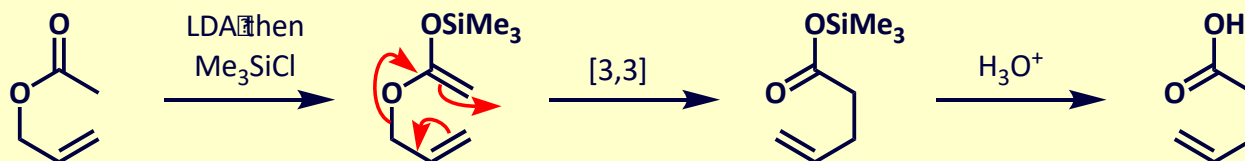
- synthesis of γ,δ -unsaturated esters *via* ketene acetal



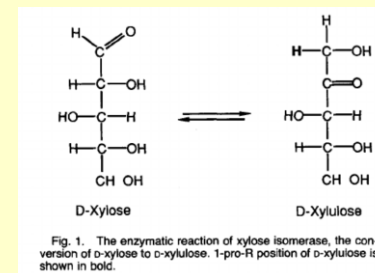
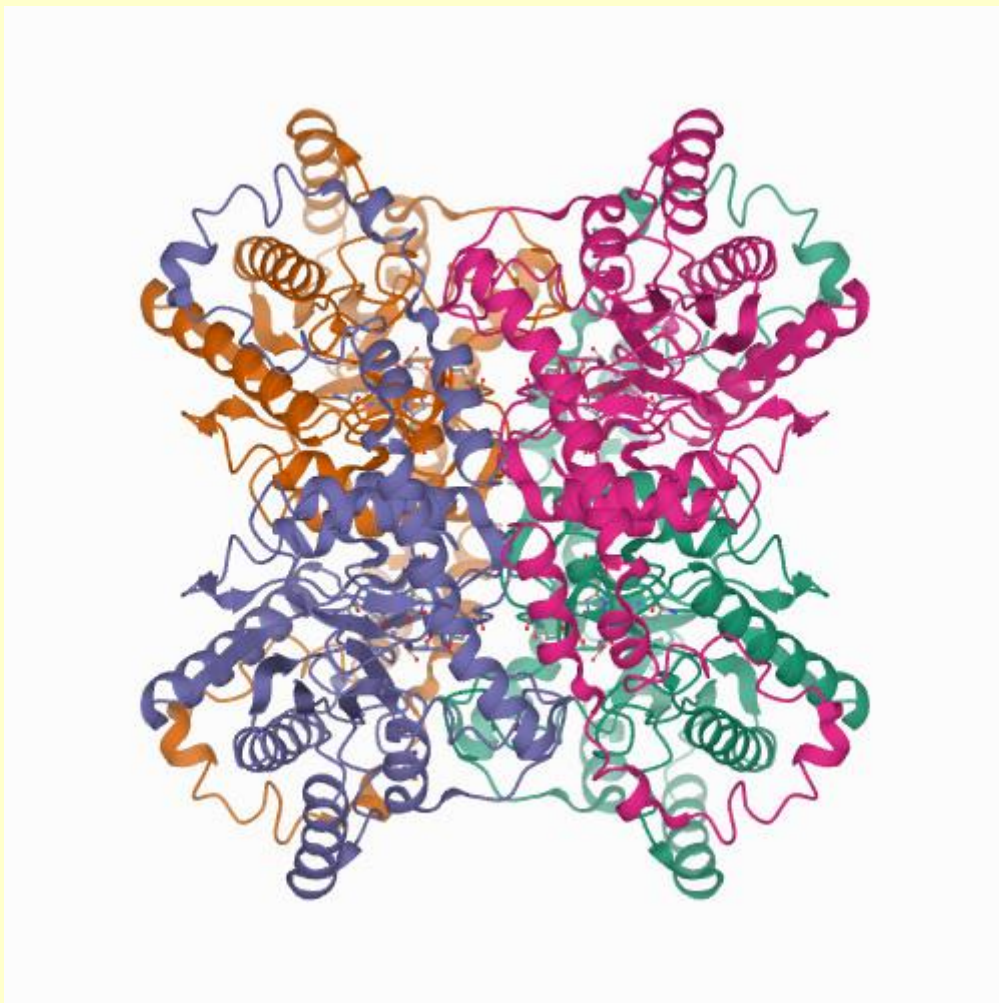
W-H approach

- **The Ireland-Claisen rearrangement**

- Synthesis of γ,δ -unsaturated acids *via* silyl ketene acetal



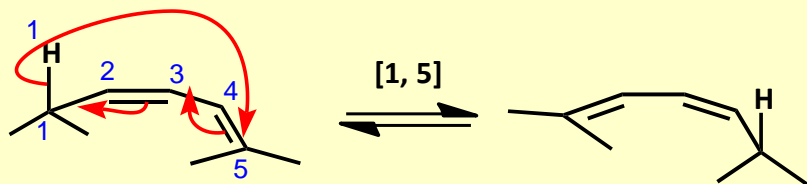
[1,n]-Hydride and alkyl shifts



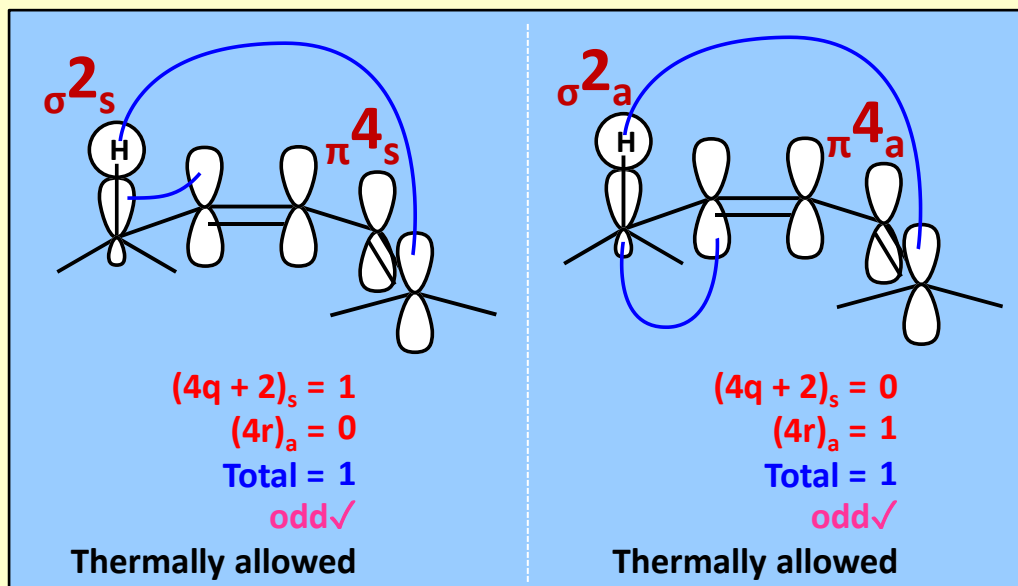
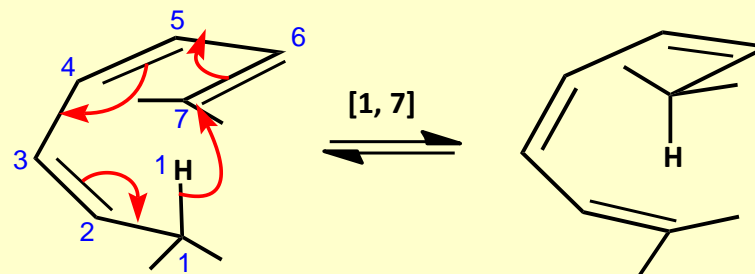
The conversion of D-xylose to D-xylulose is known as the Lobryde Bruyn-Alberda van Ekenstein transformation. The enzyme-mediated version of this reaction is proposed to involve a 1,2-hydride shift! It is catalysed by D-xylose isomerase (EC 5.3.1.5, PDB: [1XIS](https://doi.org/10.1002/prot.340090302)).

[1,n]-Hydride shifts

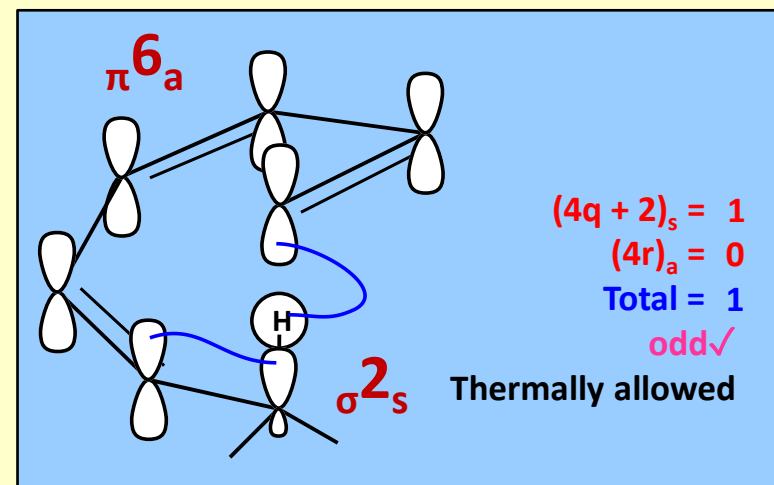
■ A *suprafacial* 1,n-hydride shift involves the hydrogen moving from one end of the conjugated system to the other across one face of the conjugated system



■ An *antarafacial* 1,n-hydride shift involves the hydrogen moving from one end of the conjugated system to the other and moving from one face of the conjugated system to the opposite face



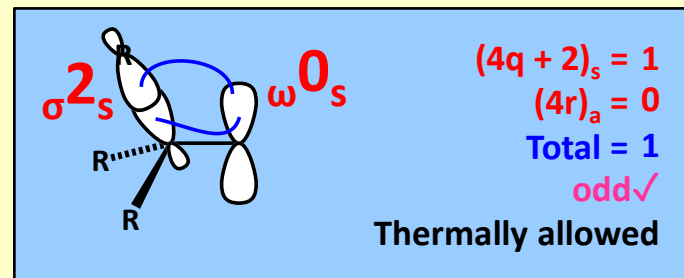
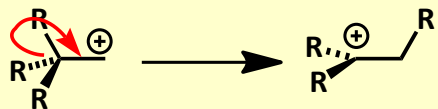
W-H approach



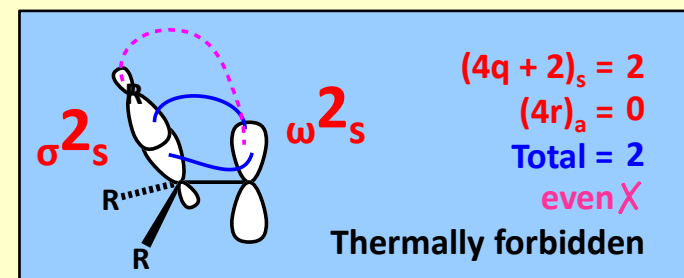
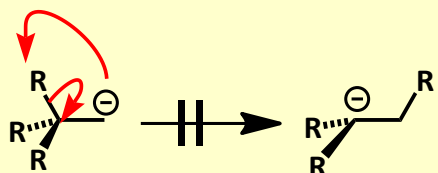
W-H approach

[1,2]-Alkyl shifts

- Carbocationic [1,2]-shifts of alkyl groups can be pericyclic:

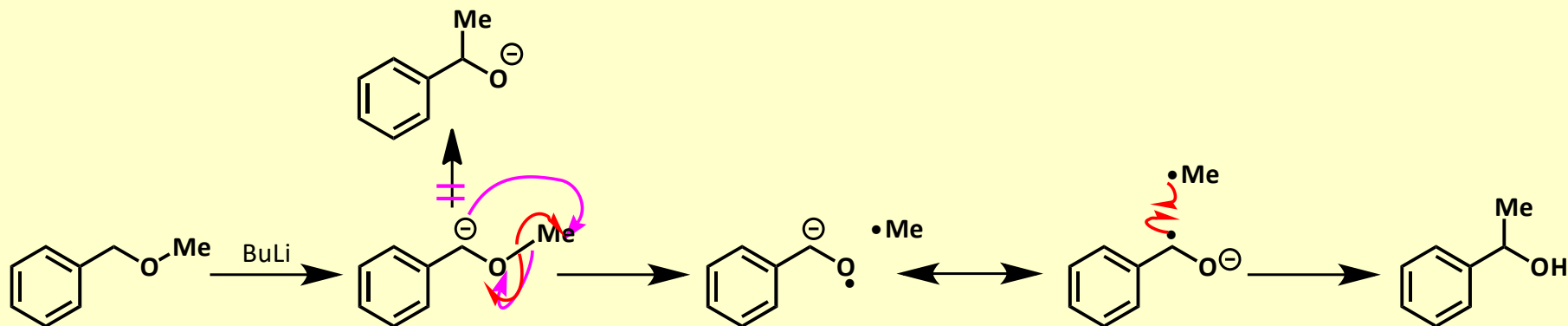


- Allowed, concerted [1,2]-shifts of carbanions are geometrically impossible



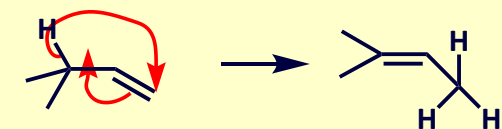
- [1,2]-Shifts of carbanions occur by a radical mechanism

– [1,2]-Wittig & [1,2]-Stevens rearrangements

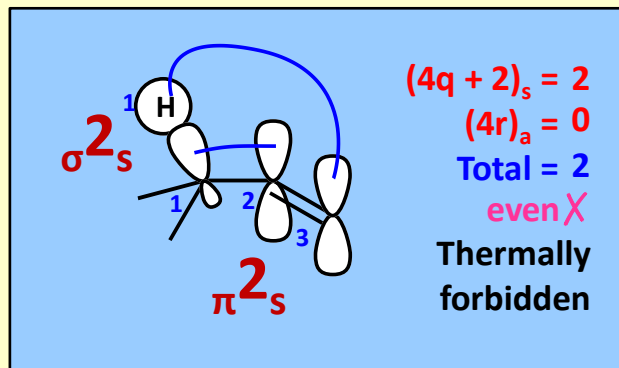


[1,3]-Hydride and Alkyl shifts

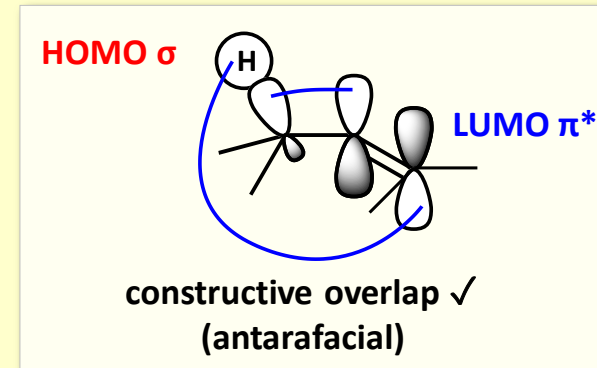
- **[1,3]-Hydride shifts** - do not occur thermally
 - geometrically reasonable suprafacially, but thermally disallowed
 - antarafacially thermally allowed, but geometrically unreasonable:



antarafacial shift allowed
but geometrically unreasonable

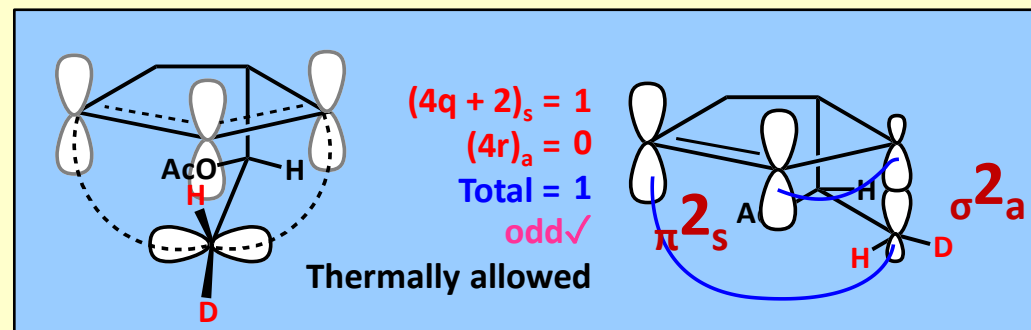
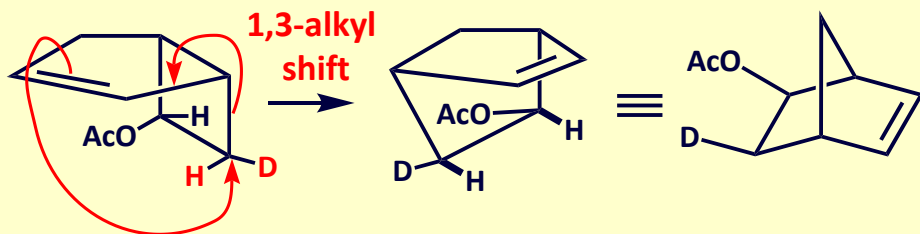


W-H approach



FMO approach

- **1,3-Alkyl shifts** – do occur thermally
 - ...with inversion of configuration in the migrating group

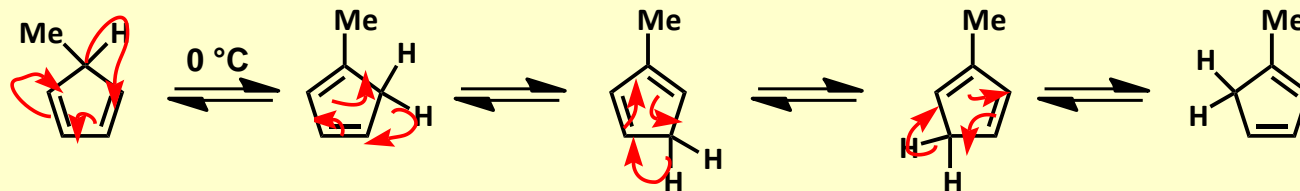


W-H approach

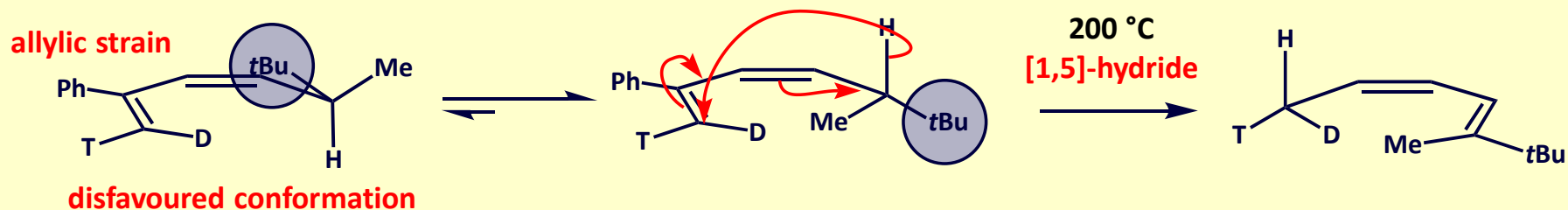
[1,5]-Hydride and Alkyl shifts

• [1,5]-Hydride shifts

- thermally suprafacial reactions; fast when ends of diene are held close:

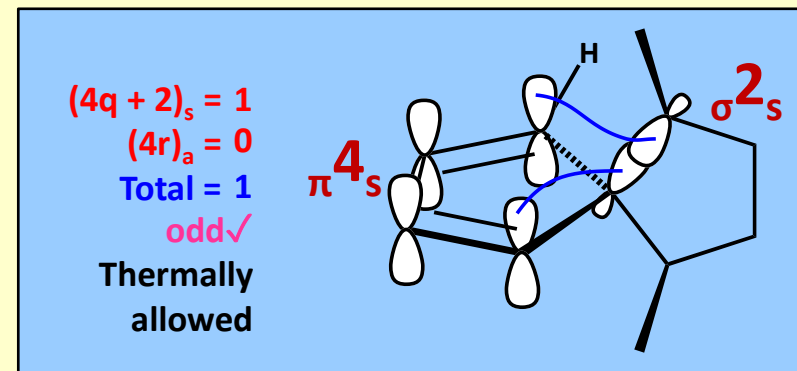
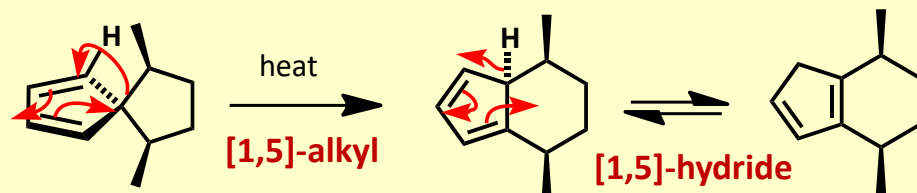


- In acyclic systems, 1,5-hydride shifts can be much slower:



• [1,5]-Alkyl shifts

- thermally suprafacial reactions
- ...with retention of configuration in the migrating group:



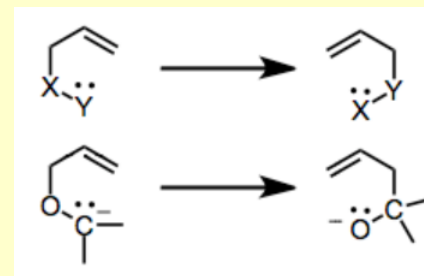
W-H approach

[2,3]-Sigmatropic rearrangements



Georg Wittig (1897-1987)

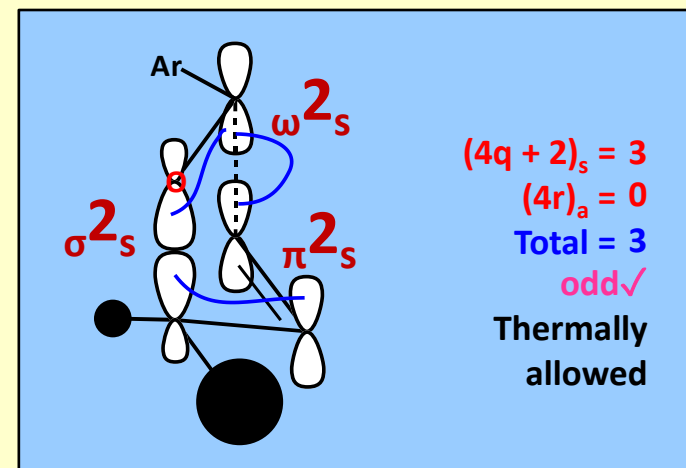
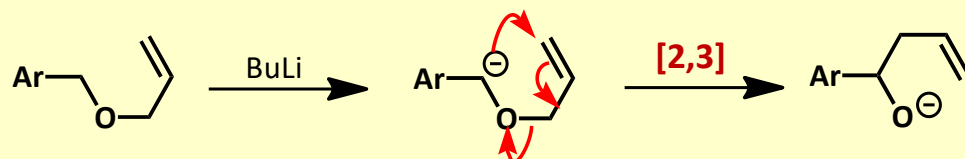
The discoverer of the Wittig reaction and also the **[2,3]-Wittig rearrangement** among other reactions. He shared a Nobel prize with Herbert C. Brown in 1979: *“for their development of the use of boron- and phosphorus-containing compounds, respectively, into important reagents in organic synthesis.”*



[2,3]-Rearrangements

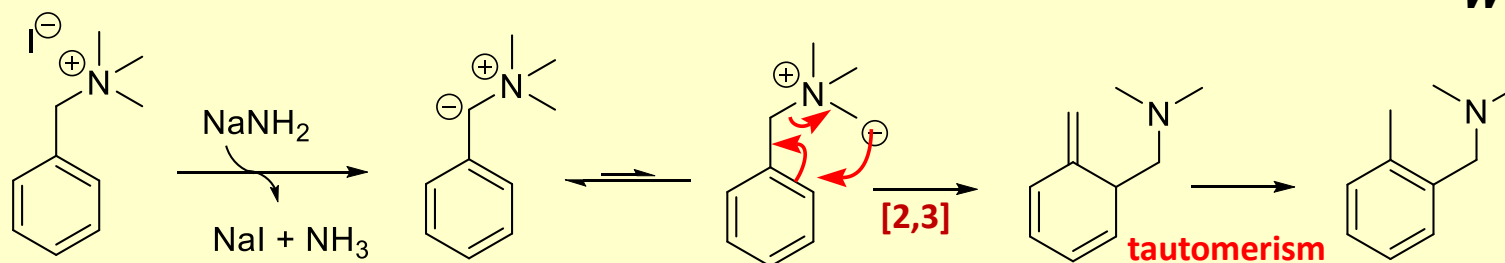
- **[2,3]-Wittig rearrangements**

- thermally suprafacial
- envelope transition state
- large groups at the allylic position -> *pseudo-equatorial* position



- **Sommelet-Hauser rearrangement**

- Thermally suprafacial:



W-H approach

- **[2,3]-Rearrangements of allyl sulfoxides (Mislow-Evans), sulfinimines and sulfonium ylids**

- thermally suprafacial (see lecture 4 for FMO and W-H analysis):

