CHEM95002:
Orbitals in Organic Chemistry - Stereoelectronics

LECTURE 3 *Stereoelectronics of Transition States – Familiar Reactions under Kinetic Control*

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Format & scope of lecture 3

- ***Thermodynamic vs. Kinetic Control***
  - Stereoelectronics of products *vs.* transition states
  - Thermodynamic control: Ley spiroacetal formation
  - Kinetic control: 1,2-diaxial processes
- ***Ring-closure Reactions***
  - Baldwin's rules
- ***Reactions of the Carbonyl Group***
  - Nucleophilic addition to carbonyls (Bürgi-Dunitz angle)
  - Deprotonation α to carbonyls – enolate formation
    - Stereoselective lithium enolate formation

Themodynamic *vs.* kinetic reaction control

– *Thermodynamic control:*

- the reaction is **reversible** under the conditions & so **equilibrium** is attained between starting materials & products.

- the **most stable product predominates:**

stereoelectronic analysis of PRODUCTS required
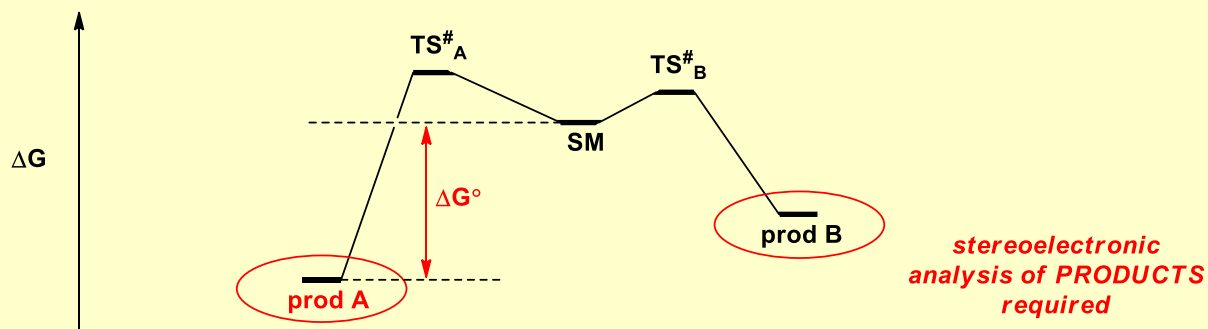
– *Kinetic control:*

- the reaction is **irreversible** under the conditions & so the transition state represents a 'point of no return'

- the **most rapidly formed product predominates** (*i.e.* that reached *via* the lowest energy transition state):

*stereoelectronic analysis of TRANSITION STATES required*
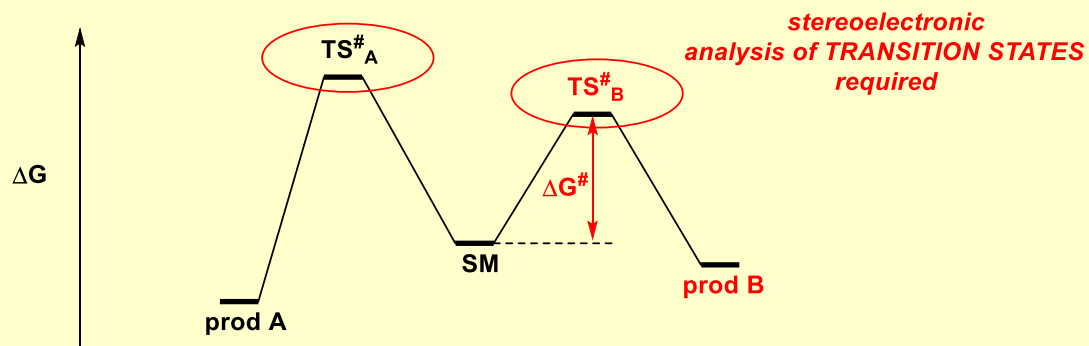
HAMMOND'S POSTULATE:

the starting material, intermediate or product CLOSEST IN ENERGY to the transition state of interest will be most similar in structure.

SM closest in energy -> early TS$^{\#}$
Prod closest in energy -> late TS$^{\#}$

Thermodynamic control – *e.g. Ley 'dispoke' protection*

- *Reaction of **1,2-Diols** with a **bis-enol ether** to give **dispiroketals***
  - The dispiroketal forms as a single diastereomer as the result of its formation being under ***thermodynamic control***. The ***product is stabilised by multiple anomeric effects*** (Deslongchamps theory)
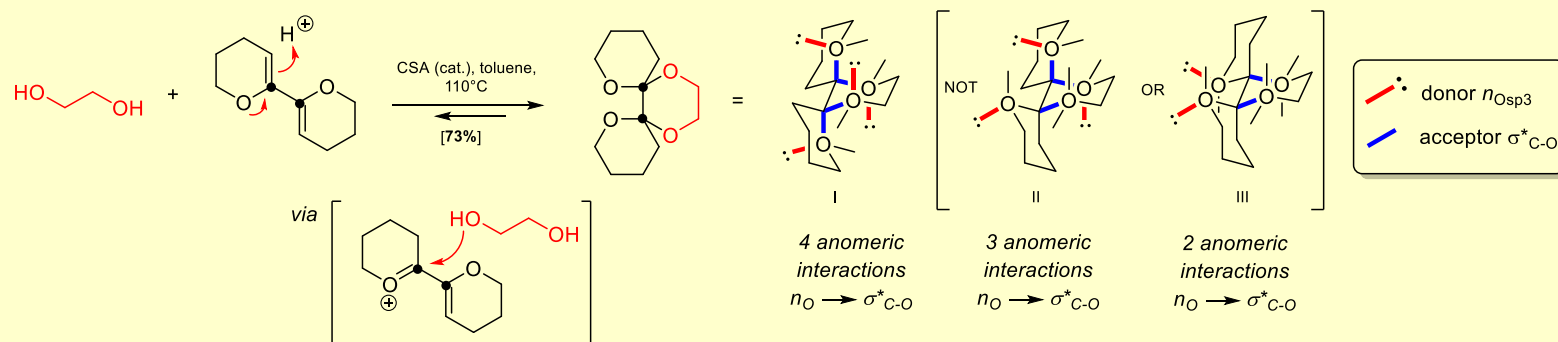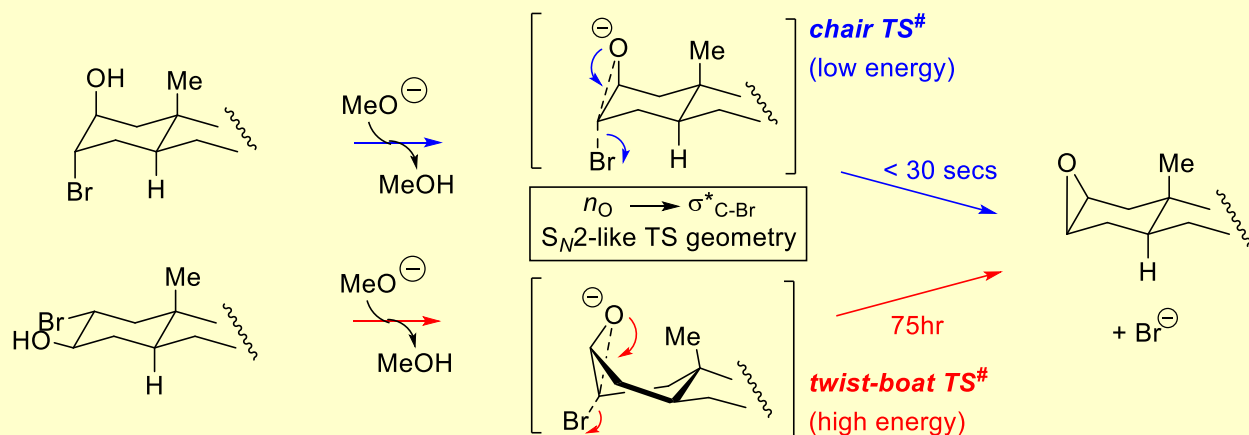

- used *e.g.* for ***selective protection of di-equatorial 1,2-diols*** (over 1,3-, 1,2-di-axial & 1,2-axial/equatorial diols)
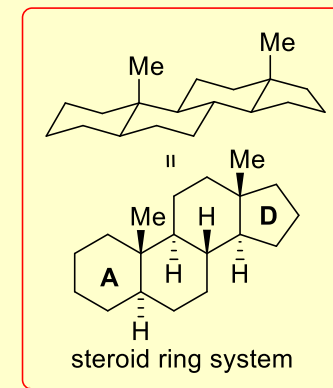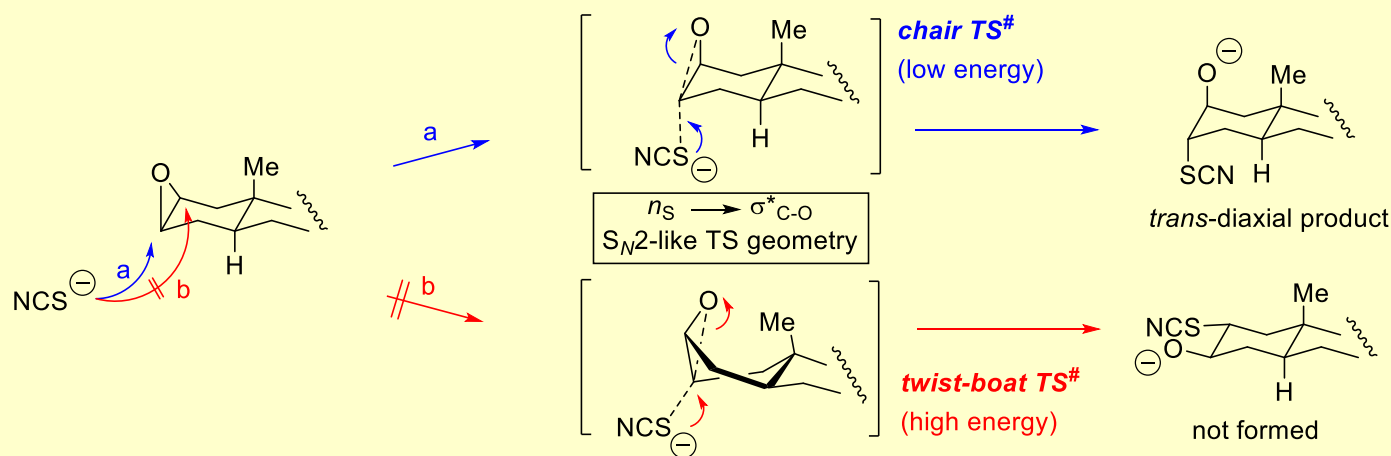

NB. most nucleophilic, primary alcohol is NOT protected
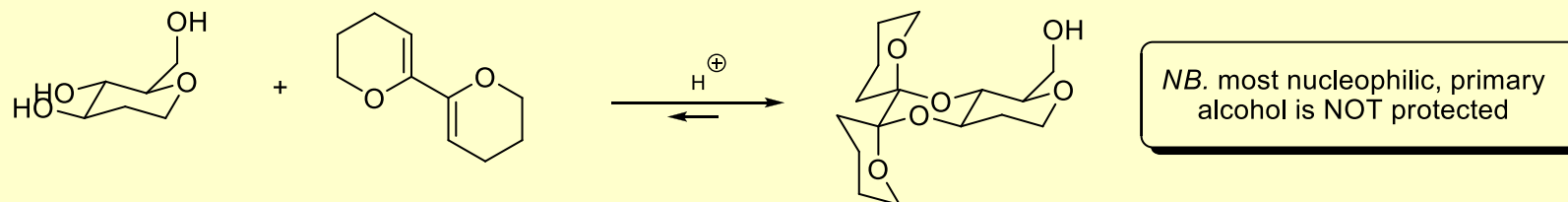
  - S. V. Ley *et al.* 'Dispiroketals: a new functional group for organic synthesis' *Contemp. Org. Synth.* **1995**, *2*, 365 [**DOI**]

Kinetic Control – *1,2-diaxial processes*

- *Attainment of anti-periplanar overlap of orbitals in 1,2-disubstituted* **cyclohexanes:**
  - **epoxide formation**: *e.g.* in A-ring of steroids (*NB.* No-ring flipping possible – rigid framework)

chair TS[#] (low energy)

$n_O \longrightarrow \sigma^*_{C-Br}$
S_N2-like TS geometry

< 30 secs

75hr

twist-boat TS[#] (high energy)

+ Br⁻

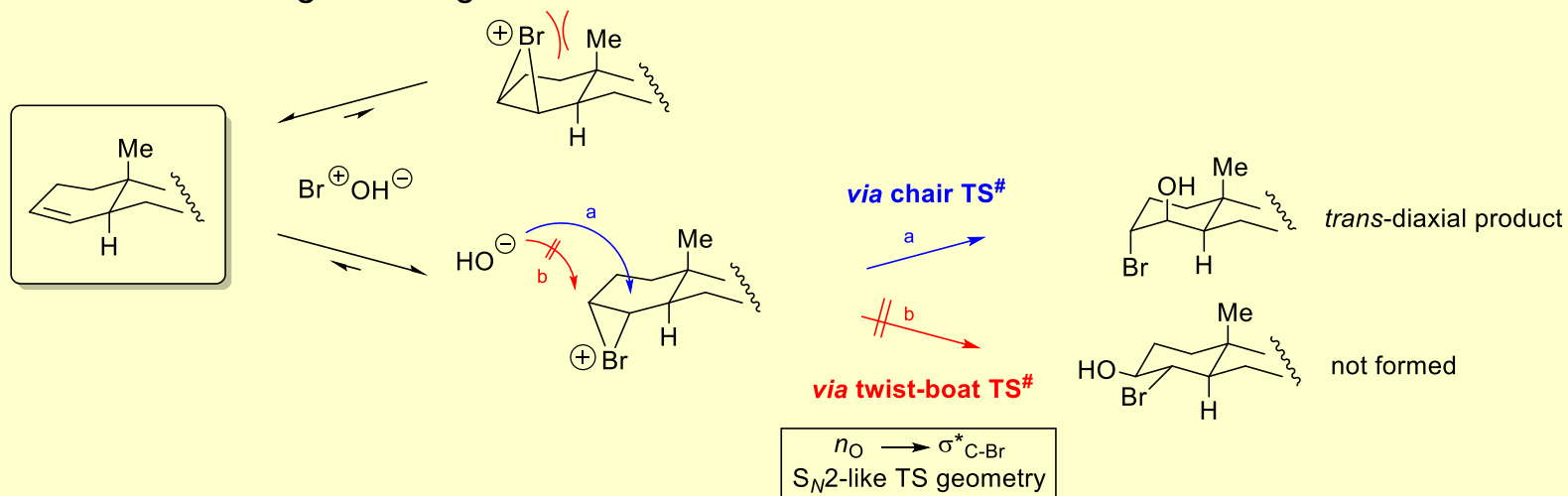 - **epoxide ring-opening**: *e.g.* in A-ring of steroids
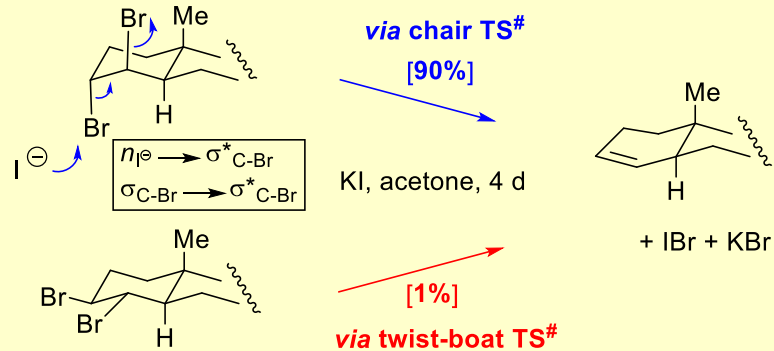   - Diaxial ring-opening ('Fürst-Plattner' rule) controls regioselectivity of nucleophilic attack

chair TS[#] (low energy)

$n_S \longrightarrow \sigma^*_{C-O}$
S_N2-like TS geometry

trans-diaxial product

twist-boat TS[#] (high energy)

not formed

steroid ring system

Kinetic control – *1,2-diaxial processes*

- *Attainment of anti-periplanar overlap of orbitals in 1,2-disubstituted **cyclohexanes:***
  - **HOBr addition**: *e.g.* in A-ring of steroids

via **chair TS**#

trans-diaxial product

via **twist-boat TS**#

$$n_O \longrightarrow \sigma^*_{C-Br}$$
S_N2-like TS geometry

not formed

  - **E2 elimination**: *e.g.* in A-ring of steroids

via **chair TS**#

[**90%**]

$$n_{I^\ominus} \longrightarrow \sigma^*_{C-Br}$$
$$\sigma_{C-Br} \longrightarrow \sigma^*_{C-Br}$$

KI, acetone, 4 d

+ IBr + KBr

[**1%**]

via **twist-boat TS**#

Baldwin's Rules for Ring Closure

- **_For <u>kinetically</u> controlled ring closures:_**
  - Baldwin *J. Chem. Soc., Chem. Commun.* **1976**, 734 [**DOI**] & *ibid* 736 [**DOI**] & *ibid* 738 [**DOI**]
  - For a review see: Gilmore *Chem. Rev.* **2011**, *111,* 6513 [**DOI**]
  - the relative facility of ring-closure depends critically on the ring size, the hybridisation of the reacting centres & the mode of ring-closure (*exo* or *endo*)

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nomenclature

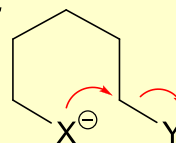***Exo*** - the bond being broken in the ring closure is exocyclic *i.e.* outside the ring
Endo - the bond being broken in the ring closure is endocyclic *i.e.* inside the ring
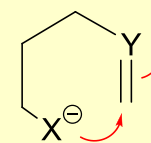***Tet*** - electrophilic centre has sp^3 hybridisation
Trig - electrophilic centre has sp^2 hybridisation
Dig - electrophilic centre has sp hybridisation
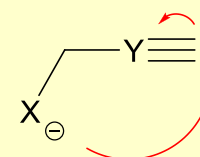
e.g.

6 - exo - tet   **6 - endo - trig**   **4 - endo - dig**

- tetrahedral systems:
  - 3 to 7-*exo-tet* are all favoured processes
  - 5 to 6-*endo-tet* are disfavoured

- trigonal systems:
  - 3 to 7-*exo-trig* are all favoured processes
  - 3 to 5-*endo-trig* are disfavoured; 6 to 7-*endo-trig* are favoured

- digonal systems:
  - 3 to 4-*exo-dig* are disfavoured processes; 5 to 7-*exo-dig* are favoured
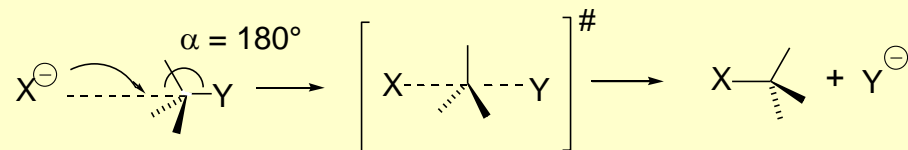 - 3 to 7-*endo-dig* are favoured

Baldwin's Rules for Ring Closure cont.

- ***Baldwin's rules were formulated following analysis of transition state geometries:***
  - Baldwin *J. Chem. Soc., Chem. Commun.* **1976**, 734 [**DOI**] & *ibid* 736 [**DOI**] & *ibid* 738 [**DOI**]
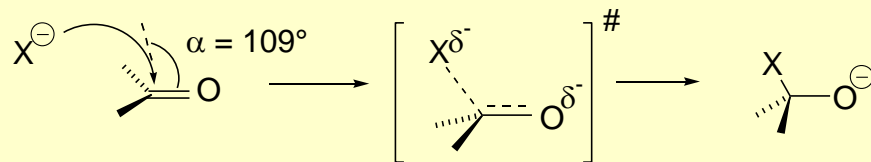
  - ***Tet*** - *electrophilic centre has sp³ hybridisation - S_N2 reaction*
    - evidence for this trajectory see: Eschenmoser *Helv. Chim. Acta* **1970**, *53*, 2059 [**DOI**]

$$X^{\ominus} \cdots\cdots \overset{\alpha = 180°}{\diagdown}Y \longrightarrow \left[X\cdots \diagdown \cdots Y \right]^{\#} \longrightarrow X\diagup\diagdown + Y^{\ominus}$$
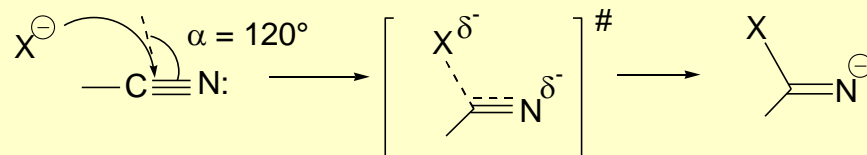
  - ***Trig*** - *electrophilic centre has sp² hybridisation - Nucleophilic addition to carbonyl/imine*
    - evidence for this trajectory see: Burgi *J. Am. Chem. Soc.* **1973**, *95*, 5065 [**DOI**] & Proctor & Dunnitz *Helv. Chim. Acta* **1981**, *64*, 471 [**DOI**]

$$X^{\ominus} \overset{\alpha = 109°}{\diagdown}=O \longrightarrow \left[X^{\delta-} \cdots O^{\delta-} \right]^{\#} \longrightarrow X \diagdown O^{\ominus}$$

  - ***Dig*** - *electrophilic centre has sp hybridisation - Nucleophilic addition to nitrile/alkyne*
    - evidence for this trajectory see: Procter *Helv. Chim. Acta* **1978**, *61*, 2538 [**DOI**] & **1981**, *64*, 471 [**DOI**]

$$X^{\ominus} \overset{\alpha = 120°}{—C}\equiv N: \longrightarrow \left[X^{\delta-} = N^{\delta-} \right]^{\#} \longrightarrow X \diagdown = N^{\ominus}$$

Nucleophilic attack on carbonyl functions

- **What orbitals are involved?**
  - A donor orbital on the nucleophile [typically a lone pair (n)] and the $\pi^*_{C=O}$ orbital of the carbonyl group
  - Recall the orbital co-efficient situation for a $\pi^*_{C=O}$ orbital:
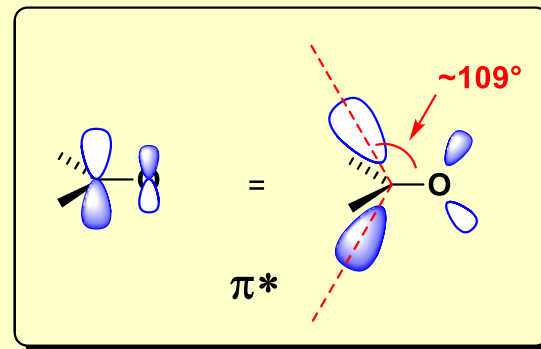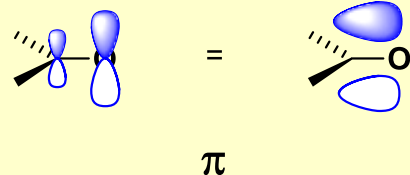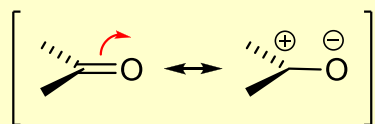

- **The Bürgi-Dunitz trajectory**
  - It follows that, at close range, a nucleophile will attack the carbonyl carbon along a trajectory that maximises overlap – the so-called **Bürgi-Dunitz trajectory** (Bürgi *J. Am. Chem. Soc.* **1973**, *95*, 5065 [**DOI**] & *Tetrahedron* **1974**, *30*, 1563 [**DOI**])
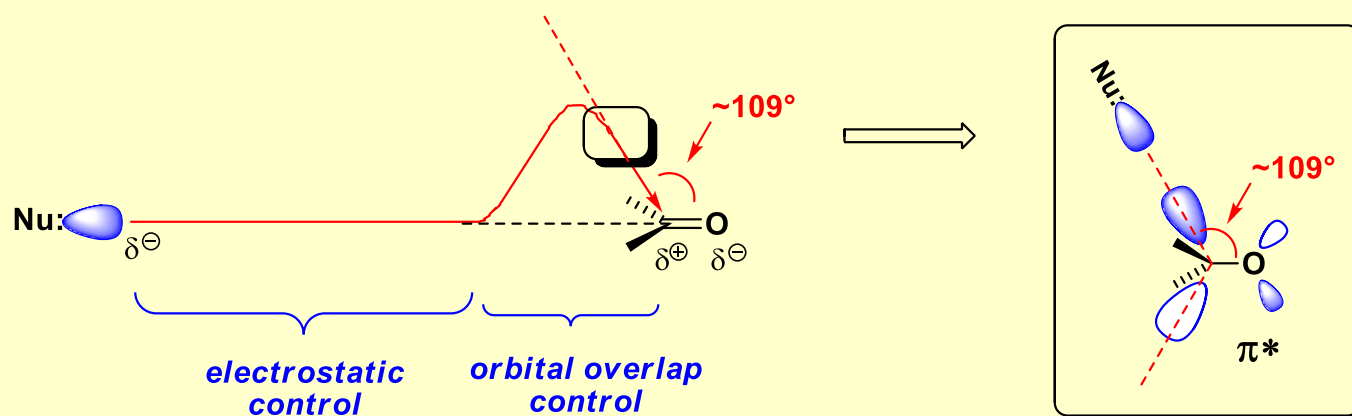
Enolisation of carbonyl functions

- **Enolisation is under stereoelectronic control**
  - This was first proposed in 1956 as 'CH-π overlap effect': Corey *J. Am. Chem. Soc.* **1956**, *78*, 6269 [**DOI**]
  - The essential requirement is that the σ_{C-H} bond α to the carbonyl must adopt a conformation *perpendicular* to the plane of the carbonyl for deprotonation to occur [*i.e.* to allow $\sigma_{C-H} \rightarrow \pi^*_{C=O}$ (pp)]
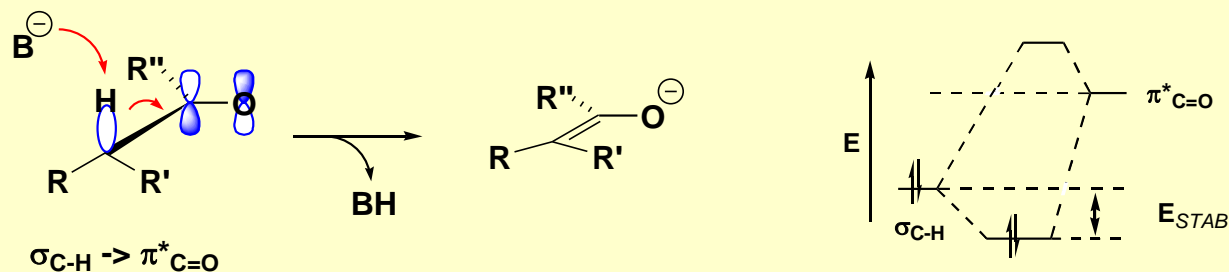

- **Evidence:**
  - Deporotonation of norcamphor at the *exo*-hydrogen is favoured over that at the *endo*-hydrogen by a factor of >700: Houk *J. Org. Chem.* **2000**, *65*, 8970 [**DOI**]
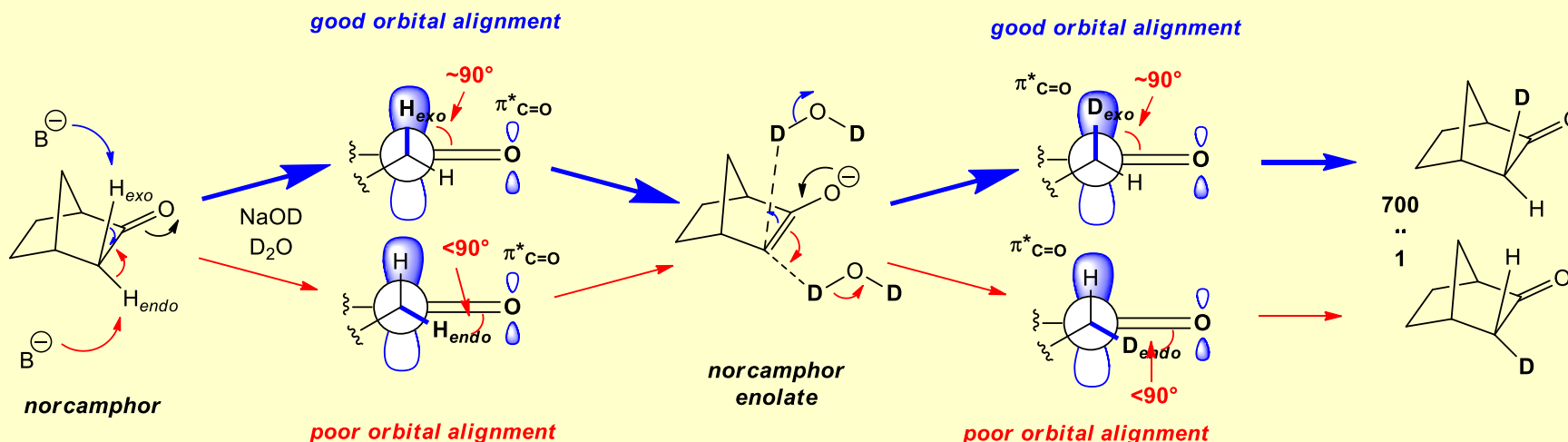
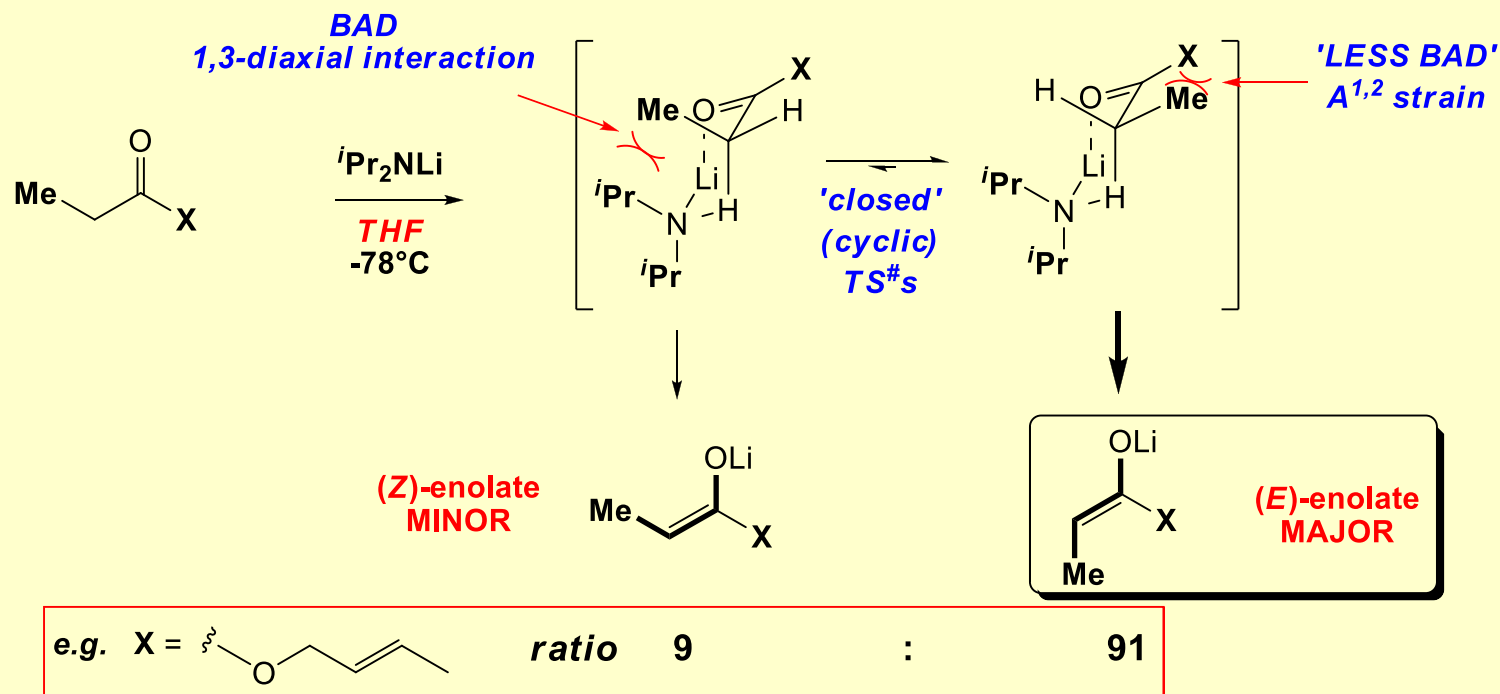# Stereoselective Li enolate formation - (E) vs (Z) stereochemistry

- **Lithium enolates of esters & ketones:**

  - When an enolate is formed there are often two different stereoisomers that can be formed depending on which α proton is removed: the (*E*)- or *trans* enolate and the (*Z*)- or *cis* enolate

  - For the formation of **lithium enolates** using **lithium amide bases** (*e.g.* lithium diisopropylamide, LDA) in THF, a six-membered chair-like 'closed' TS for deprotonation is expected and two competing factors dictate enolate geometry: $A^{1,2}$-**strain** and **1,3-diaxial interactions**:
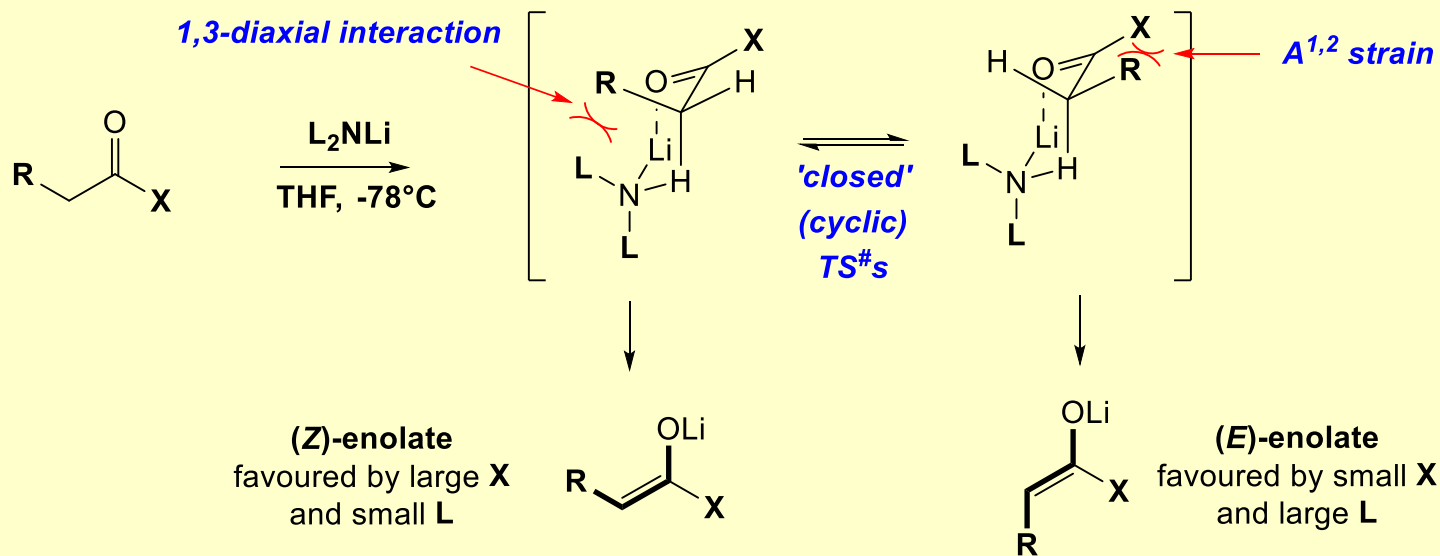
(*E*)-Selective Li-enolate formation

- **(E)-Lithium enolates of esters & ketones** (*via* closed TS# with small X group):

  - Lithium amide bases used in enolisation generally have bulky substituents (*e.g.* 2 × *i*Pr groups in the case of LDA; 2 × TMS groups in the case of LiHMDS) – this, and performing the reaction at low temperature, ensures that the reagent acts as a **base** and NOT as a **nucleophile**
  - Consequently, the **1,3-diaxial interactions** (which involve these substituents) generally override the $A^{1,2}$-**strain** for enolisation of standard esters & ketones (*e.g.* **X = Me or OMe**).
  - This leads to the predominant formation of **(E)-enolates** when using LDA in THF at -78°C:

(Z)-Selective Li enolate formation

- **(Z)-Lithium enolates of esters & ketones** [*via* closed TS# with large X group OR *via* open TS#]:

  - Substrates containing very **bulky X groups** (*e.g.* **X** = *t*Bu or an **Evans oxazolidinone**) will lead to predominant formation of (Z)-enolates when using LDA in THF at -78°C because the $A^{1,2}$-**strain** now overrides the **1,3-diaxial interactions** in the '**closed' TS**

  - However, when using LDA at -78°C in a **mixed solvent system** of THF & hexamethylphosphoroustriamide (HMPA) even standard esters & ketones give predominant formation of **(Z)-enolates** because the HMPA strongly co-ordinates to the lithium cation breaking up the 'closed' TS and leading to an '**open' TS**
  - This removes the 1,3-diaxial interaction leaving the $A^{1,2}$ **strain** as the dominant/only factor: