CHEM60001:
An Introduction to Reaction Stereoelectronics

LECTURE 4 *Chemistry of the Carbonyl Group*

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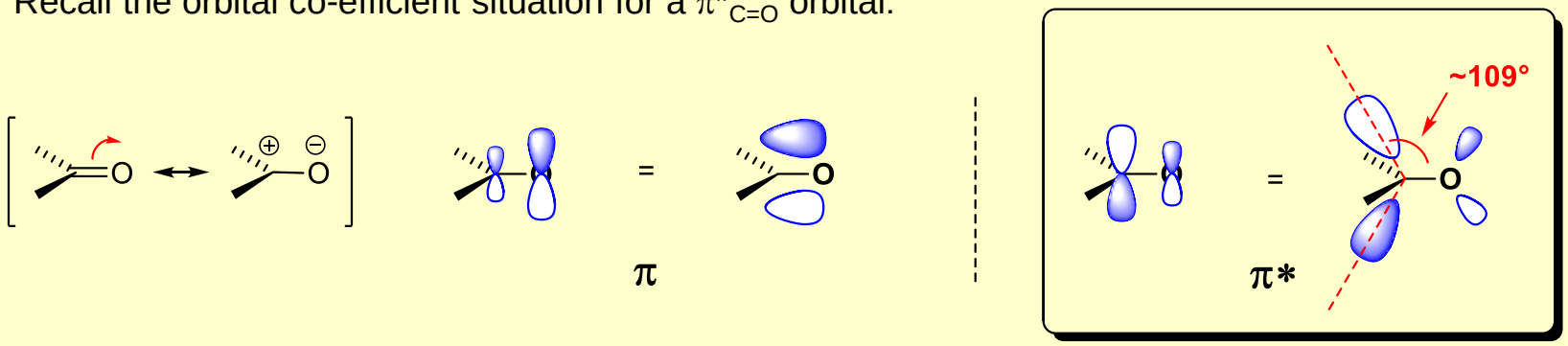
Format & scope of lecture 3

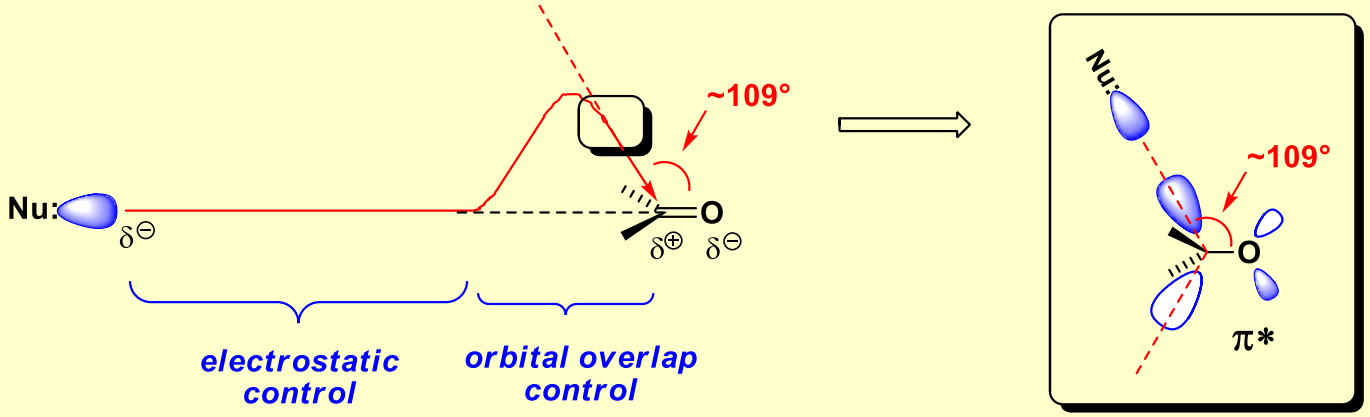
- ***Reactions of the Carbonyl Group***
  - Nucleophilic addition to carbonyls (Bürgi-Dunitz angle)
  - Felkin-Anh model for diastereoselective addition to α-chiral carbonyl compounds
  - Deprotonation α to carbonyls – enolate formation
    - Stereoselective lithium enolate formation

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:

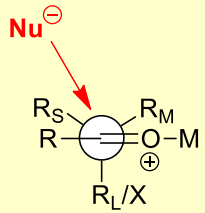


- ***The Bürgi-Dunitz trajectory***
  - It follows that, at close range, a nucleophile will attack the carbonyl carbon along a trajectory that maximises overlap – the so-called ***Bürgi-Dunitz trajectory*** (Bürgi *J. Am. Chem. Soc*. **1973**, *95*, 5065 [DOI] & *Tetrahedron* **1974**, *30*, 1563 [DOI])



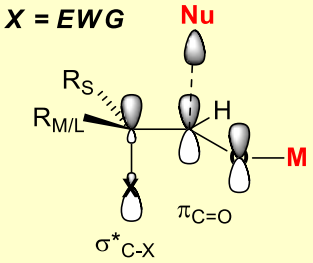
Diastereoselective addition to α-chiral carbonyls

- ***The Felkin-Anh Model:***
  - ***Review:*** Reiser *Chem. Rev*. **1999**, *99*, 1191 [DOI]; O'Brien *Tetrahedron*, **2011**, *67*, 9639 [DOI]
  - Felkin *Tetrahedron Lett.* **1968**, *9*, 2199 [DOI]; Anh *Nouv. J. Chem*. **1977**, *1*, 61.



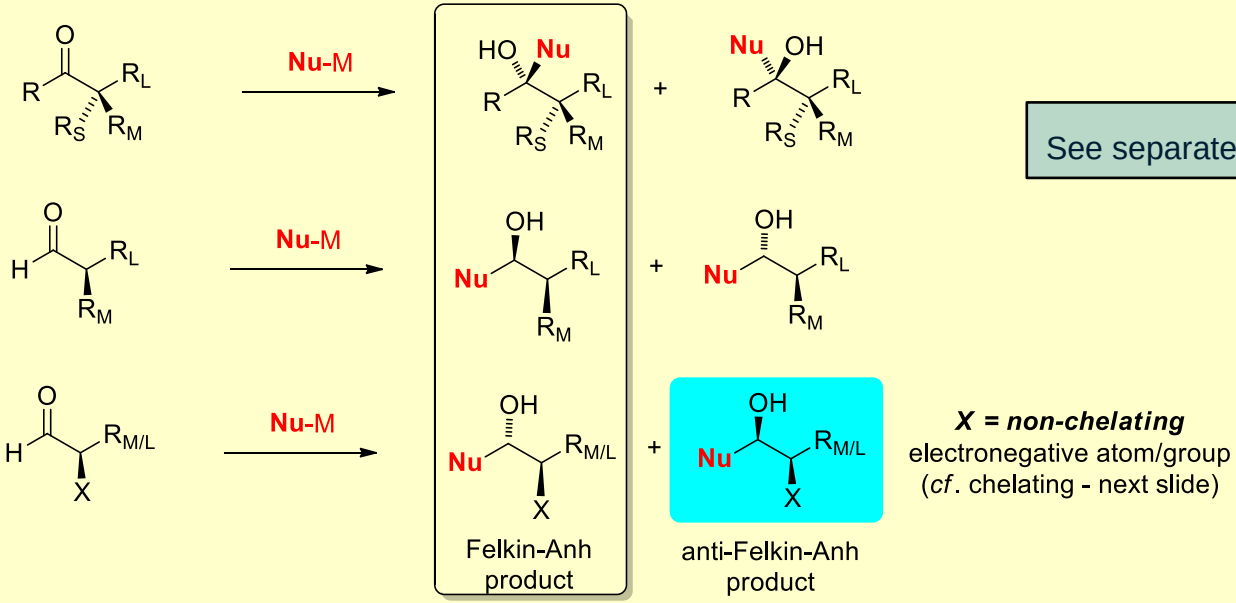
R_L = bulkiest group
X = electronegative atom/group "polar-Felkin-Anh"

Features:
1) R_L/X perpendicular to carbonyl
2) **Nu** approaches over R_S at Burgi-Dunitz angle
3) R_S distal to carbonyl irrespective of size of R (even R = H) to facilitate approach of **Nu**



best acceptor σ* orbital perpendicular to C=O
n_{Nu} -> σ^*_{C-X}
$\pi_{C=O}$ -> σ^*_{C-X}

- Applicable to:

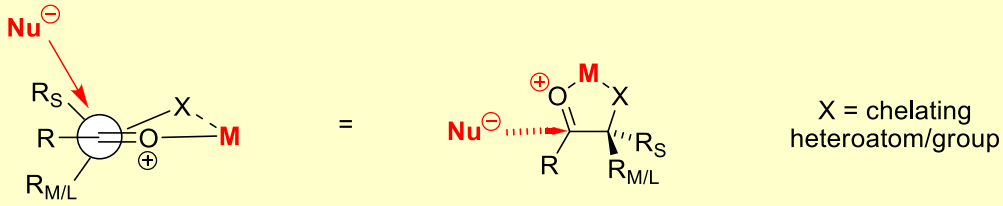


See separate handout for details

X = non-chelating
electronegative atom/group
(*cf*. chelating - next slide)

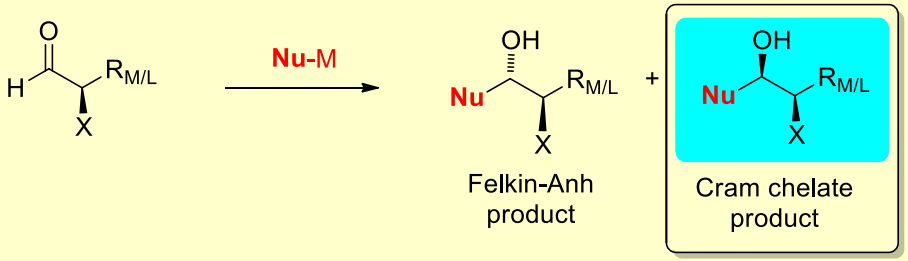
Diastereoselective addition to α-chiral carbonyls

- ***The Cram Chelate Model:***
  - ***Review:*** Reetz *Angew. Chem. Int*. Ed. **1984**, *23*, 556 [DOI]
  - Cram *J. Am. Chem. Soc.* **1959**, *81*, 2748 [DOI]



X = chelating heteroatom/group

  - Applicable to:



X = chelating heteroatom/group

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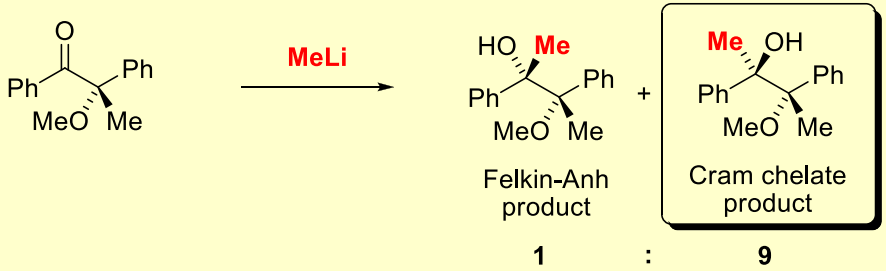
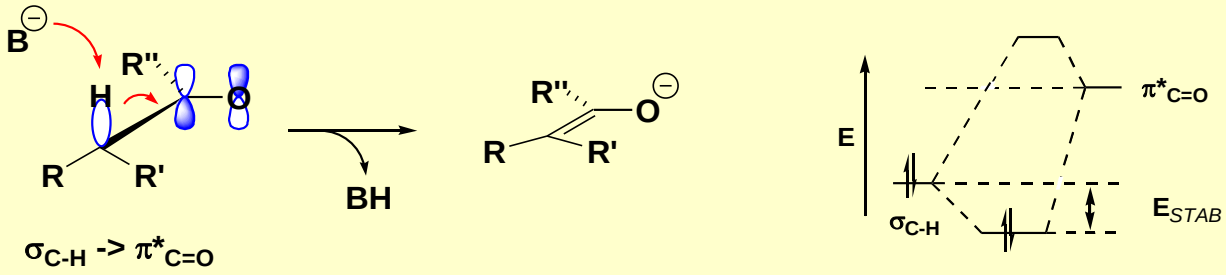
  - Example:

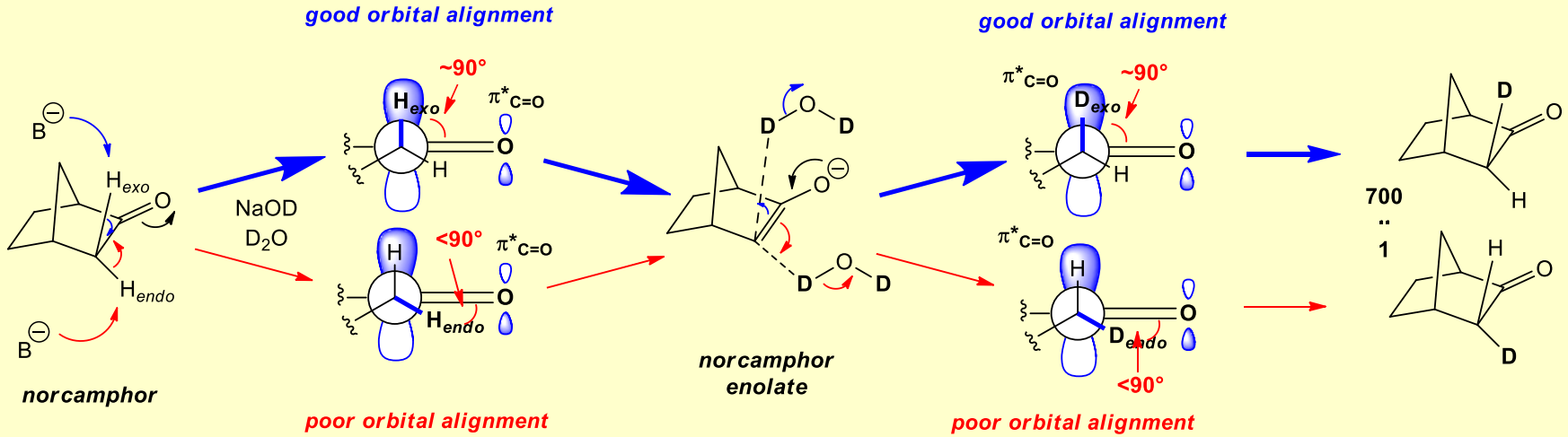


Enolisation of carbonyl functions

- ***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 $\sigma_{C\text{-}H}$ bond α to the carbonyl must adopt a conformation *perpendicular* to the plane of the carbonyl for deprotonation to occur [*i.e.* to allow $\sigma_{C\text{-}H} \rightarrow \pi^*_{C=O}$ (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]

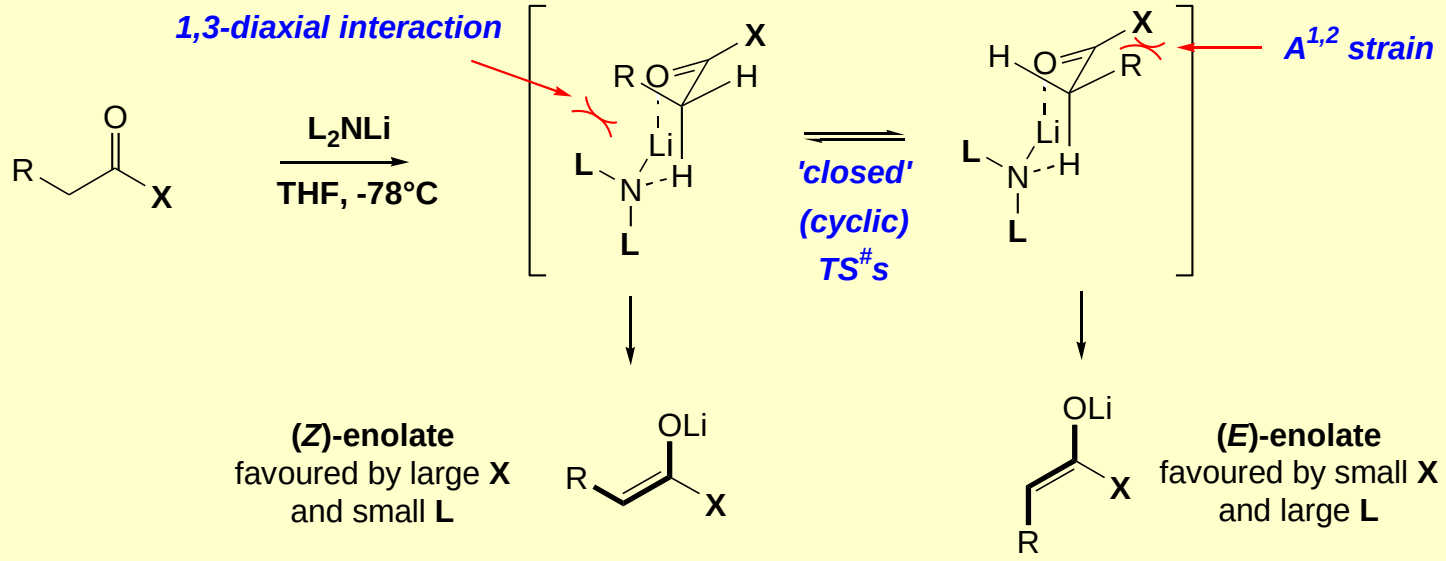


Stereoselective Li enolate formation - *(E) vs (Z) stereochemistry*

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

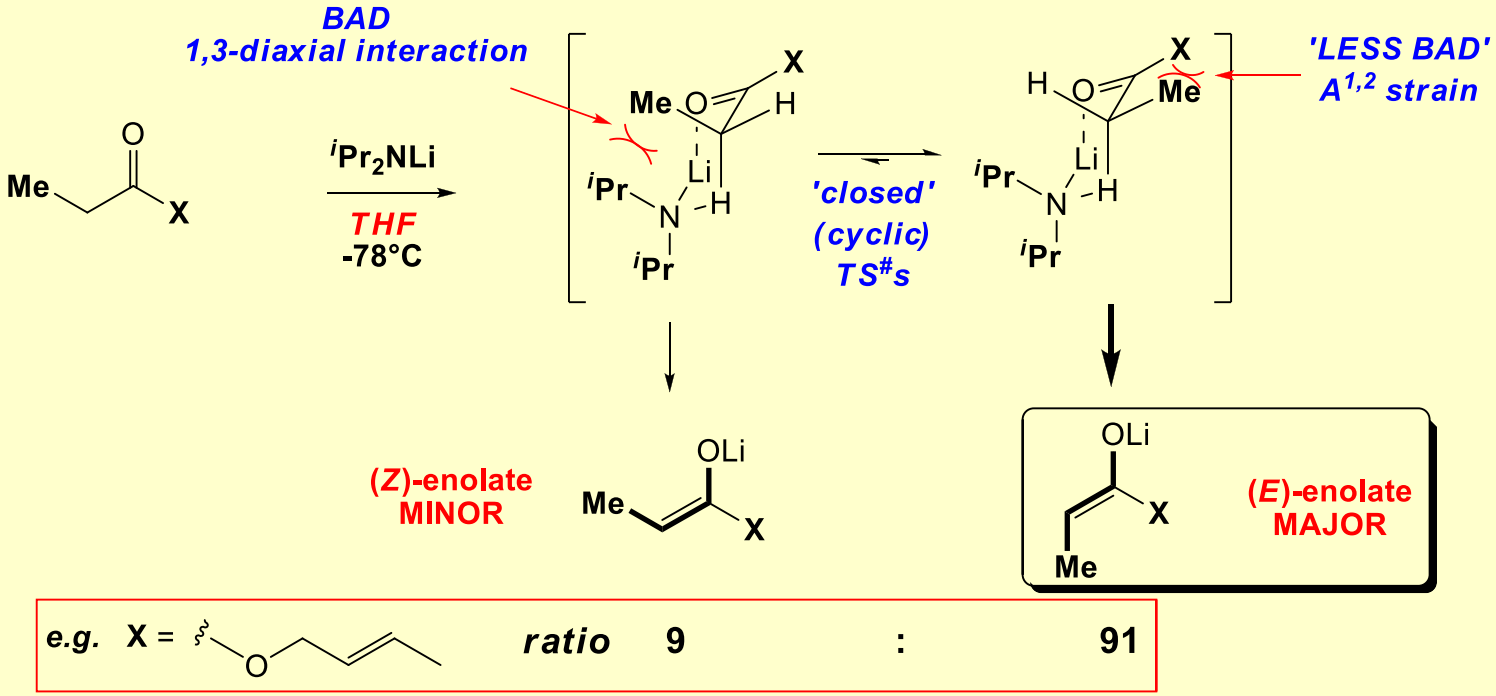
  – When an enolate is formed there are often two different stereoisomers that can be formed depending on which α proton is removed: the (*E*)- or *trans* enolate and the (*Z*)- or *cis* enolate

  – 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 R 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 factor: