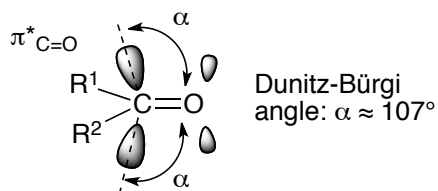


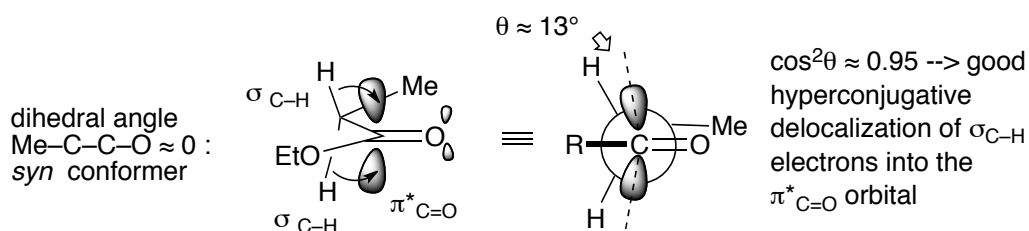
## CHEM 330

### Topics Discussed on Nov. 9

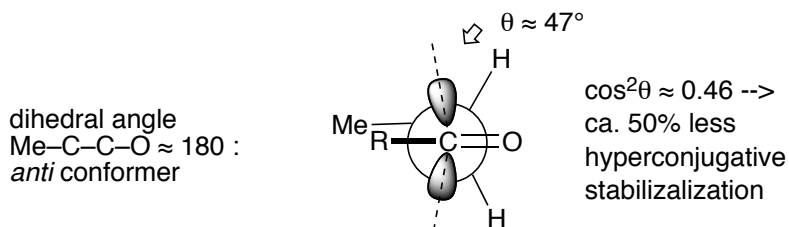
Dunitz-Bürgi angle: the angle of ca.  $107^\circ$  between the axes of the C-lobes of a  $\pi^*_{C=O}$  orbital and the axis of the  $\sigma_{C=O}$  bond:



Rationale for the preference for a syn (eclipsed) conformation in carbonyl compounds: more efficient  $\sigma_{C-H} \rightarrow \pi^*_{C=O}$  hyperconjugation:



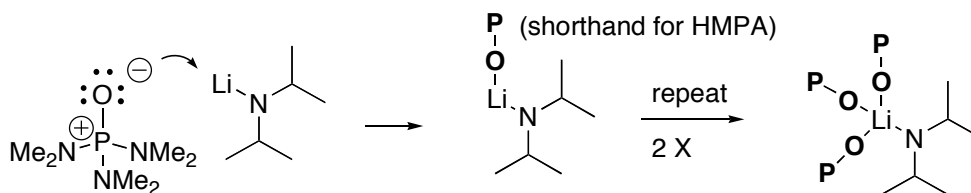
whereas:



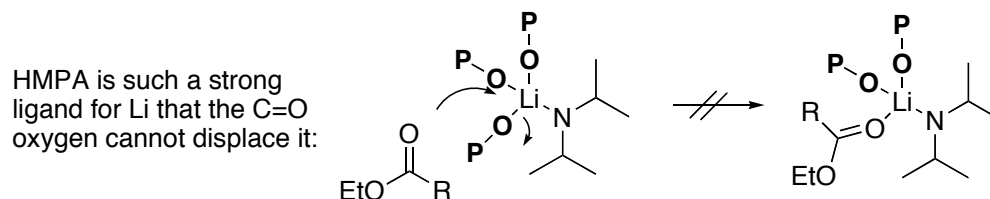
Formation of *Z* enolates by deprotonation of an ester under conditions that do not perturb the innate conformational preferences of the substrate

Mechanistic model (**NOT** "mechanism") for *Z*-enolate formation:

- (i) deprotonation must occur through a mechanism that involves **no preliminary interaction between reagent and substrate**. This may be achieved by coordinating the Li ion with a ligand so powerful that the ester C=O group will be unable to displace it from the metal.
- (ii) strong coordination Li-HMPA

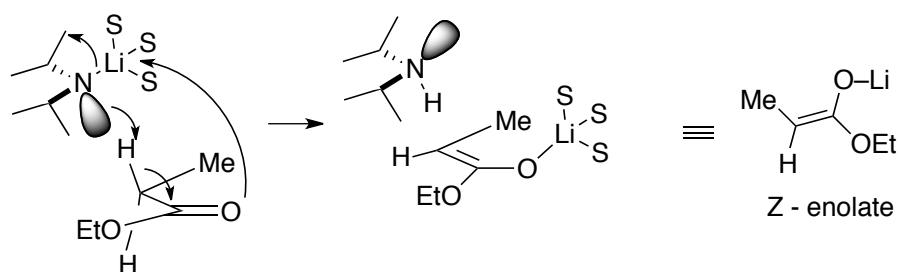


(iii) suppression of Lewis acid-base interactions between Li ligated by HMPA and carbonyl oxygen



(iv) possible intervention of "naked" forms of LDA in the presence of HMPA

(v) deprotonation through a non-associated transition state (no preliminary interaction between reagent and substrate before bond reorganization):



Description of the above technique as the Ireland method for Z-enolate formation

Tightly bound (closed, highly associated) transition state: one during which reacting molecules are tightly held together by non-covalent interactions that take place *prior to the main bond reorganization event*.

**Examples of reactions that are believed to proceed via a tightly bound transition state:**

- (i) Zimmermann-Traxler aldol reaction of enolates containing strongly oxophilic metals
- (ii) Deprotonation of carbonyl compounds with LDA

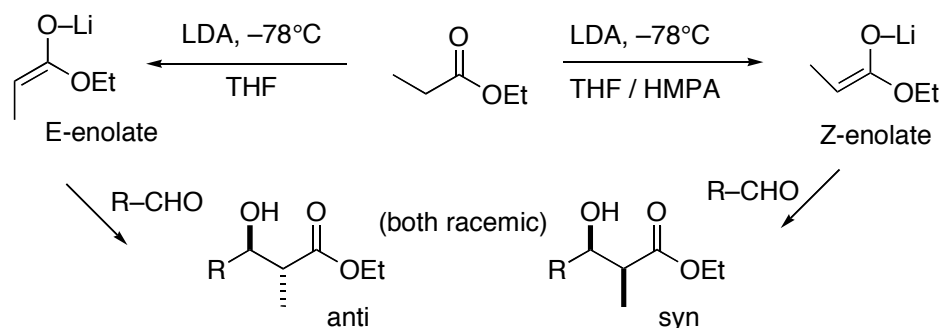
Non-associated (or extended, or open, or Yamamoto-type) transition state: one during which no interaction subsists between reacting molecules prior to the main bond reorganization event.

**Examples of reactions that are believed to proceed via a non-associated transition state:**

- (i) Ireland deprotonation of esters with LDA/HMPA
- (i) Mukaiyama aldol reactions

Principle: good diastereoselectivity is often observed in organic reactions that proceed through *either* a strongly associated (= Zimmerman-Traxler-type) *or* a non-associated (= Yamamoto-type) transition state. Weak stereoselectivity may result if reactions proceed through weakly associated (= neither Zimmerman-Traxler-type nor Yamamoto-type) transition states.

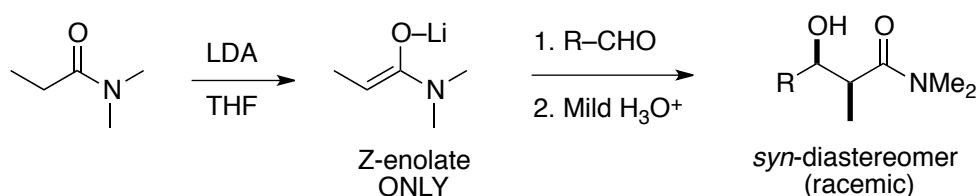
Summary: stereoselective preparation of ester enolates and their aldol reaction:



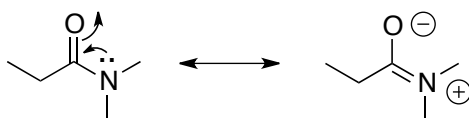
### Preparation of enolates of tertiary amides

**reminder;** primary and secondary amides undergo preferential N-deprotonation ( $\text{pK}_a$  of the N-H group  $\approx 16$ ), and the resulting anion resists further deprotonation at the carbonyl  $\alpha$ -position

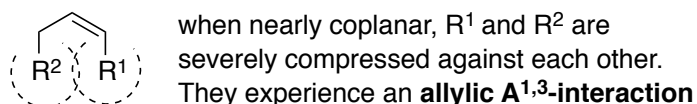
Deprotonation of tertiary amides: only Z-enolates form, due to a number of steric and conformational effects:



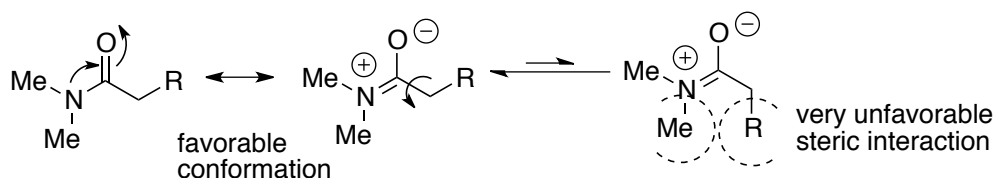
Significant double bond character between the N atom and the carbonyl C (resonance):



$A^{1,3}$  interaction: an energetic steric interaction that exists between an allylic group  $\text{R}^2$  and a *cis*-vinylic group  $\text{R}^1$  separated by 3 atomic positions when  $\text{R}^1$  and  $\text{R}^2$  are nearly coplanar:

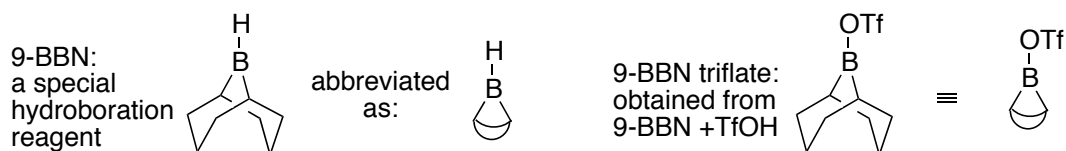


Existence of an extremely energetic,  $A^{1,3}$ -type interaction in that conformer of a tertiary amide that would lead to an E-enolate:

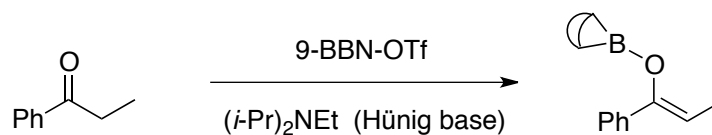


Aldol reactions of ketones: stereoselective preparation of boron enolates by the Paterson method

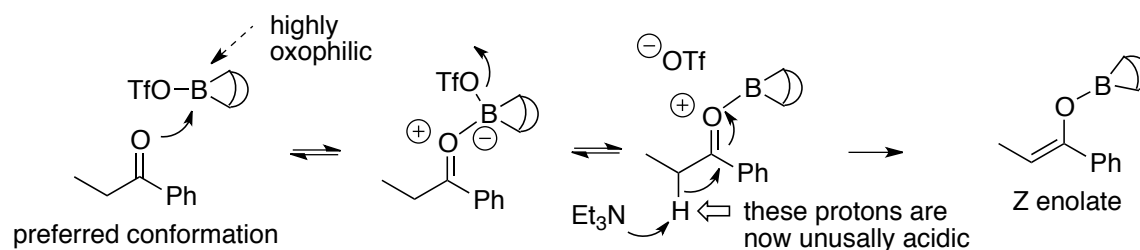
9-Borabicyclononane (9-BBN) and 9-BBN triflate:



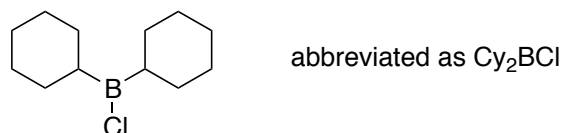
Stereoselective preparation of Z ketone enolates with 9-BBN-OTf and Hünig base, e.g:



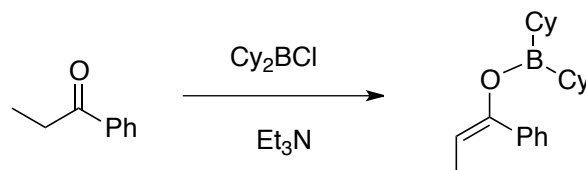
Plausible mechanism for Z-enolate formation: stereoselectivity controlled by the conformational preferences of the ketone:



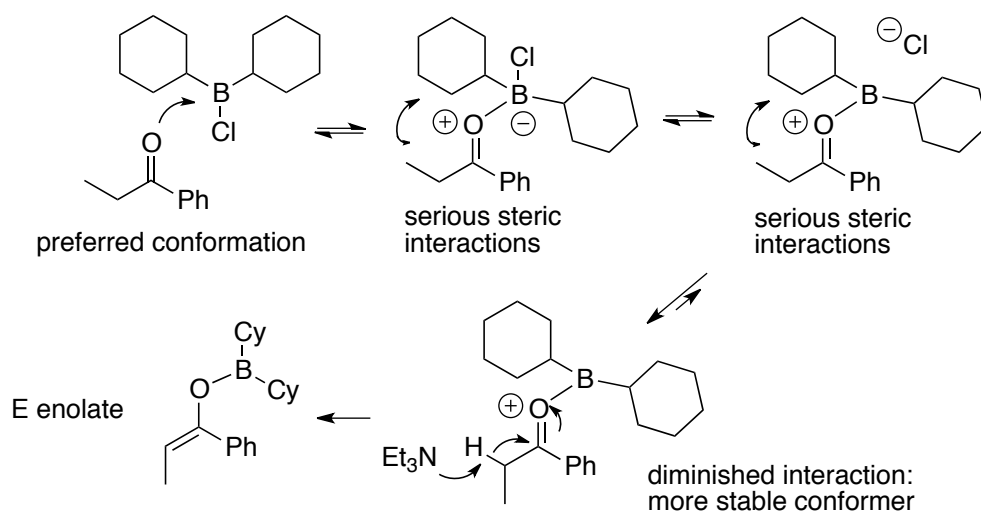
Dicyclohexyl boron chloride (= dicyclohexyl chloroborane):



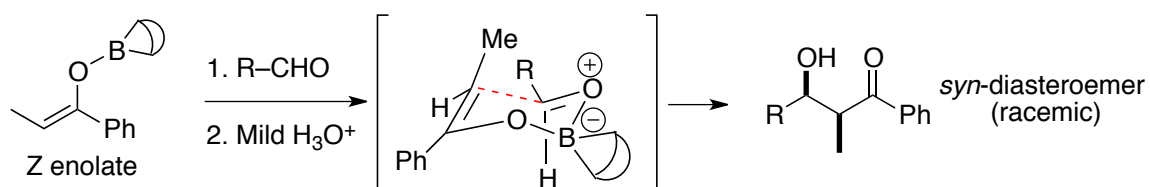
Stereoselective preparation of E ketone enolates by reaction with dicyclohexylboron chloride and Et<sub>3</sub>N, e.g.:



Plausible mechanism for E enolate formation: stereoselectivity controlled by steric interactions between the cyclohexyl groups and the alkyl groups connected to the ketone carbonyl:



Aldol reaction of a Paterson (Z)-enolate of diethylketone through a Zimmermann-Traxler type mechanism:



Aldol reaction of a Paterson (E)-enolate of diethylketone with, e.g., benzaldehyde through a Zimmermann-Traxler -type mechanism:

