

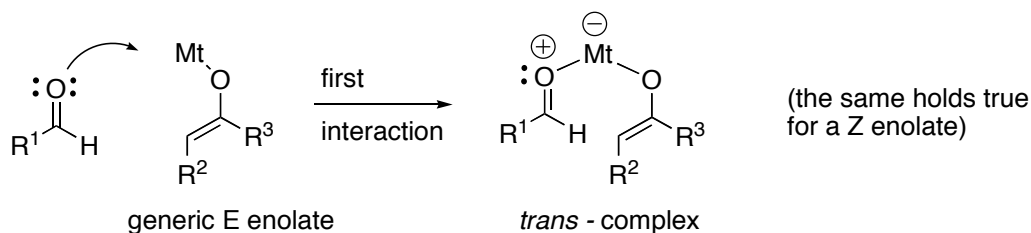
## CHEM 330

### Topics Discussed on Nov 6

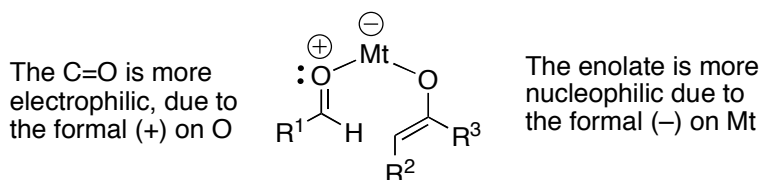
The **Zimmerman-Traxler** mechanistic model (NOT "mechanism") for a kinetically controlled aldol reaction of an achiral enolate containing an oxophilic metal with an achiral aldehyde:

First interaction between an aldehyde and an enolate containing an oxophilic metal:  
complex formation

Selective formation of the *trans*-type complex for steric reasons; e.g., with an E-enolate:



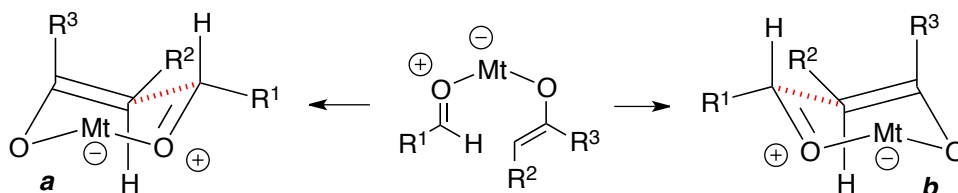
Increased electrophilicity of the aldehyde and increased nucleophilicity of the enolate as a consequence of complex formation:



"Double activation" of the aldehyde-enolate complex toward C-C bond formation due to increased electrophilicity of the aldehyde and increased nucleophilicity of the enolate

Evolution of the aldehyde-enolate complex toward a chair-like conformer that juxtaposes nucleophilic and electrophilic carbons for C-C bond formation, and in which as many groups as possible are pseudoequatorial

Existence of two enantiomeric variants of the conformation (transition state model) that permits C-C bond formation:

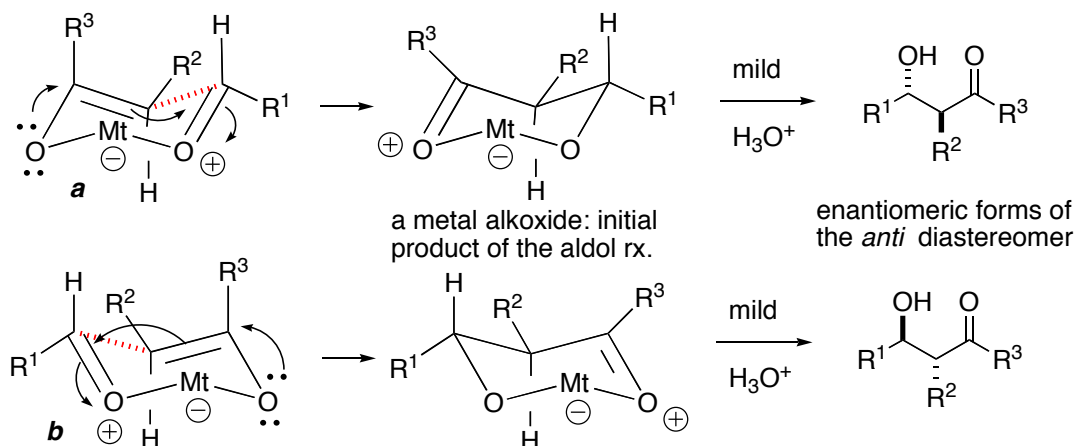


**a** and **b** are enantiomeric structures. In red: incipient C-C bond. Notice the equatorial orientation of R<sup>1</sup> and R<sup>2</sup> in these chair-like constructs

**note:** the coordination sphere of the metal is completed by an appropriate number of solvent molecules

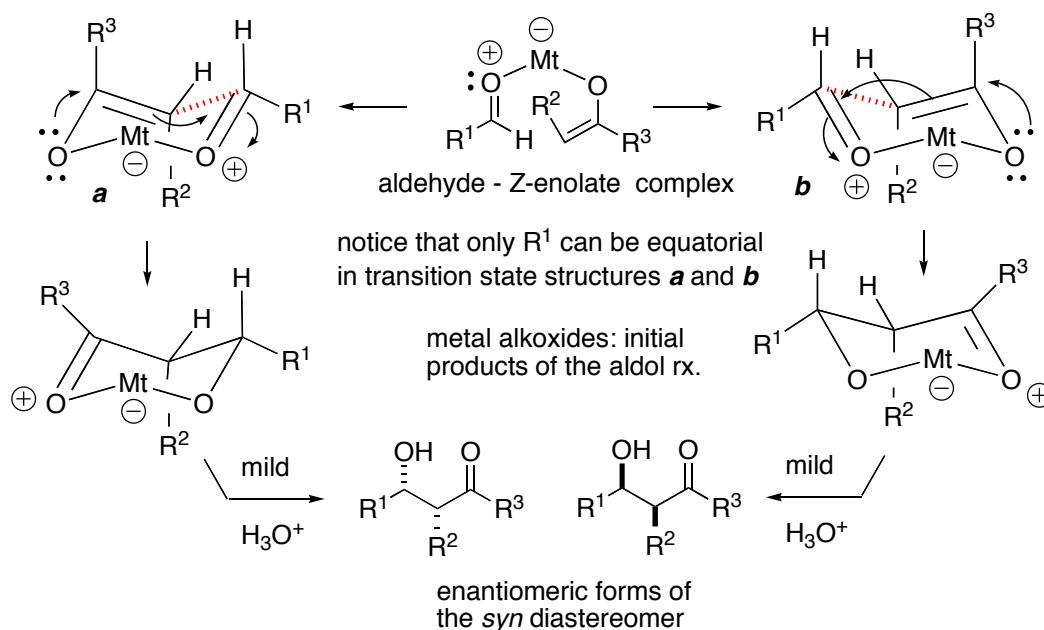
Principle: the enolate-aldehyde complex will partition equally between the two enantiomeric conformers **a** and **b** above, because **a** and **b** possess identical thermodynamic properties

C–C bond formation from structures **a** and **b** through a pericyclic mechanism (one involving a cyclic movement of electrons):



Selective formation of the racemate of the *anti* diastereomer of the aldol product in the reaction between an aldehyde and an E-enolate containing a strongly oxophilic metal such as  $\text{Li}^+$

Selective formation of the racemate of the *syn* diastereomer of the aldol product in the reaction between an aldehyde and a Z-enolate containing a strongly oxophilic metal such as  $\text{Li}^+$ , e.g.:



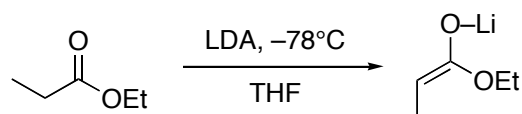
Diastereoselectivity of a kinetically controlled aldol reaction between aldehydes and enolates containing strongly oxophilic metals:

E-enolate  $\rightarrow$  *anti* aldol product

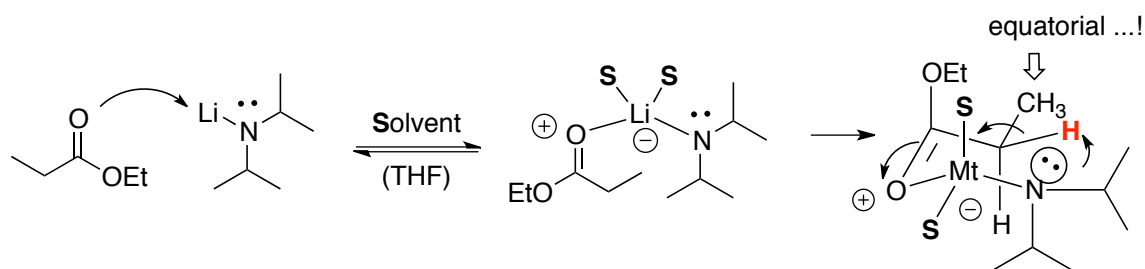
Z-enolate  $\rightarrow$  *syn* aldol product

Principle: because enolate geometry determines which diastereomer of the aldol product is going to form, it is essential to be able to create E and Z enolates diastereoselectively from any carbonyl compound.

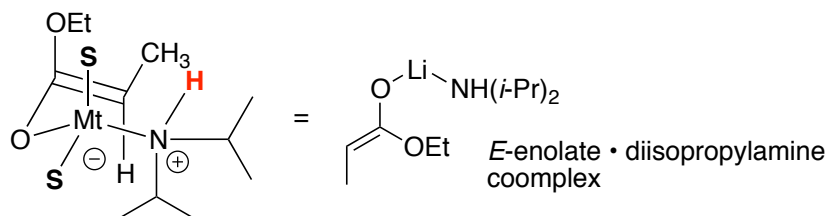
Ester enolates: stereoselective preparation of E enolates by deprotonation with LDA in tetrahydrofuran (THF), e.g.:



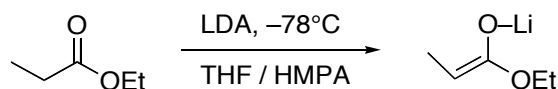
Mechanistic model (**NOT** "mechanism") for E-enolate formation:



only the "red" H is properly aligned with the  $\pi^*_{C=O}$  orbital . . .



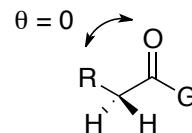
Stereoselective preparation of Z ester enolates by deprotonation with LDA in THF/HMPA: the **Ireland** method. E.g.:



**note:** HMPA (hexamethylphosphoramide) is an apolar, aprotic, strongly Lewis basic (=donor) solvent, which — unfortunately — is rather hazardous: see notes of Oct. 2.

Conformational properties of acyclic carbonyl compounds: preference for a syn (eclipsed) conformation about the  $sp^2$ - $sp^3$  C–C bond:

for the generic carbonyl compound shown on the right, the preferred conformation is the one in which the R group eclipses the carbonyl oxygen; i.e., the one in which  $\theta_{(R-C-C-O)} = 0$



R = alkyl (e.g., Me)  
G = H, alkyl, OR', NRR', etc.

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

