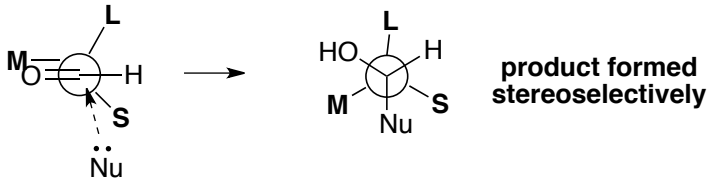
CHEM 330

Topics Discussed on Nov. 13

Generalization of the Cram-Felkin model:

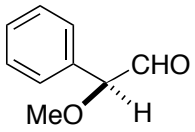
- applicable to many aldehydes possessing a stereogenic carbon at the α-position
- applicable ONLY to aldehydes possessing C or H substituents at the α-position
- description of the α-substituents as the small (**S**; typically H), medium (**M**) and large (**L**) groups (as determined by their A-value). In the Cram aldehyde, the Ph (A-value ≈ 3) is **L**, the Me (A-value = 1.8) is **M**, and the H is **S**.
- preferential reaction of such aldehydes from the favorable conformation depicted below, in which (i) a good hyperconjugative interaction subsists between **S** and the $\pi^*_{C=O}$ orbital, (ii) the O atom eclipses the **M** substituent and (iii) the approaching nucleophile interacts with **S**:



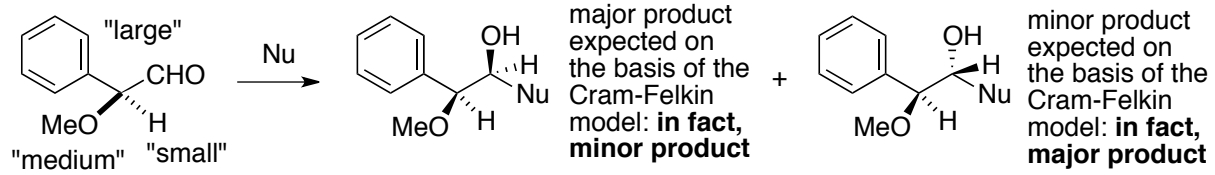
"Faciality" of a nucleophilic attack on a C=O group: description of which face, *Si* or *Re*, of the C=O system interacts preferentially with the incoming nucleophile on the basis of, e.g., the Cram-Felkin reactivity model

"Topology" of an aldol process: description of whether the reaction proceeds through a tightly bound, Zimmermann-Traxler transition state (or in accord with other reactivity models not covered in CHEM 330), and whether an E or a Z enolate is employed.

Substrate-controlled aldol reactions: case of those aldehydes in which one of the α-substituents is a heteroatom such as O, N, or halogen (F, Cl, etc.), for instance:

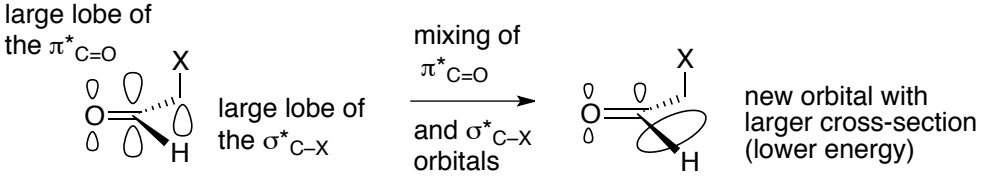


Principle: an α-heterosubstituted aldehyde, such as the one above, tends to react with nucleophiles in a manner that is *opposite* that anticipated on the basis of the Cram-Felkin reactivity model (phenyl = L; OMe = M; H = S):

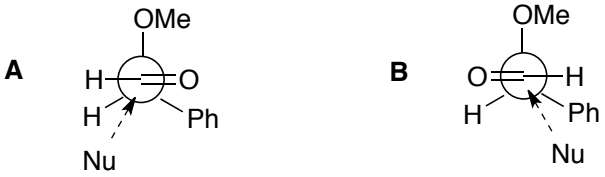


The Felkin-Anh model of nucleophilic addition to an α-heterosubstituted aldehyde:

the aldehyde is most reactive when the C–α-heteroatom σ bond (σ^*_{C-X}) bond is approximately perpendicular to the plane of the C=O group. In this manner, mixing of the σ^*_{C-X} and the $\pi^*_{C=O}$ orbitals creates a "hybrid" acceptor orbital of lower energy. This accelerates the nucleophilic addition process:

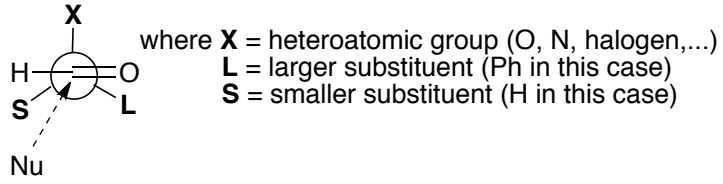


There are two conformations of the aldehyde, **A** and **B**, in which the above condition is satisfied:

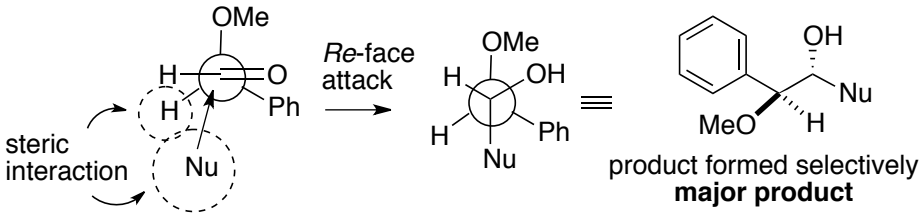


However, conformation **A** is more reactive than **B**, because it is the one that allows the least degree of steric interaction between the incoming nucleophile and the substituents at the C=O α position. Conformer **A** is also energetically favored over **B** because of greater $\sigma_{C-H} \rightarrow \pi^*_{C=O}$ hyperconjugation

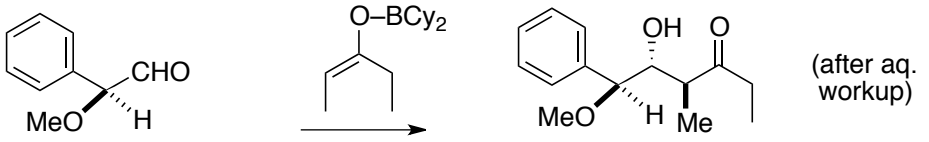
In general, an α–heterosubstituted aldehyde will be most reactive toward nucleophilic addition when it acquires the following conformation:



Preferential reaction of the aldehyde in question with a nucleophile as indicated below:



Behavior of the aldehyde in question in aldol reactions (assuming Felkin-Anh selectivity), e.g.:

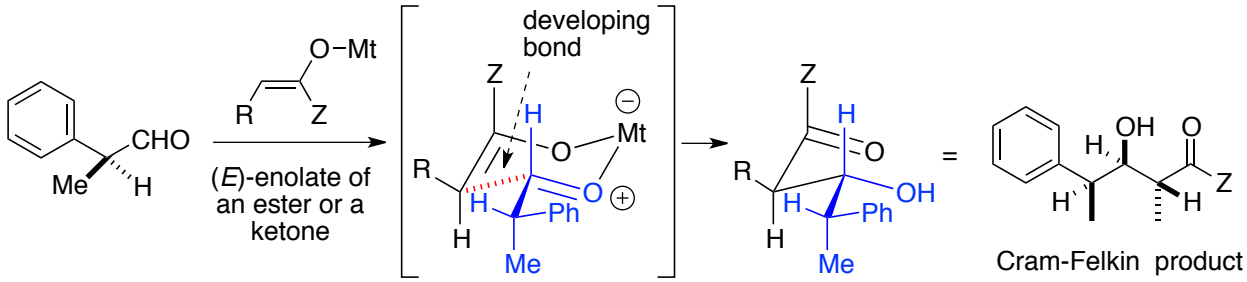


Limitations of substrate-controlled asymmetric reactions (chirality present in the substrate):

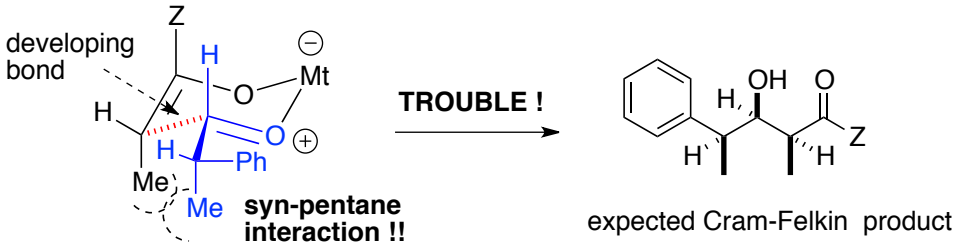
(i) the stereochemical preferences of the substrate permit the creation of only certain configurations in the products, and

(ii) effects that will not be thoroughly covered in CHEM 330 contribute to the stereochemical outcome of the process and complicate predictions based on simple models; for instance:

(a) the reaction of the Cram aldehyde and related substrates with E-enolates proceeds in accord with the Cram-Felkin reactivity model:

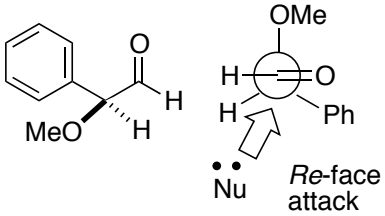


however, the reaction with *Z*-enolates may proceed with diminished – or even inverted – stereoselectivity, due to a developing *syn*-pentane interaction within a Zimmerman-Traxler transition state (cf. Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151):

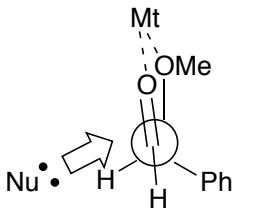


(b) the reactions of α-heterosubstituted aldehydes with enolates and other nucleophiles present the added complication that of the stereochemical outcome of the process depends on whether chelating metal ions are present in the reaction medium:

For the given configuration of the α-carbon, the Felkin-Anh model predicts *Re* -face reactivity ...



but oxophilic, chelating Mt ions (Mg^{2+}, Zn^{2+}, Ti^{4+},...) will favor a conformation in which the aldehyde exhibits *Si* face reactivity:



Principle: the stereochemical outcome of an aldol process may be rationalized, and often predicted, on the basis of a detailed analysis of (presumed) transition states structures. This

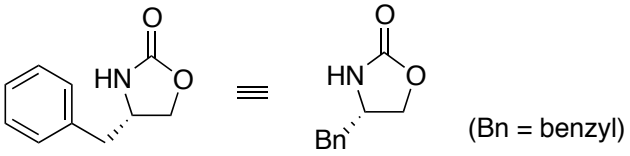
analysis must take into account factors beyond those we have addressed in class; in particular, steric interactions between the substituents attached to the α-carbon of the aldehyde and those connected to the enolate. A detailed analysis of (presumed) transition states structures involved in carbonyl addition, including aldol reactions, is well beyond the scope of CHEM 330. Accordingly, in this course we shall assume that α-chiral aldehydes always react according to the Cram-Felkin or the Felkin-Anh model, as appropriate, *with the understanding that in reality this may not be the case*.

Desirability of reagent-controlled processes (chirality present in the reagent): in the context of an aldol process, that means a chiral enolate

Chiral auxiliaries: chiral segments that are temporarily connected to a molecule in order to exert absolute stereocontrol in the course of a reaction

"Easy-on, easy-off" character of a good chiral auxiliary

Evans auxiliaries, e.g.:



(Bn = benzyl)

Description of the heterocyclic portion of an Evans auxiliary as an oxazolidinone

Evans auxiliaries as derivative of natural L-aminoacids, e.g phenylalanine, valine...