Carbonyl Chemistry II: Stereoselective Additions

> **Section Agenda**
>
> 1) Problem Set #3 (due today) will be graded by Wednesday
> 2) Handout: Carbonyl Chemistry II: Carboxylic Acid Derivatives, Felkin-Ahn-Eisenstein, Chelation Control
> 3) Handout: Practice Problem Set
> 4) Handout: Practice Solution Set

Carboxylic Acids

Structure

- The protonated oxygen is sp^2 hybridized despite having four structural pairs. This allows for favorable overlap between the unhybridized p orbital of oxygen and the the π system of the carbonyl group.

- The most stable conformation, the (Z) form, allows the protonated oxygen's sp^2 lone pair to overlap with and donate into the C–O σ^* orbital.

Reactivity

- Carboxylic acids are still electrophilic, but less so than aldehydes and ketones, because electron donation of the oxygen substituent raises the energy of the C–O π^* orbital. Deprotonated carboxylate anions are even less electrophilic.

- The hydroxyl substituent can act as a leaving group, especially if protonated so it leaves as neutral water.
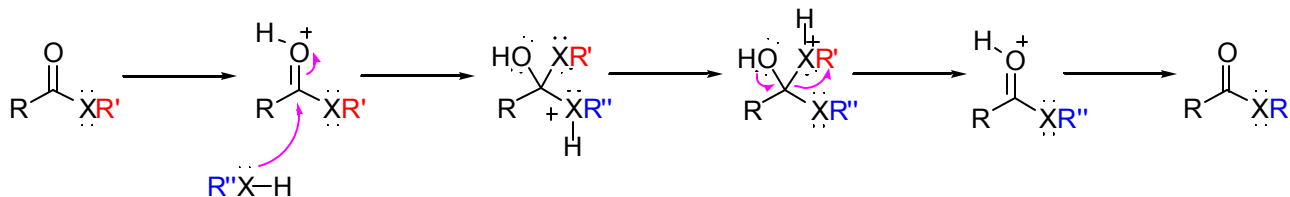
Carboxylic Acid Derivatives

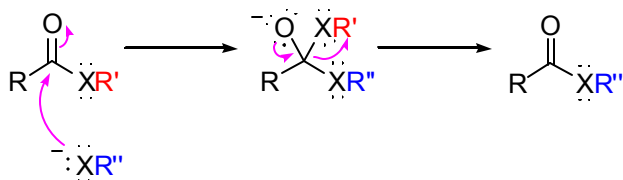### General Mechanisms for Reactions of Carboxylic Acid Derivatives

Acidic: Nucleophiles are neutral, carbonyl electrophiles are activated as cations, leaving groups are neutral
Basic: Nucleophiles are charged anions, electrophiles are neutral, leaving groups are charged anions

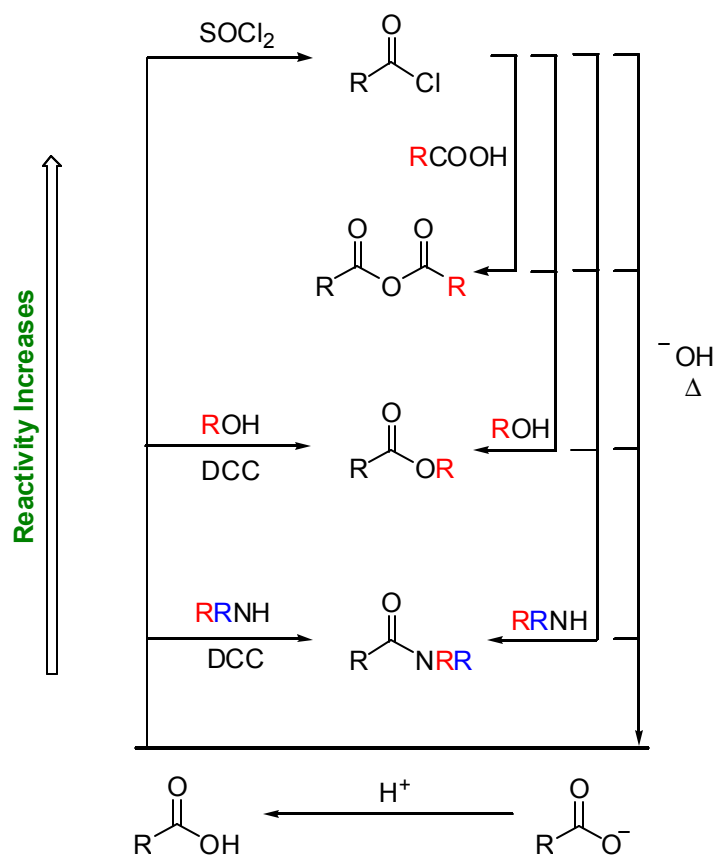### Mechanism under Acidic Conditions

Mechanism under Basic Conditions

Note that both mechanisms proceed through tetrahedral intermediates!

Carboxylic Acid Derivative Interconnectivity

Relative Reactivity of Carboxylic Acid Derivatives

- Know these transformations for synthesis

- You can go "down in energy" on the chart by reacting with a lower energy ligand. For instance, you can react an anhydride with an alcohol or alkoxide to form an ester.

- It is harder to go "up in energy" on the chart. Often, you must hydrolyze to an acid, treat the acid with thionyl chloride to go "all the way up" to an acid chloride, then perform another reaction to "come back down" to an anhydride, ester, or amide.

- Know the mechanism by which DCC activates carboxylic acids. Essentially, it makes the hydroxyl substituent a good leaving group

Converting Newman Projections to 3D Lewis Structures

- Generally you wish to draw the largest chains in the "plane of the paper" and have the smallest groups hanging off as substituents on the chain

- Make sure you are drawing the correct stereoisomer. It'd be a shame to think through a problem correctly but produce the wrong answer because you inadvertently flipped a stereocenter.
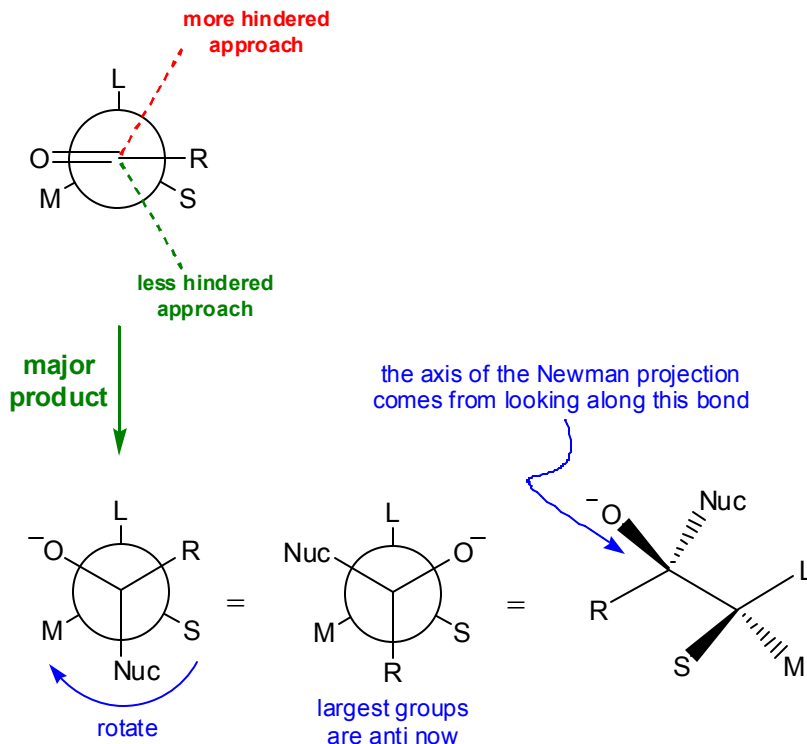

Summary

1) Rotate and redraw the Newman projection putting the largest substituents anti to each other. This is usually the most stable conformation of the molecule.

2) Draw the largest substituents and the central C–C bond as a four atom zig-zag Lewis structure.

3) Looking down this bond from "the back of the page" as shown, fill in the other substituents as a "sawhorse." The dashed wedges, which indicate the bonds going back from the plane of the page, will be the substituents on the left in the Newman projection as drawn. The solid wedges, which indicate bonds coming out of the page, will be the substituents on the right of the Newman projection.

4) Finally, you can check your drawing by assigning *R* and *S* designations to the stereocenters in the Newman projection and making sure that the same stereocenters are *R* and *S* in your Lewis structure.

Diastereoselectivity in Carbonyl Additions

General Synthetic Approaches

1) Racemic Synthesis with Subsequent Separation
2) Coupling of Chiral Building Blocks
3) Stereocontrolled Synthesis

- Carbonyl groups are sp^2 hybridized, and thus are not stereogenic centers. However, they are said to be "prochiral," because if a nucleophile is added to a non-symmetric carbonyl group, two stereoisomers are possible
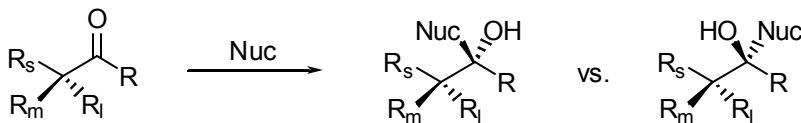
Acyclic Stereocontrol

The Felkin-Ahn-Eisenstein Model

The Felkin-Ahn-Eisenstein model applies knowledge about steric and electronic effects (conformational analysis) in a substrate to glean information as to what the transition state of a nucleophilic addition to the carbonyl group will look like. The most favored transition state leads to the major product.
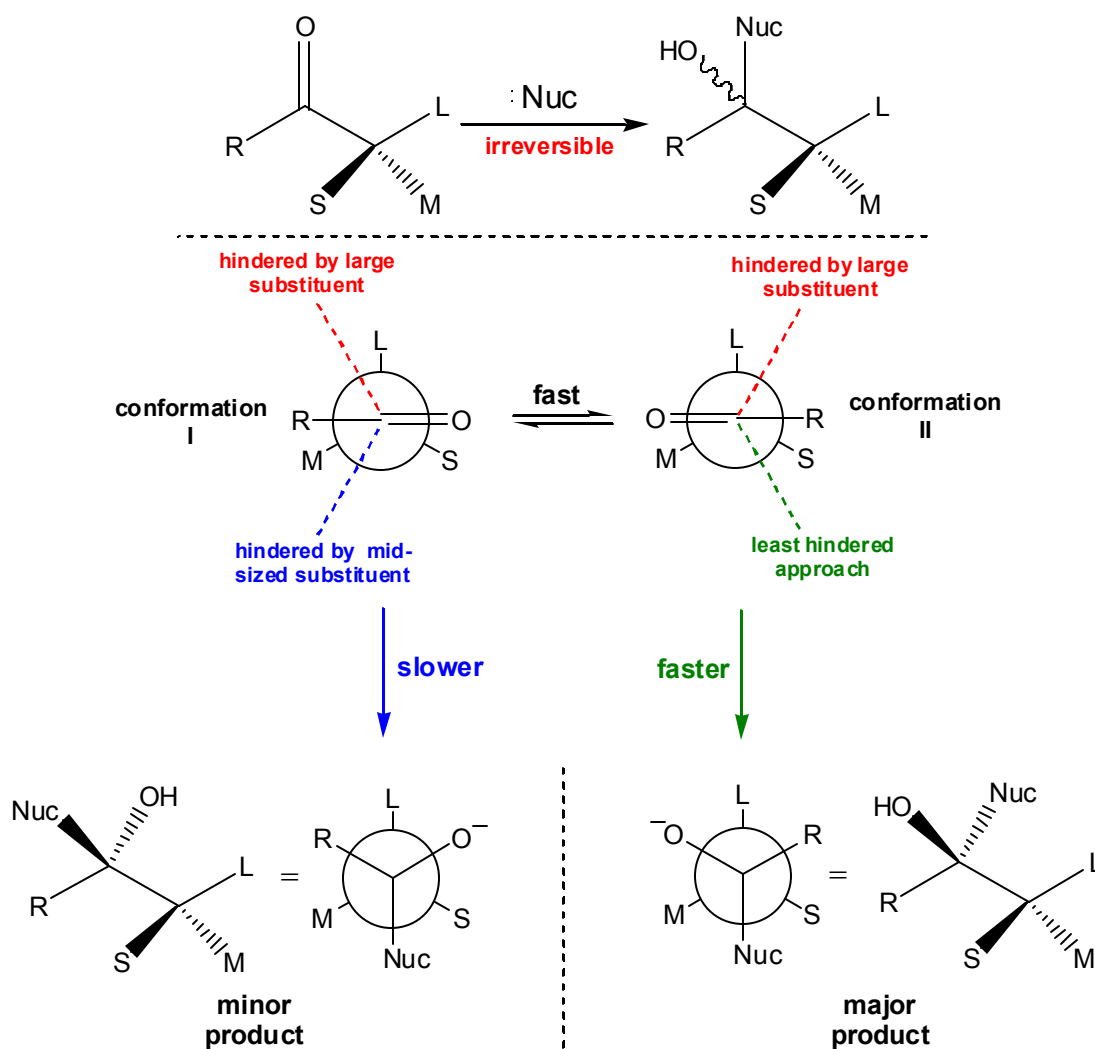

Summary

1) Recall from Section 4 that the empty π^* carbonyl MO has its largest lobes positioned ~107° behind the carbon atom. Correspondingly, nucleophiles add along this trajectory (the Bürgi-Dunitz angle)

2) The reactive moiety (the carbonyl and adjacent chiral carbon) have two important conformations, depicted as structures **I** and **II** in the above diagram. There is sufficient ambient energy at room temperature for these conformations to interconvert. This interconversion is fast relative to the nucleophilic addition.

3) Each conformation has two angles of approach (the carbonyl group has two faces). In both **I** and **II**, there is one face hindered by the largest substituent. Products resulting from addition along these trajectories are negligible.

4) In conformation **I**, the alternate approach passes by the mid-sized substituent. In conformation **II**, the alternate approach passes by the smallest substituent. Of all four approaches, the last one is the least hindered and attack along this trajectory will occur with the greatest rate. Because we are under kinetic control (the addition is irreversible, so there is no equilibrium), this addition leads to the major product.

The Chelation Control Model

When a heteroatom is located in the vicinity of the carbonyl oxygen and a chelating agent is present (*e.g.*, Zn^{II}, Mg^{II}), a complex forms and rotation about the C–C bond is hindered. This disrupts the equilibrium between conformations **I** and **II**, so now the nucleophile only has two principle trajectories open for attack. It can either pass by a larger or smaller substituent. The major product results from the latter case.
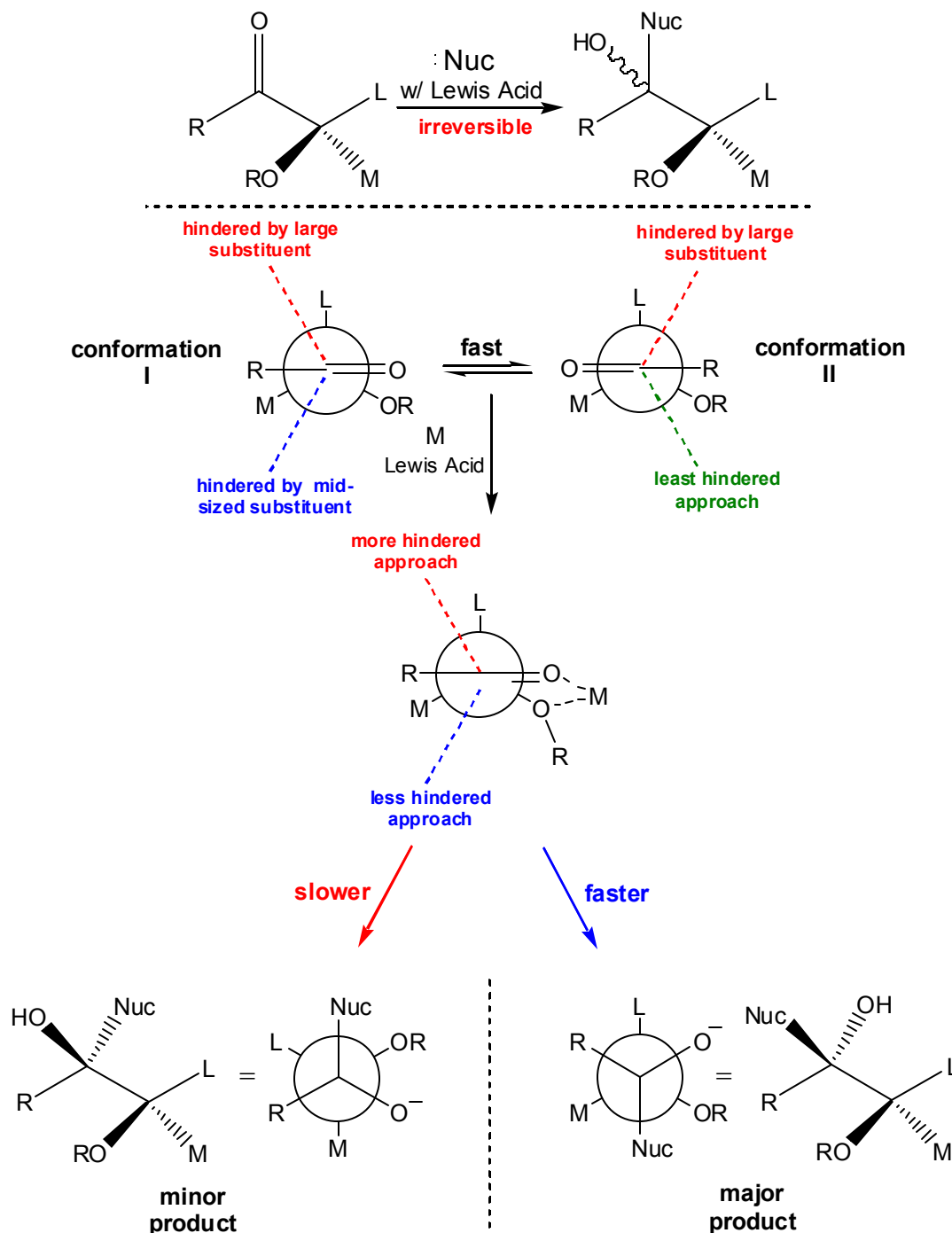
- The effect is less pronounced in polar, chelating solvents, where the solvent molecules compete with the substrate in binding the Lewis acid

- In neither case does the absolute stereochemistry of the original stereocenter change configuration