

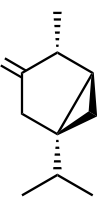
Chemistry 2600

Chapter 15

Bond Electrophiles Connected to Leaving Groups

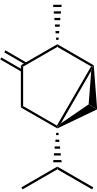
(sections 15.1-15.8 excluding 15.3.4 & 15.5.1)

Substitution Reactions of Carboxylic Acid Derivatives

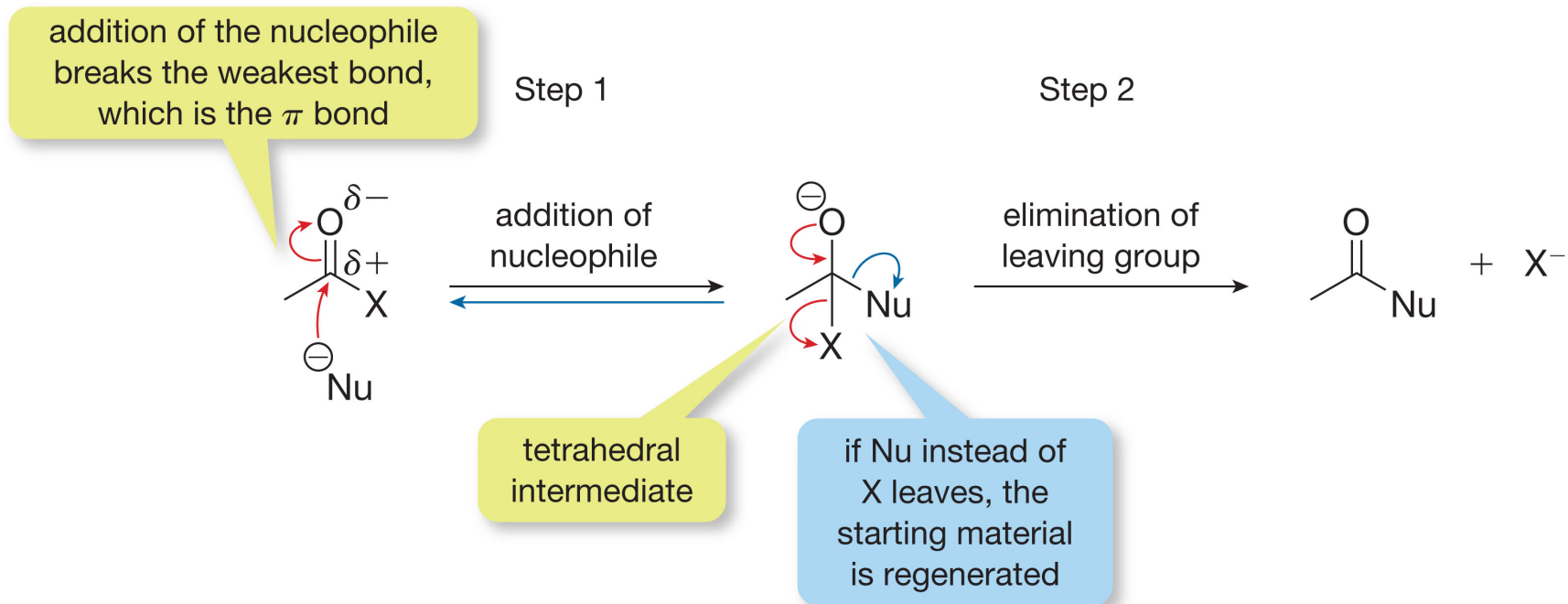


- In Chapter 7 you saw how carbonyl groups (aldehydes and ketones) are good electrophiles and undergo ***addition*** reactions.
- In this chapter we will explore the chemistry of the carboxylic acid derivatives (CADs), molecules containing a carbonyl group attached to a heteroatom.
- Carboxylic acid derivatives follow a pattern of reactivity called ***addition-elimination***.
- Addition-elimination is a 2 step reaction that adds a Nu to a π bond, and then eliminates a LG to re-form the π bond.

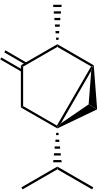
Substitution Reactions of Carboxylic Acid Derivatives



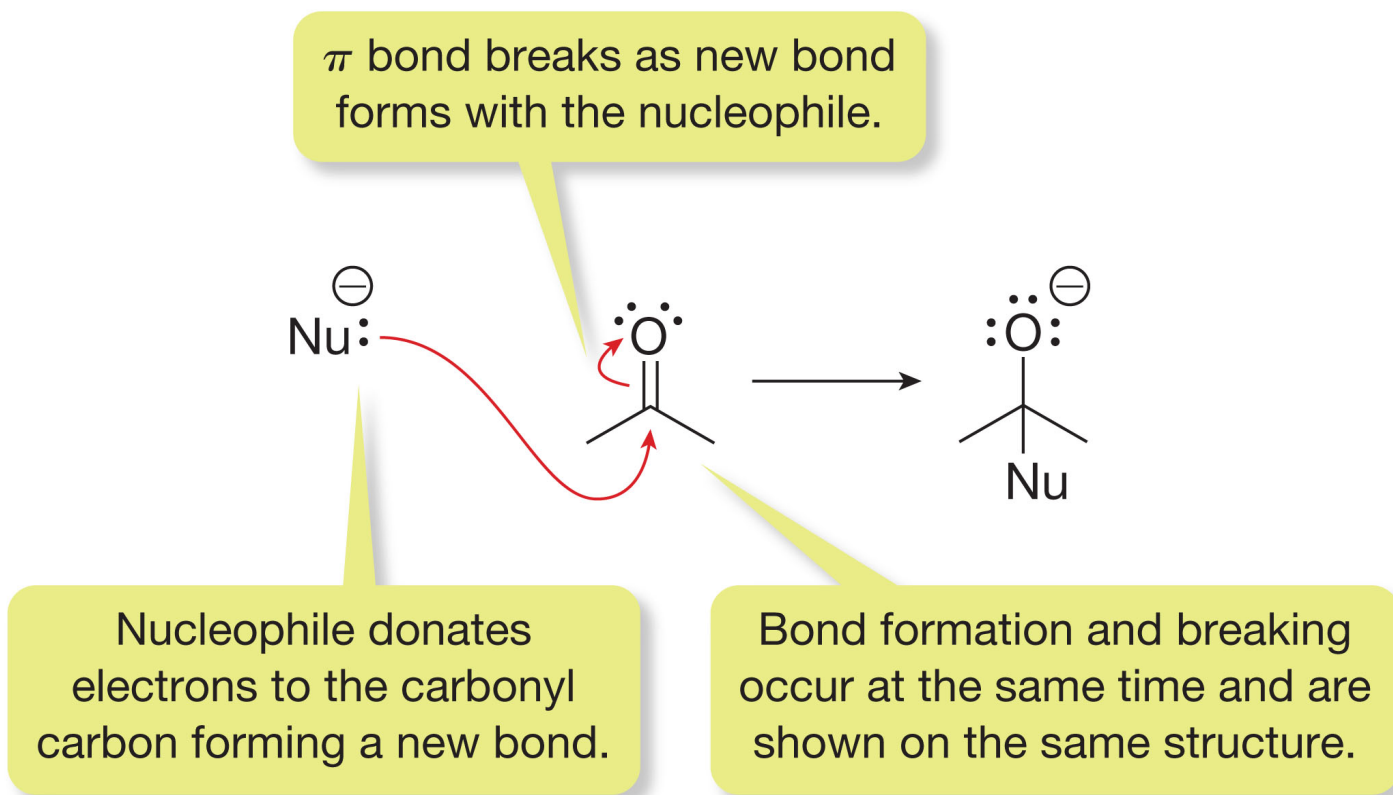
- Carboxylic acid derivatives:



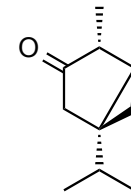
Substitution Reactions of Carboxylic Acid Derivatives



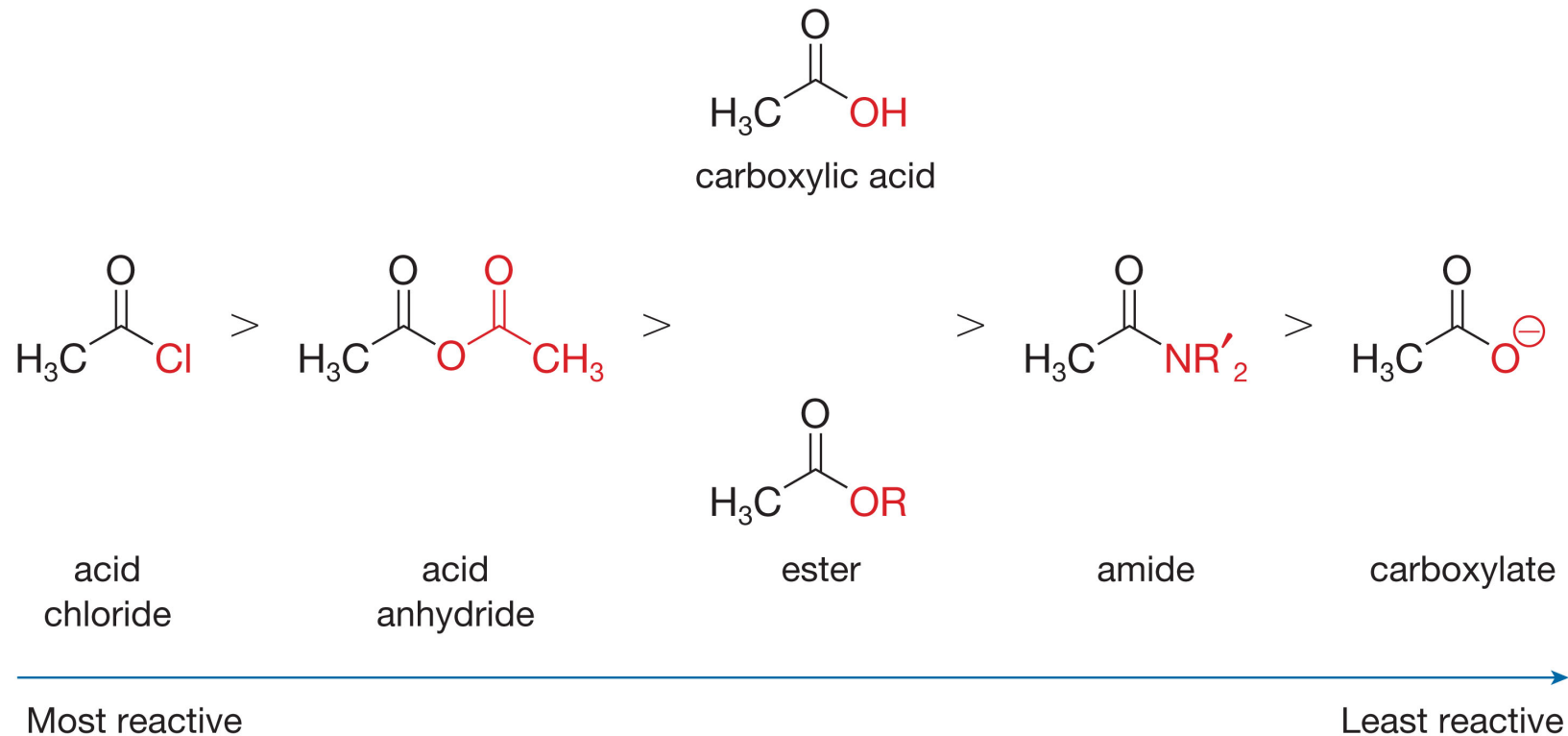
- Because aldehydes and ketones do not have a good LG, they only undergo addition reactions.
- Aldehyde/Ketones:



Relative Reactivity of the CADs

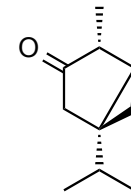


- Carboxylic acid derivative relative reactivity:

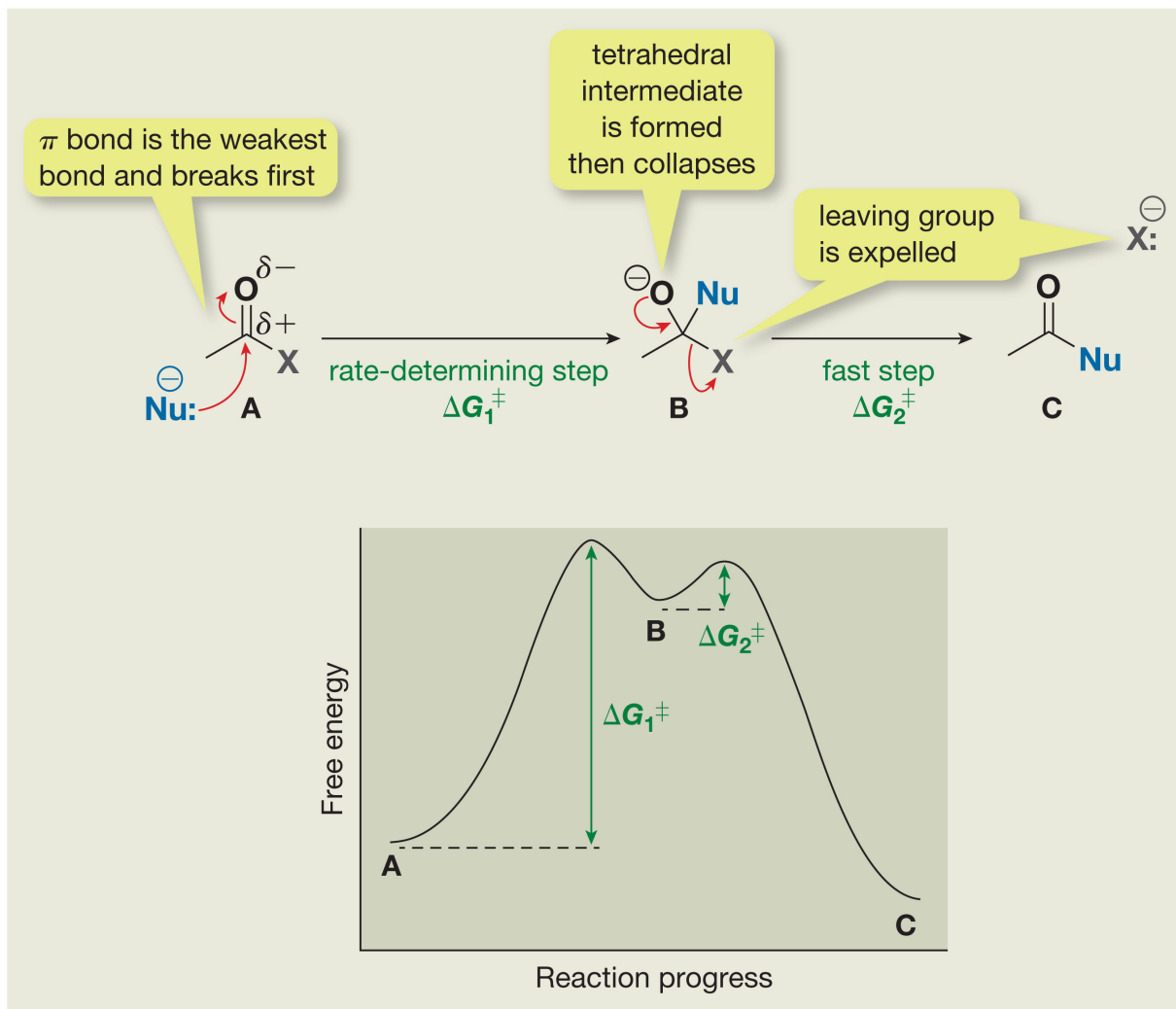


- Where do aldehydes and ketones fit on this list?

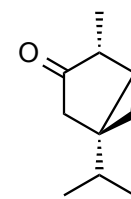
Relative Reactivity of the CADs



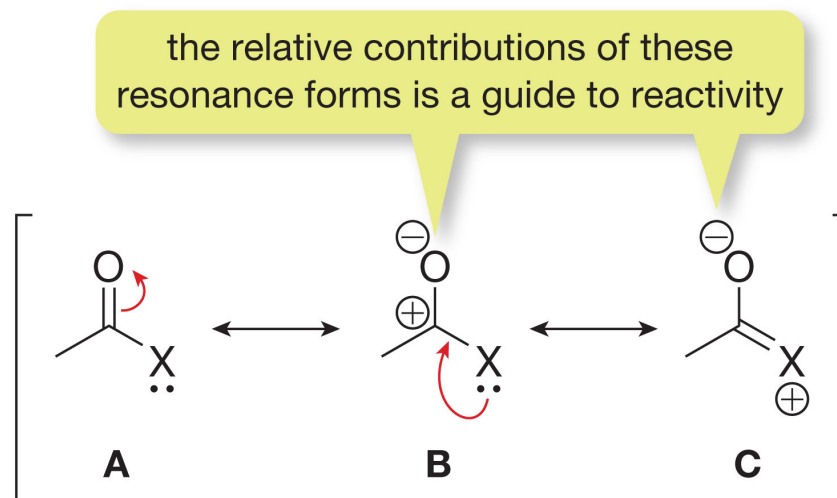
- The formation of the tetrahedral intermediate is the RDS:



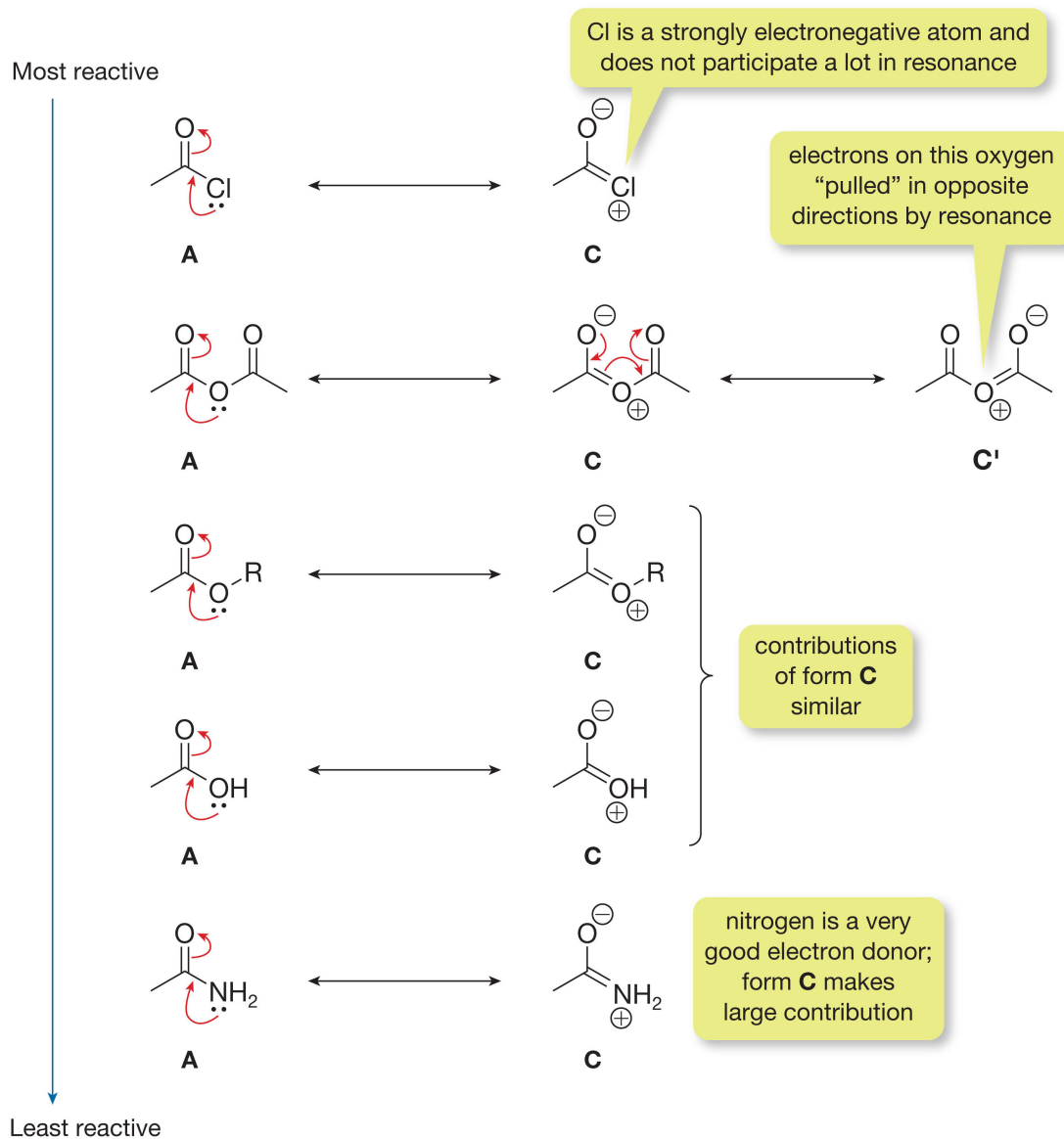
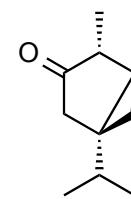
Relative Reactivity of the CADs



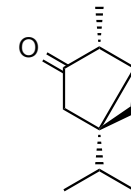
- The relative reactivity of the CADs can be understood by looking at 2 factors:
 - The electrophilicity of the carbonyl carbon
 - The stability of the leaving group
- The electrophilicity of the carbonyl carbon is dependent on the ability of the heteroatom to donate an electron pair.



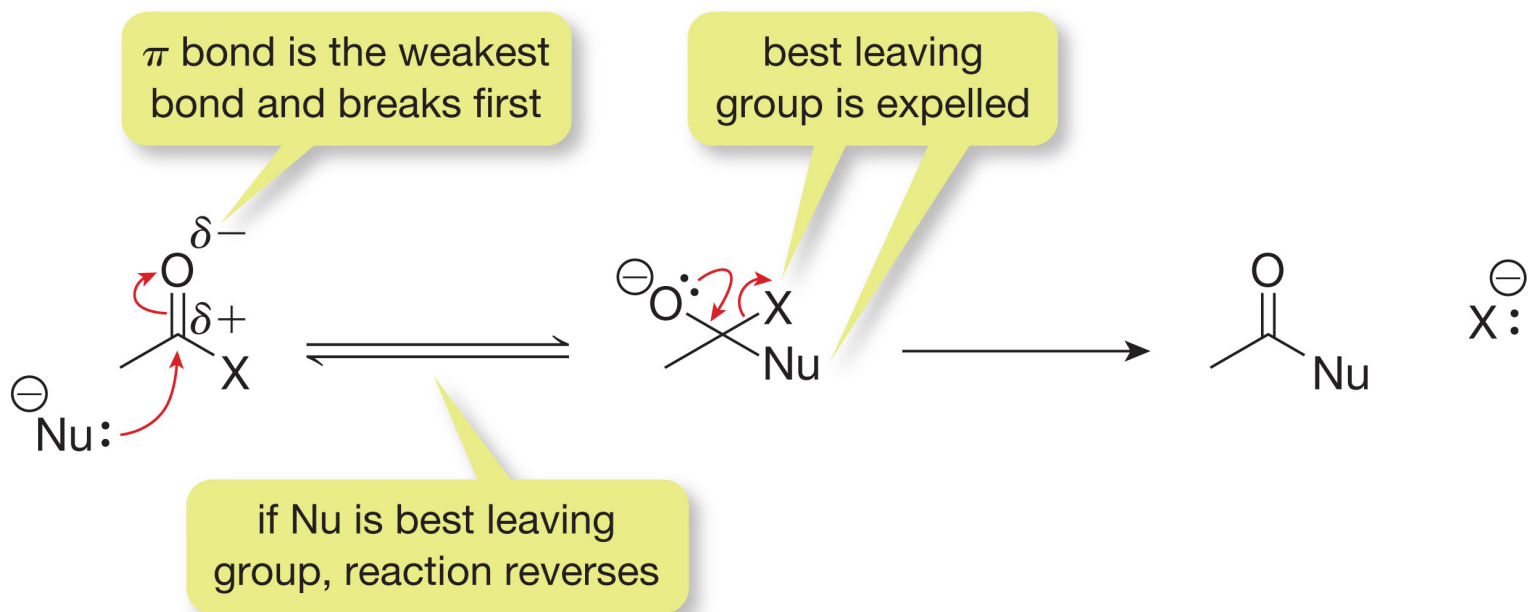
Relative Reactivity of the CADs



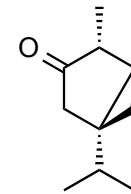
Relative Reactivity of the CADs



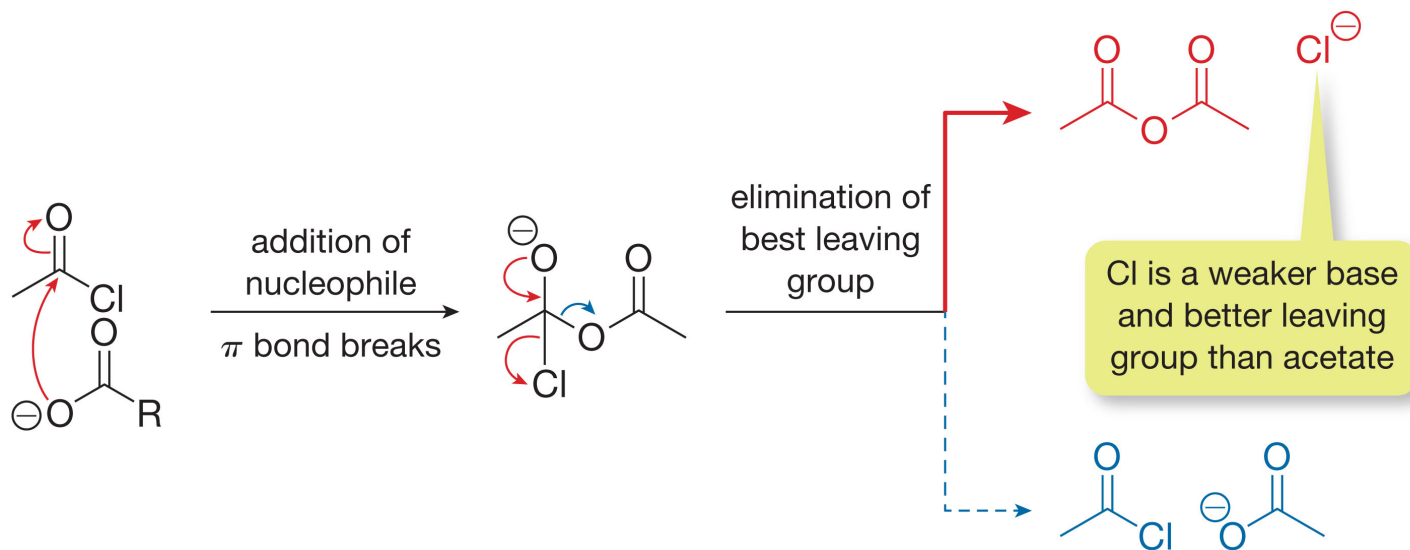
- If the X group in the CADs is a better LG than the incoming nucleophile, a reaction is possible.
- If not, then the tetrahedral intermediate will transform back to the starting material.



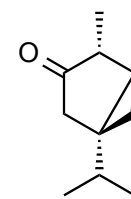
Relative Reactivity of the CADs



- If the X group in the CADs is a better LG than the incoming nucleophile, a reaction is possible.
- If not, then the tetrahedral intermediate will transform back to the starting material.
- e.g.



Relative Reactivity of the CADs

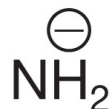
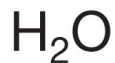


- Recall, the weaker the base, the better the LG.

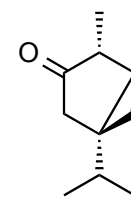
Best leaving group
(weakest base)



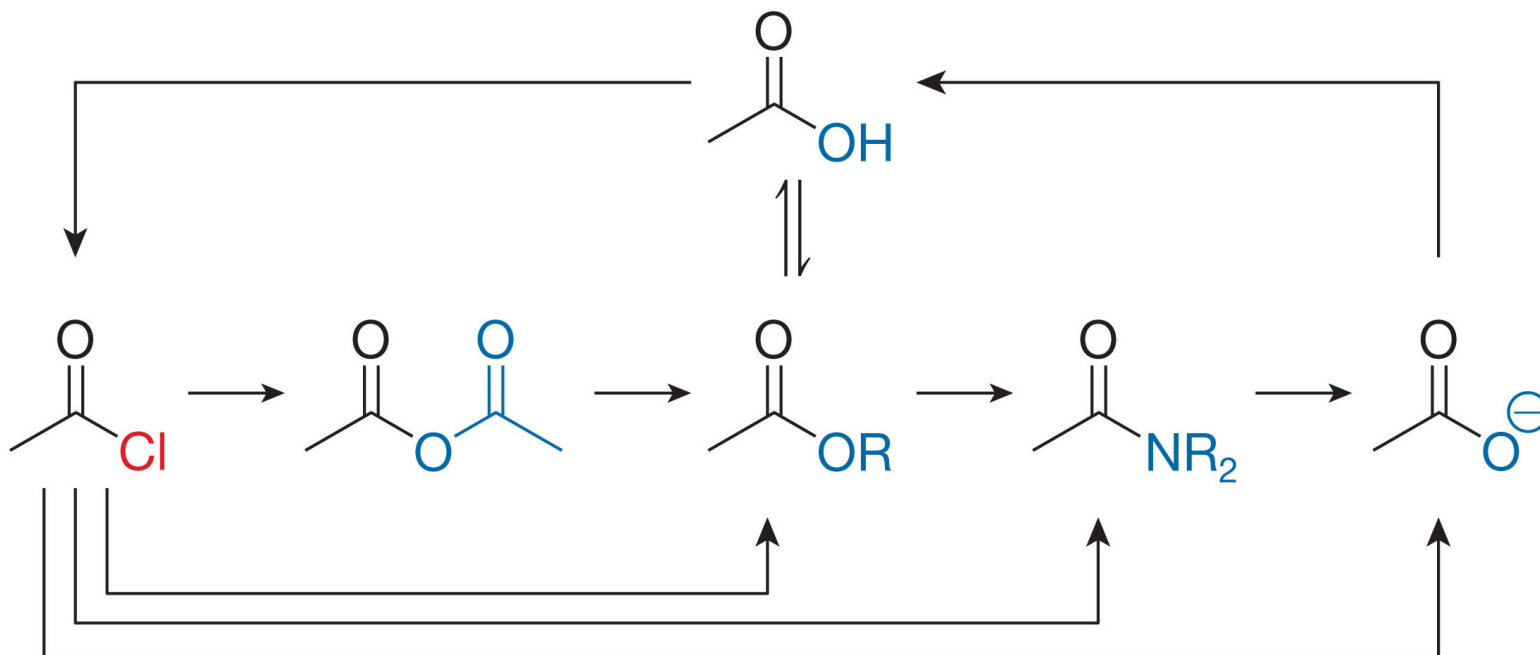
Worst leaving group
(strongest base)



Relative Reactivity of the CADs

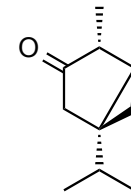


- The interconversion of carboxylic acid derivatives:

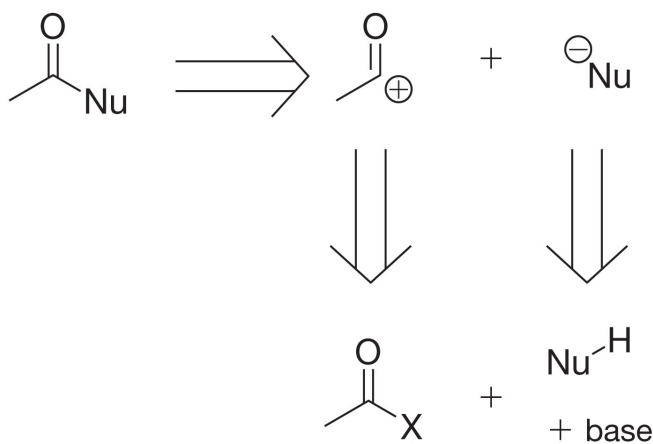


- The more electrophilic CADs (on the left) can be converted to any of the less reactive forms (on the right) by the addition of the appropriate nucleophile.

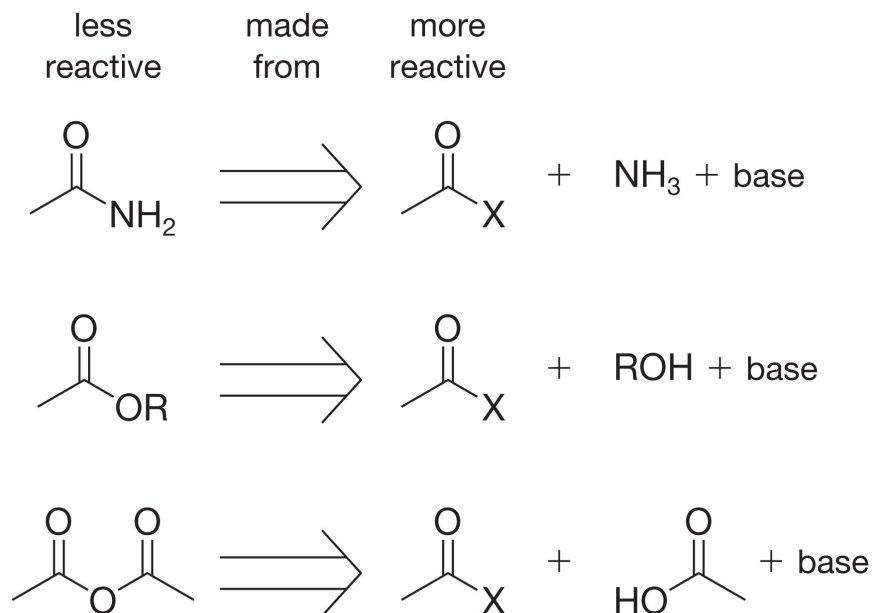
Retrosynthetic Analysis



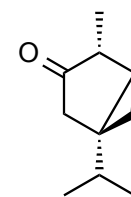
- Acyl substitution reactions produce one acyl compound from another by substituting a Nu for a LG on a carbonyl compound.



X group must be a better leaving group than Nu

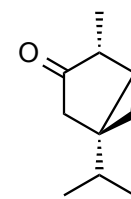


Reactions of the CADs



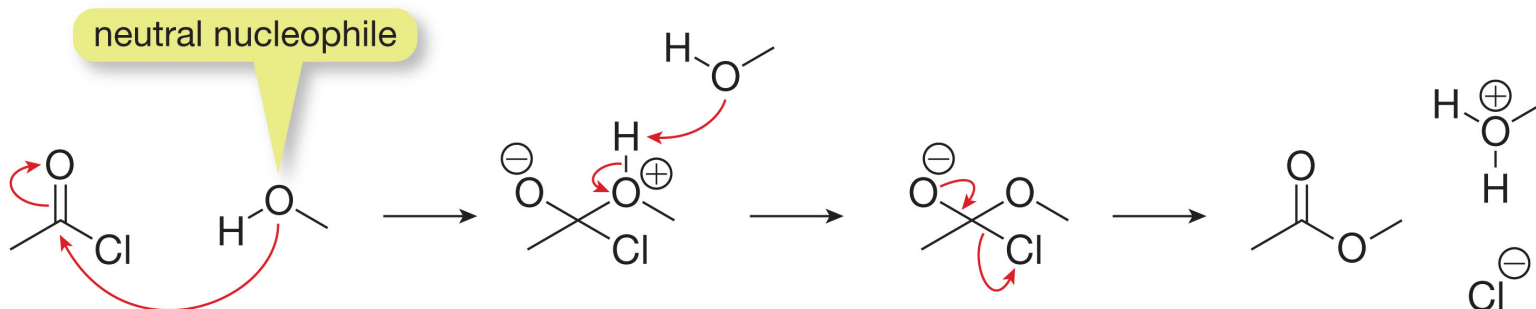
- While the addition-elimination steps of the CADs are mechanistically identical, the reaction conditions can vary from reaction to reaction.
- Factors to consider:
 1. Strength of the electrophile
 2. Strength of the nucleophile
 3. Reaction conditions (acidic or basic)

Reactions of the CADs

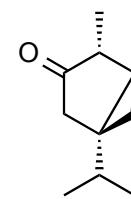


1. Strength of the Electrophile.

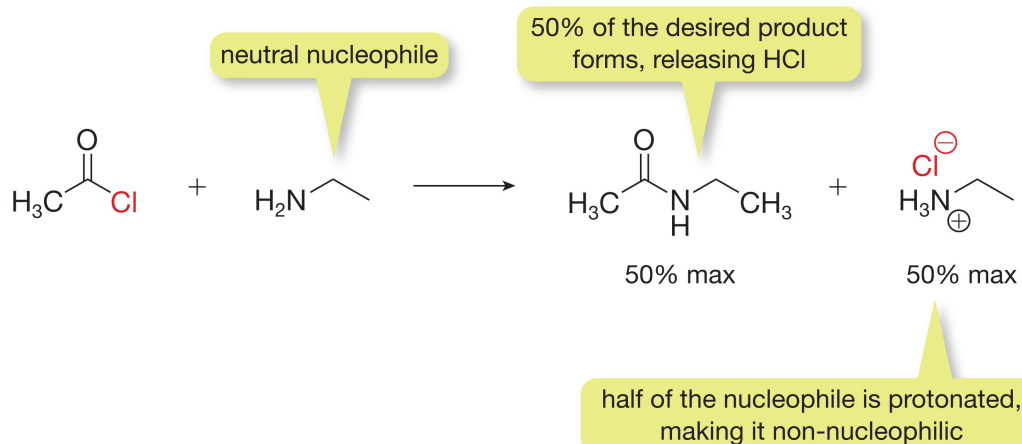
- The most reactive of the CADs are acid chlorides and anhydrides. These can usually react with neutral nucleophiles without the aid of a catalyst.
- Ester from acid chloride:



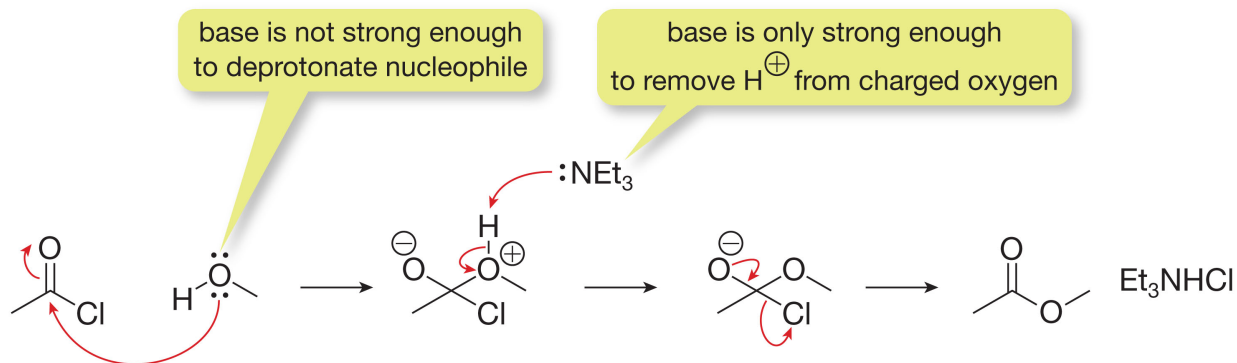
Reactions of the CADs



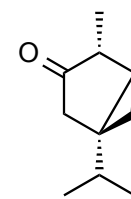
- Amide from acid chloride:



- Neutral nucleophile with external base:

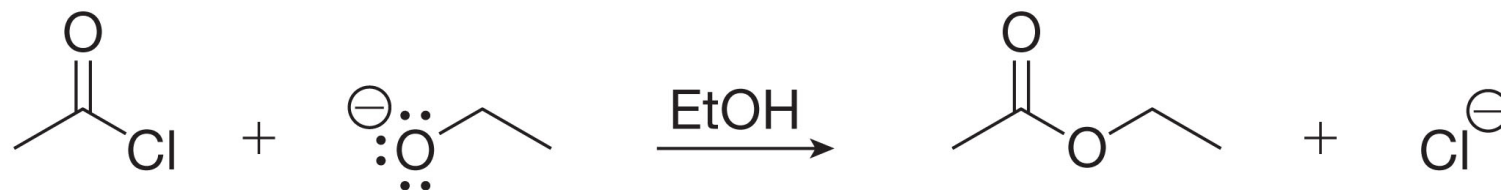


Reactions of the CADs

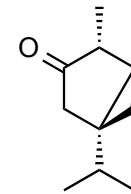


2. Strength of the Nucleophile.

- Nucleophiles in their conjugate base form are usually used with acid chlorides, anhydrides, or esters, and are only practical with oxygen based nucleophiles (negatively charged nitrogen nucleophiles are too basic).
- Ester from an acid chloride:

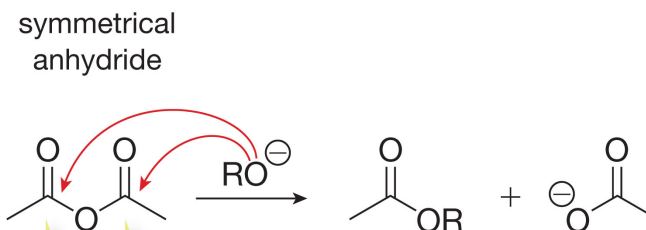


Reactions of the CADs



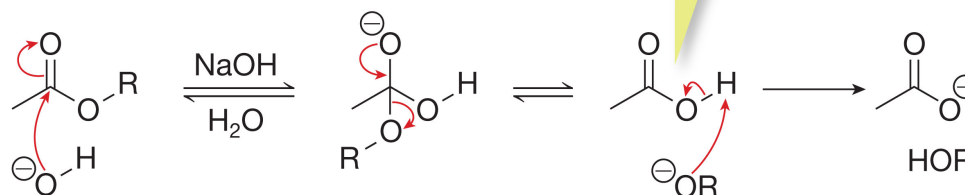
2. Strength of the Nucleophile.

- Ester from an anhydride:



either carbonyl electrophile will give the same product

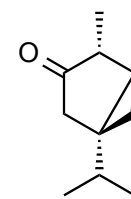
- Ester hydrolysis (saponification):



the acid deprotonates and prevents backwards reaction

$\ominus\text{OR}$ and $\ominus\text{OH}$ are similar leaving groups—reaction can go either direction

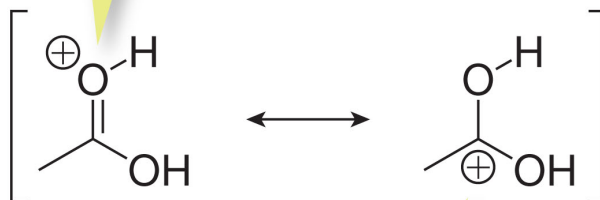
Reactions of the CADs



3. Reaction Conditions (Acid catalysis).

- The less reactive electrophiles can be made to react faster under acidic conditions (acids generally activate electrophiles, while bases activate nucleophiles)

Protonating the carbonyl oxygen...



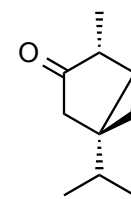
... increases the + charge on the carbon.

Addition of base deprotonates the nucleophile...

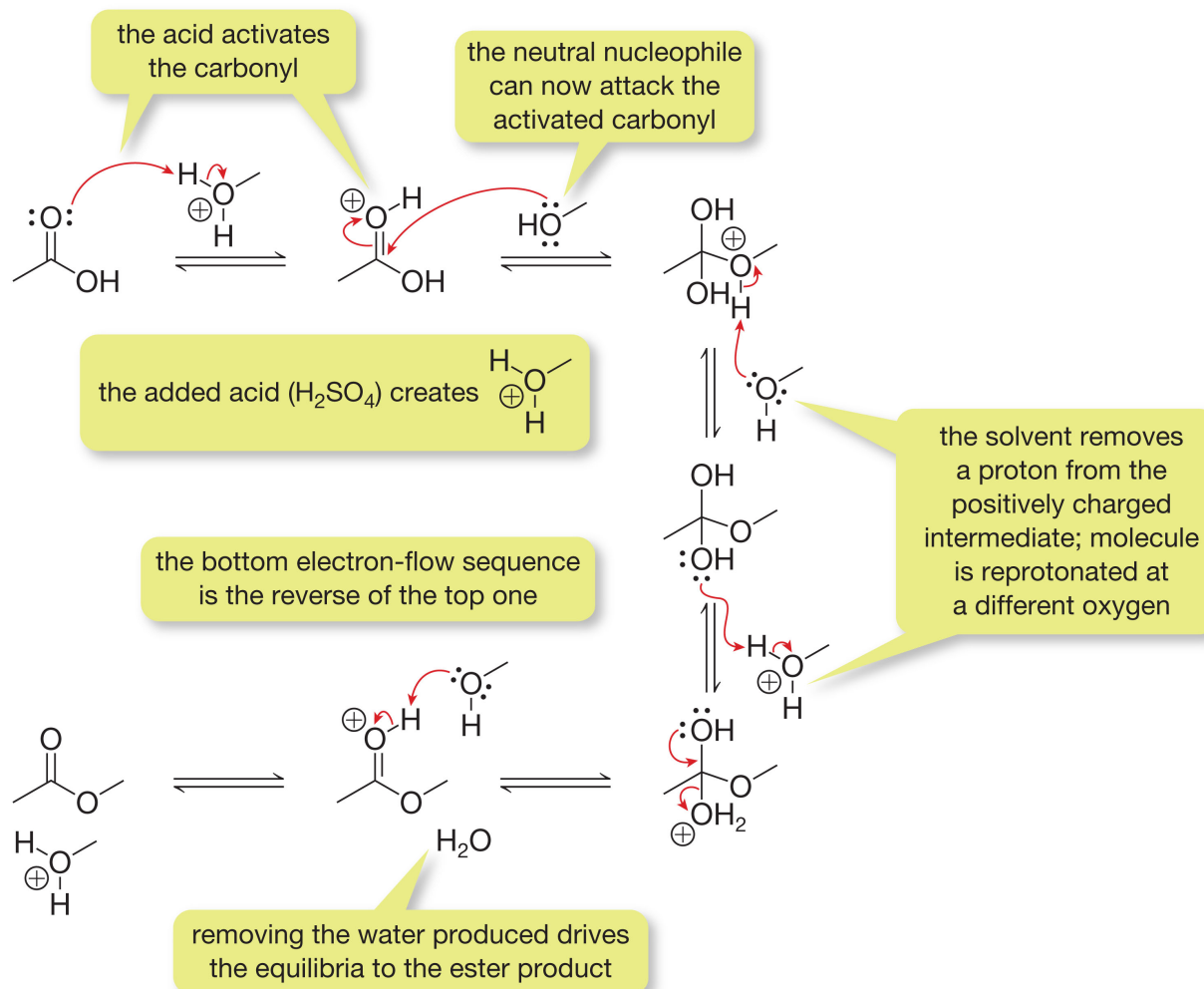


... which converts it to a strong nucleophile.

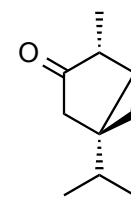
Reactions of the CADs



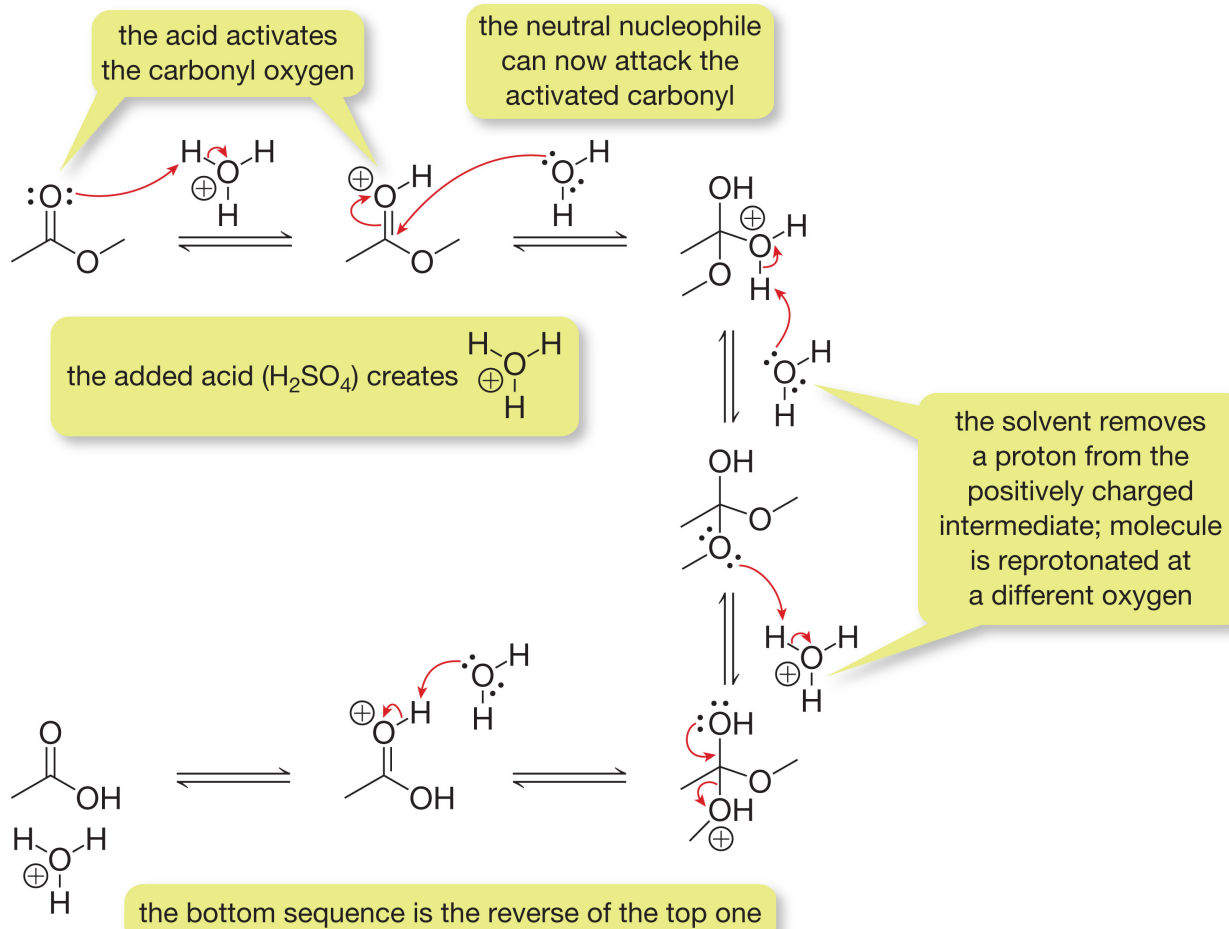
- Ester from carboxylic acid (acid catalyzed).



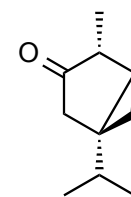
Reactions of the CADs



- Acid from ester – ester hydrolysis (acid catalyzed).

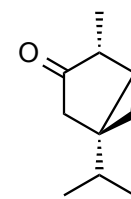


Reactions of the CADs

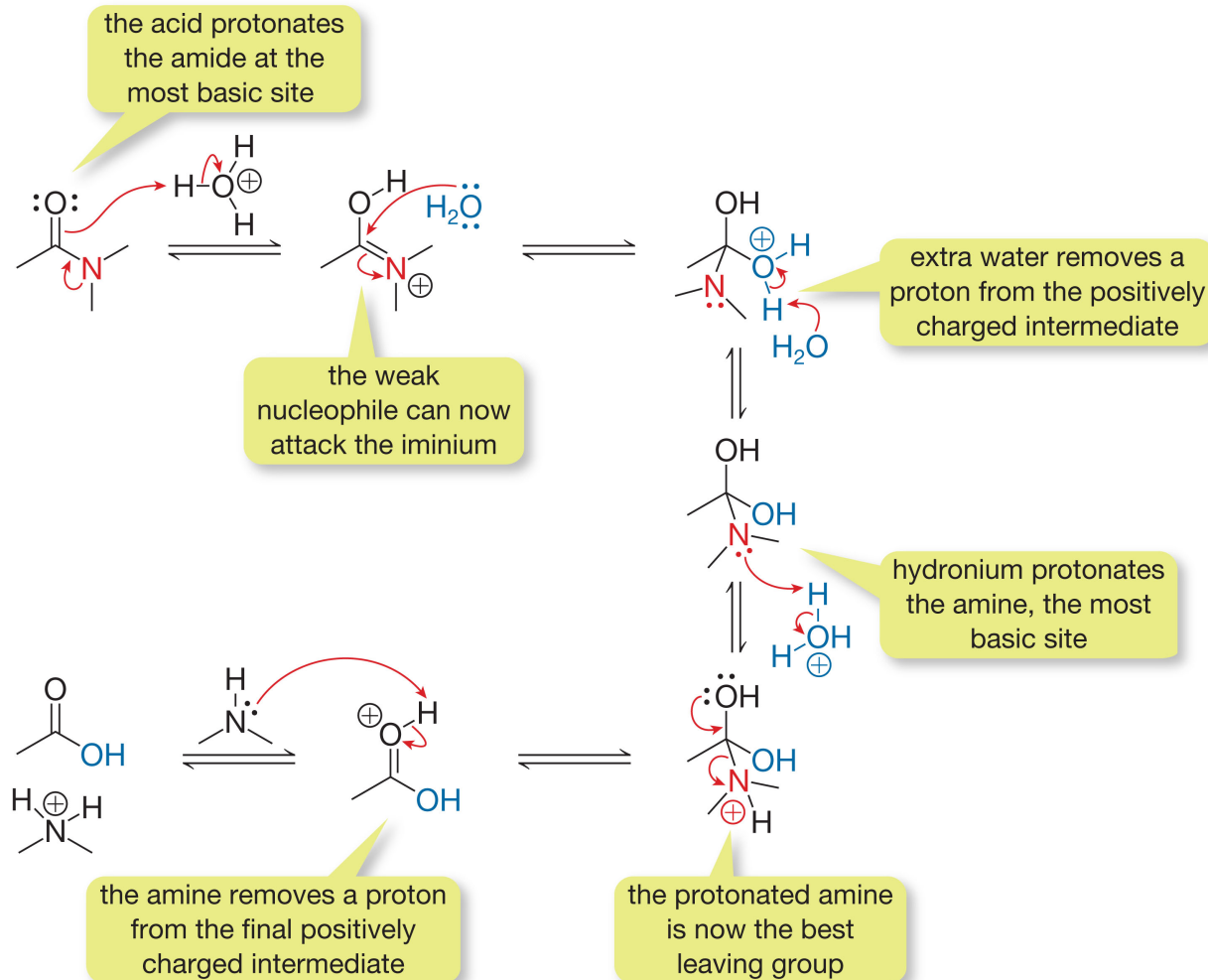


- Amides are among the least reactive CADs but can be made to react.
- The most useful transformation of amides is into carboxylic acids.
- This requires high temperatures and an acid or base catalyst (easier under acidic conditions).

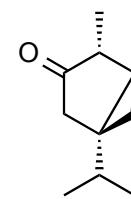
Reactions of the CADs



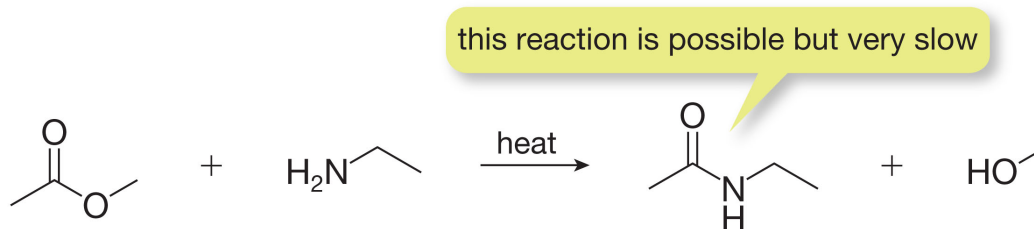
- Acid from amide - amide hydrolysis (acid catalysis).



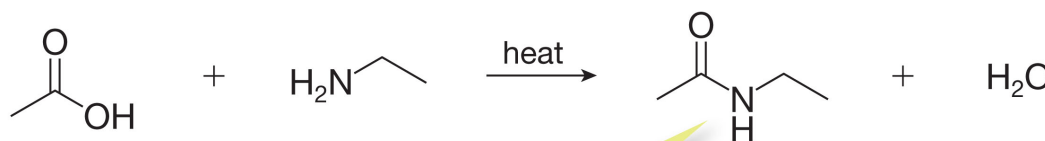
Reactions of the CADs



- Amides from esters:
 - This reaction is slow and requires heat:

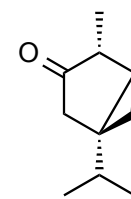


- Amides from acids:
 - This reaction requires extreme heat to complete because of both the electrophile and nucleophile are deactivated (why?).

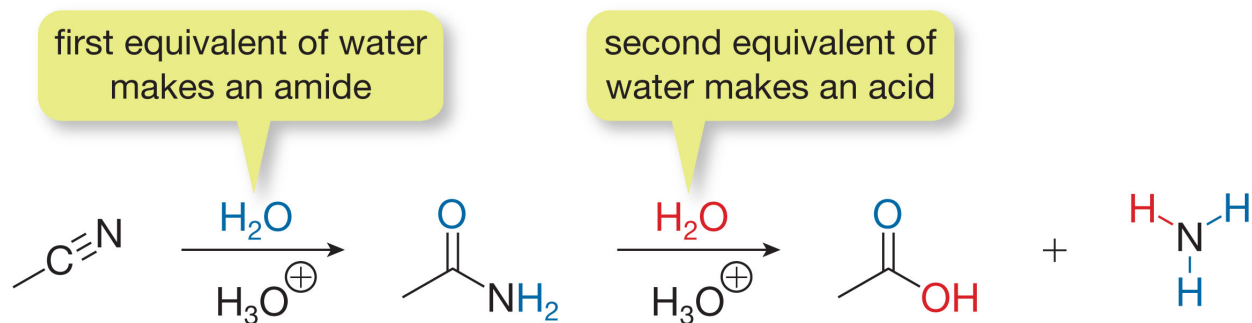


This reaction is possible but requires very high temperatures. It can only be performed with very simple compounds or to make rings.

Reactions of the CADs

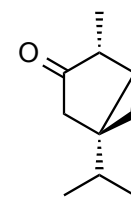


- Nitriles behave similarly to amides:

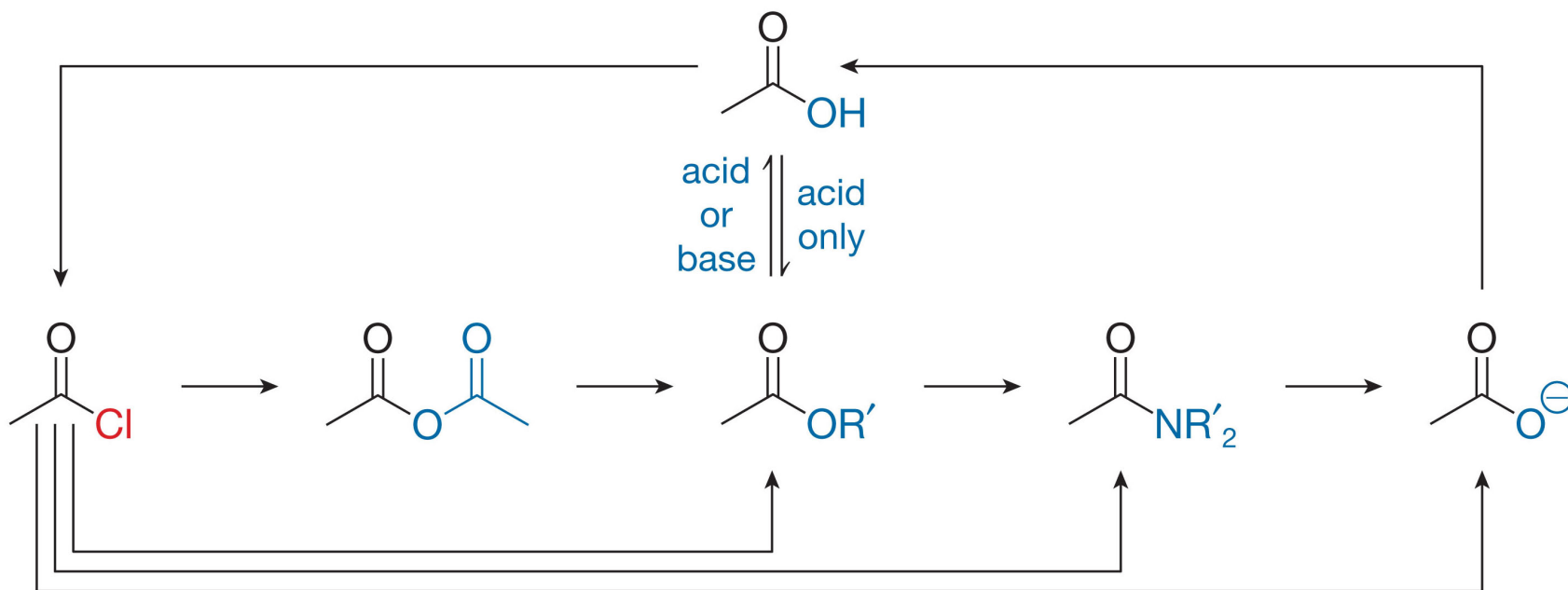


- Draw the mechanism for the first step of this reaction:

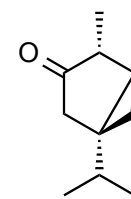
Reactions of the CADs



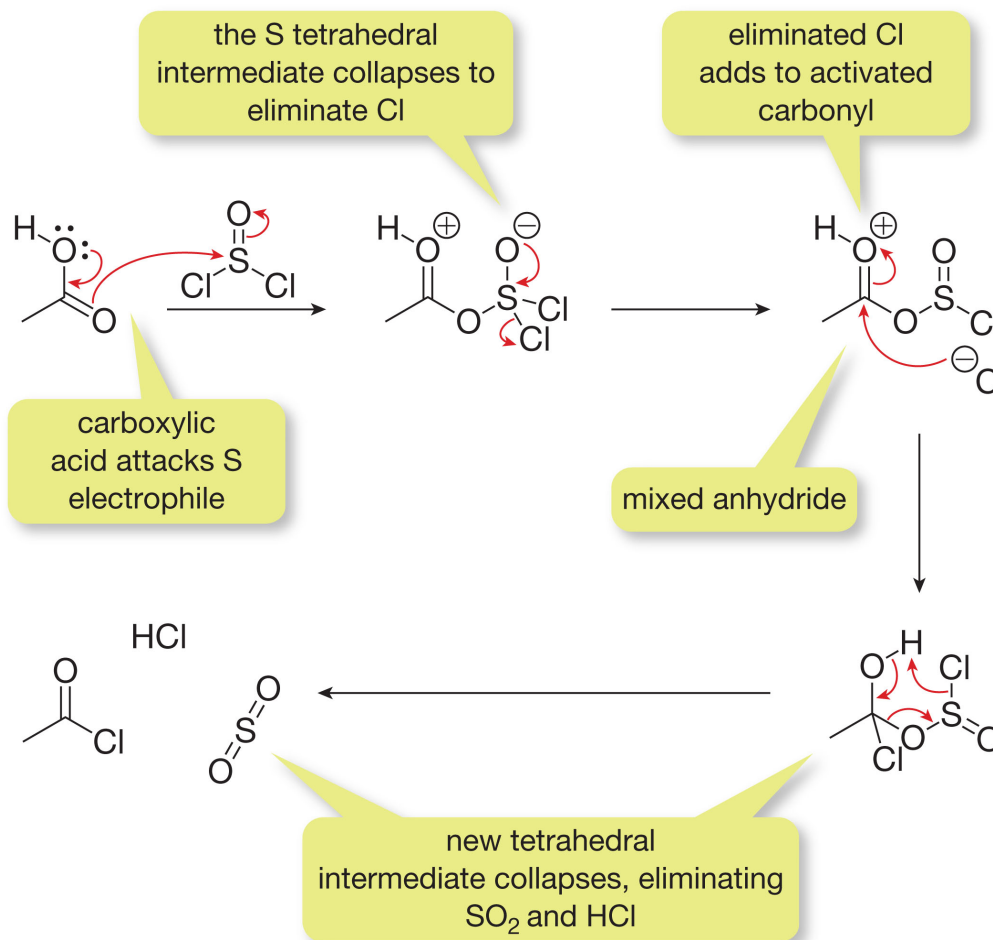
- Carboxylic acids are special because under the right conditions, they can be used to make all other derivatives.



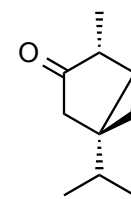
Reactions of the CADs



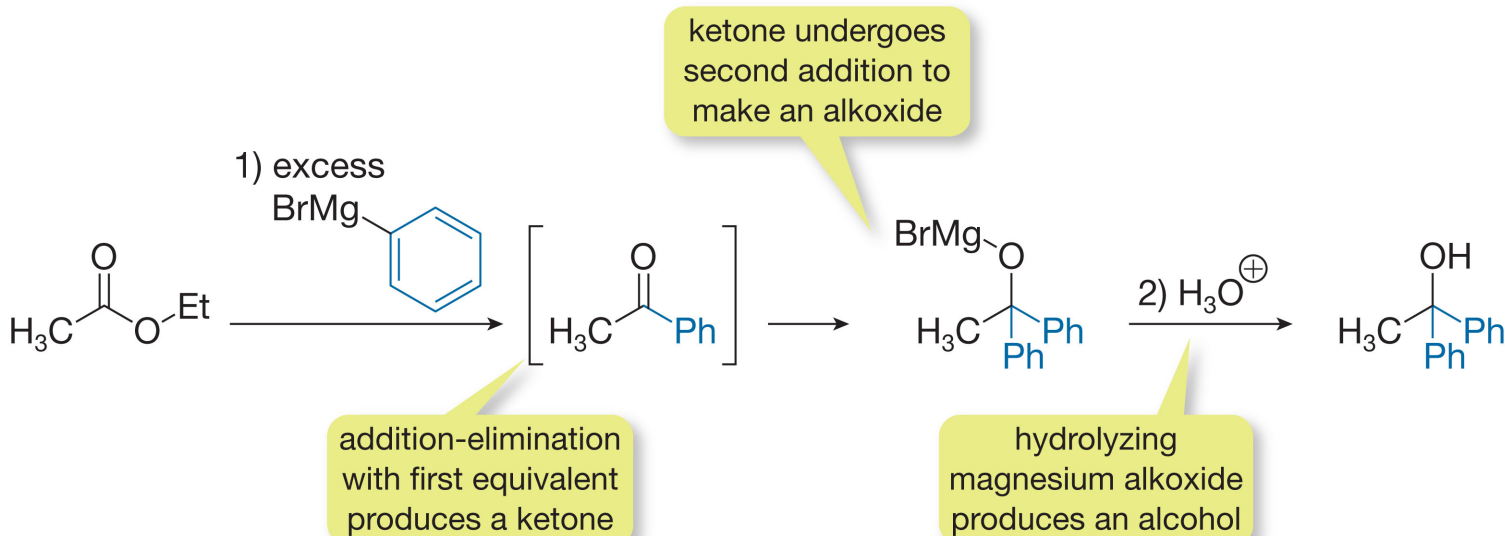
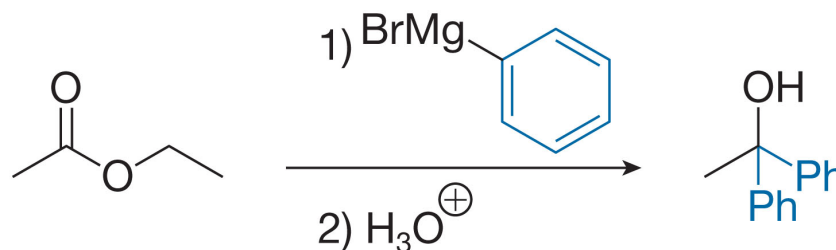
- Acid chlorides are made by reacting carboxylic acids with thionyl chloride (SOCl_2).



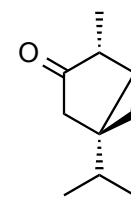
Reactions of the CADs



- Carbon nucleophiles undergo 2 addition-elimination reactions with CADs to give 3° alcohols.

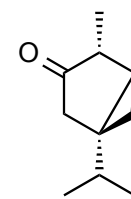


Reduction of Carboxylic Acid Derivatives

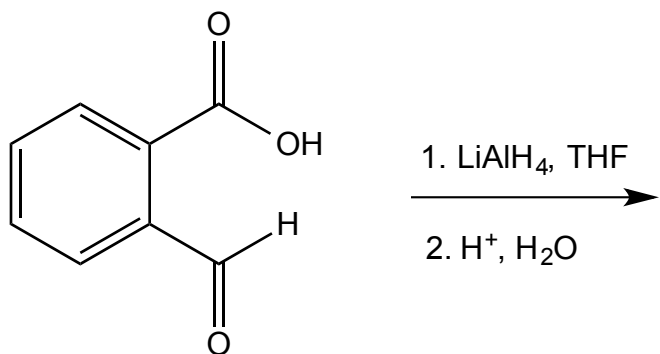
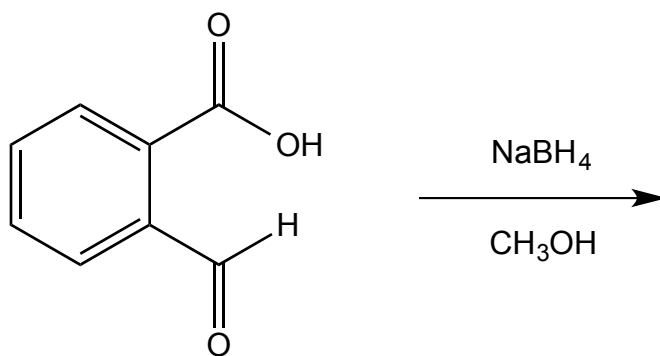


- In Chem 2500, you learned that aldehydes and ketones are reduced by nucleophilic hydride reagents such as LiAlH_4 and NaBH_4 .
- This reaction is simply the addition of a nucleophile to a polar π bond.
- If the carbonyl has a leaving group (the CADs), the addition-elimination mechanism then forms an aldehyde, which in turn is reduced to the alcohol.
- LiAlH_4 is a powerful reducing agent and will reduce esters, carboxylic acids, and amides. NaBH_4 is not strong enough to reduce these derivatives.

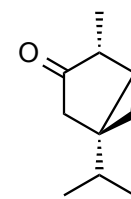
Reduction of Carboxylic Acid Derivatives



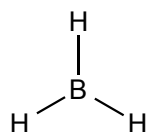
- Thus, we can use NaBH_4 to selectively reduce one type of carbonyl group in the presence of another.



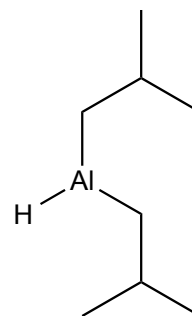
Reduction of Carboxylic Acid Derivatives



- By using an electrophilic reducing agent, we can selectively reduce the less electrophilic carbonyl groups.
- Typical electrophilic reducing reagents are borane (BH_3) and DIBAL (diisobutylaluminum hydride).



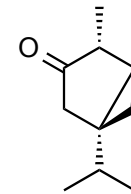
borane



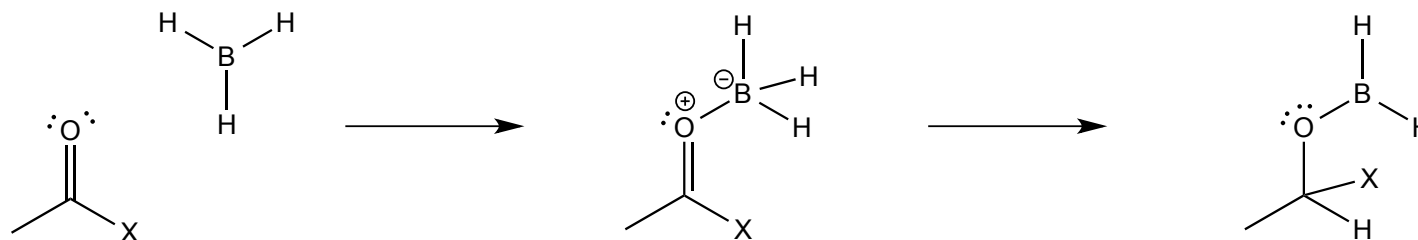
DIBAL

- Carbonyls that are less reactive toward LiAlH_4 and NaBH_4 are more reactive towards BH_3 or DIBAL.
- Similarly, carbonyls that are more reactive toward LiAlH_4 and NaBH_4 are less reactive towards BH_3 or DIBAL.

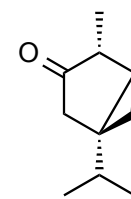
Reduction of Carboxylic Acid Derivatives



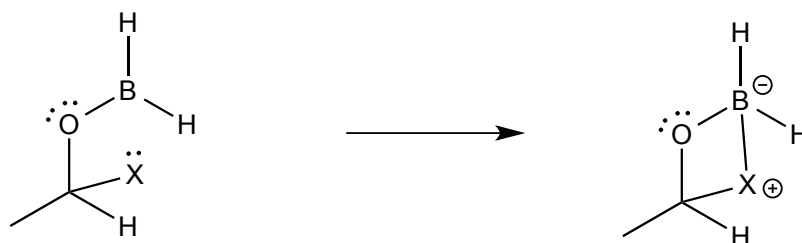
- Both BH_3 and DIBAL are Lewis acids and will immediately form an adduct with the Lewis basic carbonyl group.
- Once the Lewis acid-base adduct is formed, a hydride is transferred over to the carbonyl group.



Reduction of Carboxylic Acid Derivatives

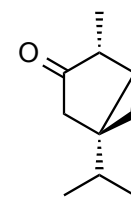


- In the case of the CADs, the 'x' group has a lone pair which can complex again to the electron deficient boron atom giving an intermediate which is stable at low temperatures.

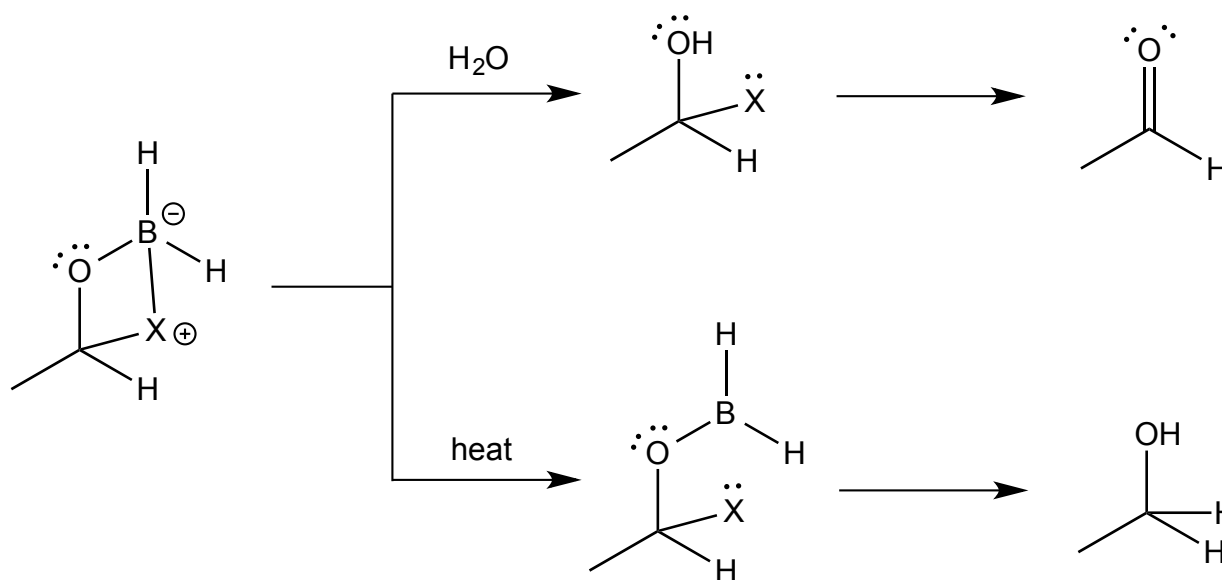


- If the intermediate is treated with water, excess reducing agent is destroyed and the reduction product is released. If the intermediate is warmed up first, the intermediate will collapse on its own and the product will be further reduced.

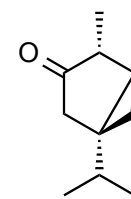
Reduction of Carboxylic Acid Derivatives



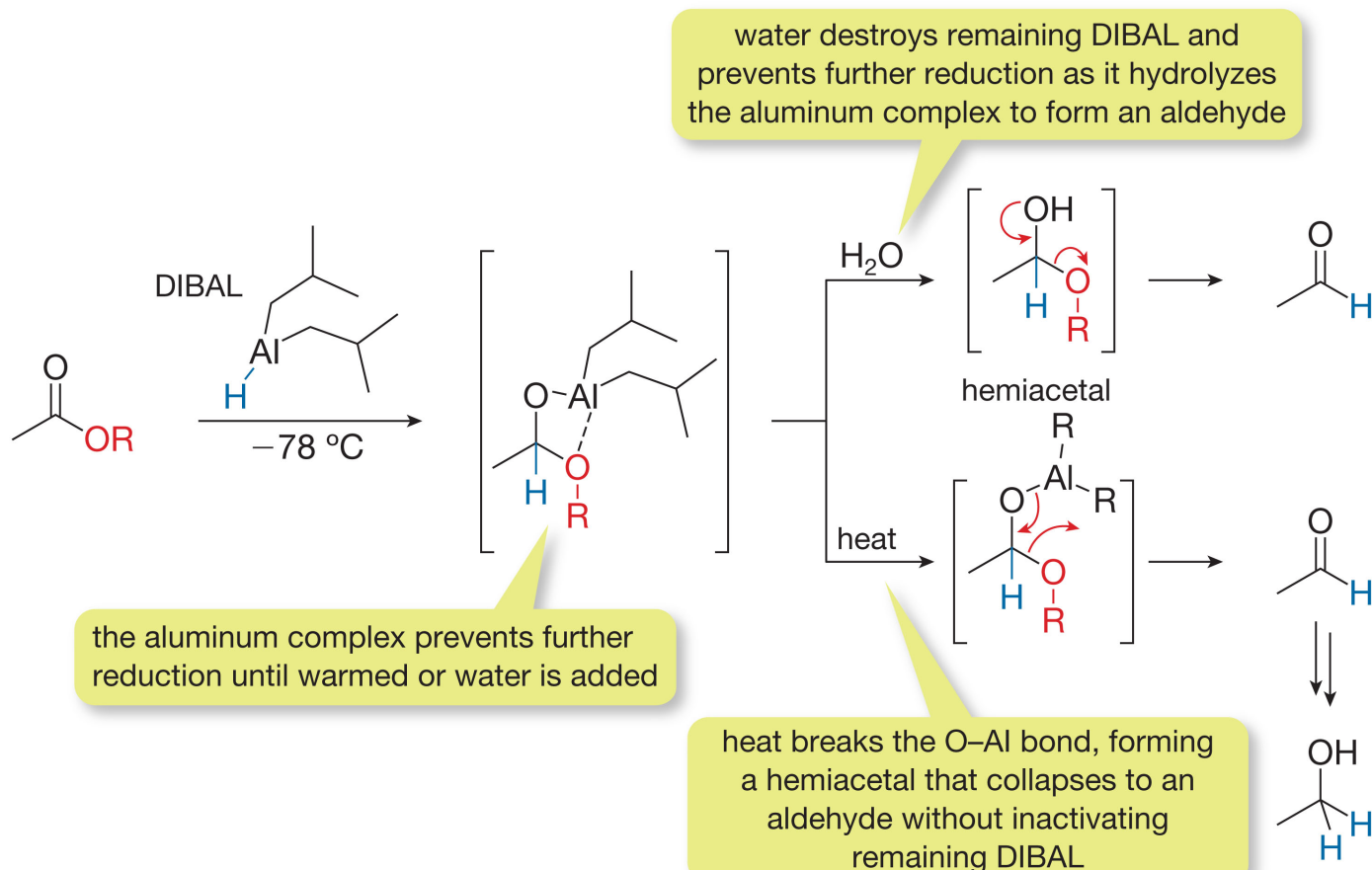
- If the intermediate is treated with water, excess reducing agent is destroyed and the reduction product is released. If the intermediate is warmed up first, the intermediate will collapse and the product is further reduced.



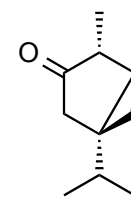
Reduction of Carboxylic Acid Derivatives



- Reduction of an ester with DIBAL:

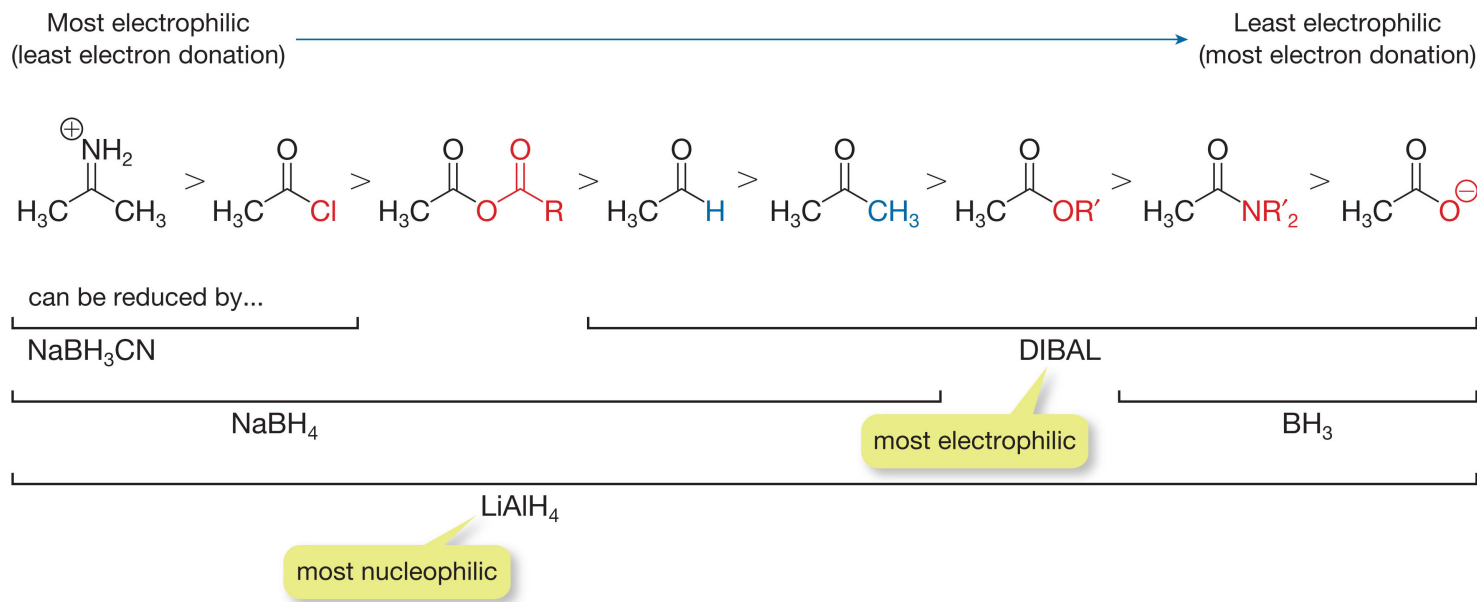


Reduction of Carboxylic Acid Derivatives

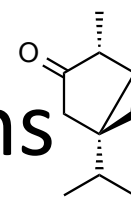


DIBAL reduction summary:

- To reduce an ester or amide to an aldehyde, use low temperatures (-78°C) followed by an aqueous acidic workup.
- To reduce an ester to a primary alcohol or an amide to a primary amine, use higher temperatures followed by an aqueous acidic workup.

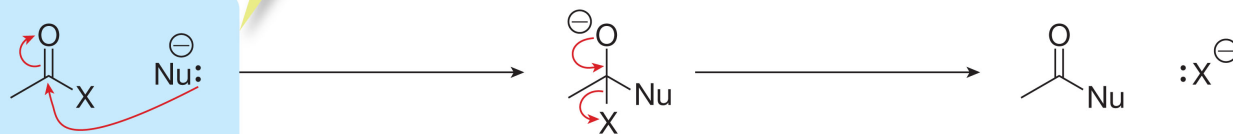


Patterns in Addition-Elimination Reactions

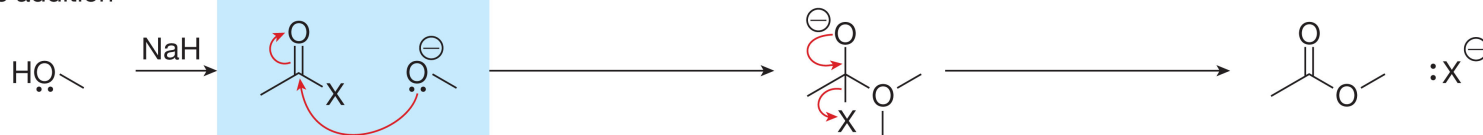


π bond always breaks as nucleophile adds

Neutral nucleophiles generate acid



Basic nucleophiles accelerate addition



Acid catalyzes addition

