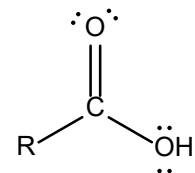# CHEMISTRY 2600

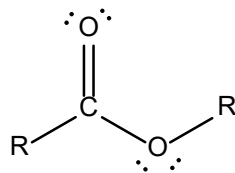Topic #6: Carboxylic Acid Derivatives

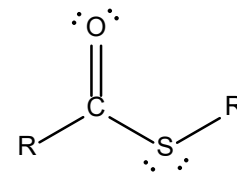Spring 2021

Dr. Susan Findlay

Carboxylic Acid Derivatives

- Carboxylic acid derivatives are frequently grouped together because the carbonyl carbon has the same oxidation state), so they can be interconverted via substitution reactions.

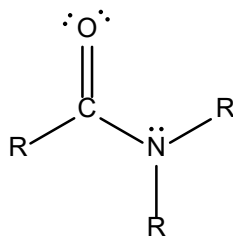- The most common carboxylic acid derivatives include:

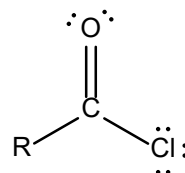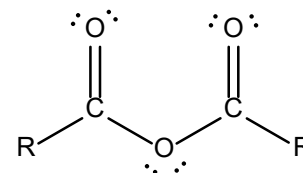carboxylic acid   ester   thioester

amide   acid chloride   anhydride

For these examples, note that

- R groups may be carbon-based or hydrogen. R groups in the same molecule are not necessarily the same.

- R' groups must be carbon-based. If any of them were hydrogen, that would change the functional group.
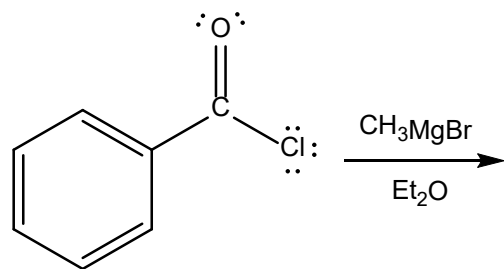
Carboxylic Acid Derivatives as Electrophiles

- In CHEM 2500, you saw what happens when a nucleophile attacks a ketone or aldehyde:
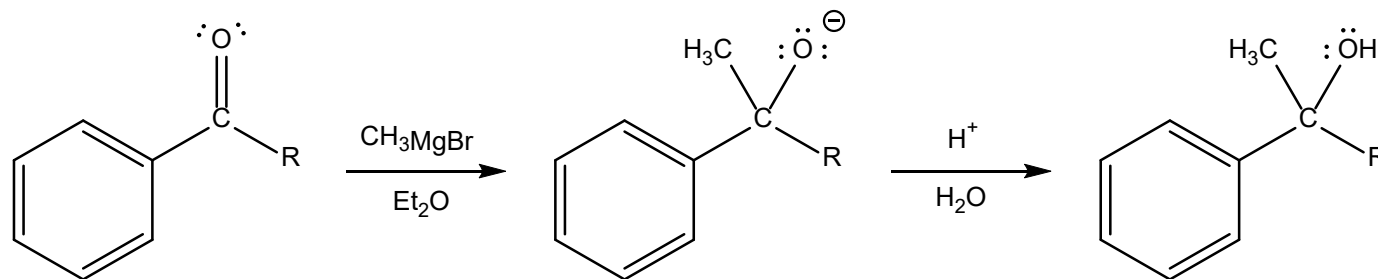
Carboxylic Acid Derivatives as Electrophiles

- Imagine replacing the R group with a leaving group. How would you expect this reaction to change? What would stay the same?
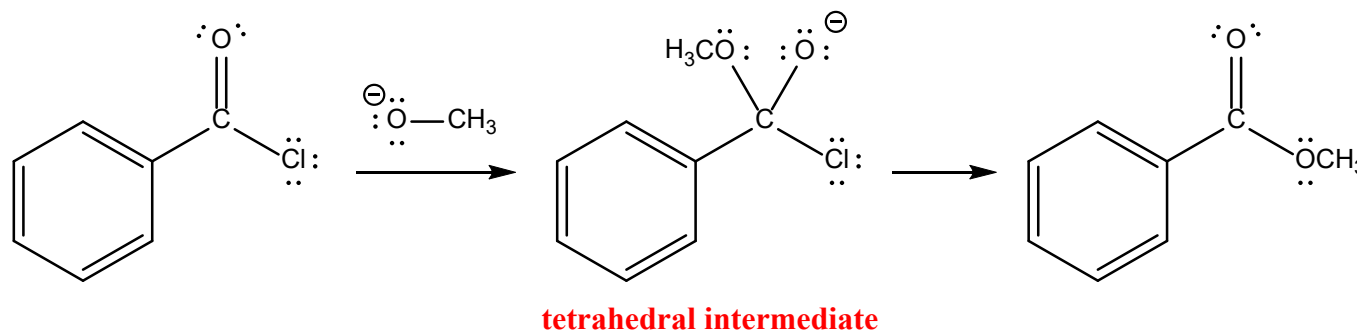
Carboxylic Acid Derivatives as Electrophiles

- Whenever a nucleophile attacks a carboxylic acid derivative, a **tetrahedral intermediate** is formed. The nucleophile attacks the electrophilic carbon, breaking the weakest bond (pi bond).

- If a leaving group is present, a lone pair on the oxygen atom can be used to regenerate the C-O pi bond, pushing out the leaving group and giving back the carbonyl group.

- The nucleophile will NEVER displace the leaving group directly in an S_N2 reaction. Why not?

Carboxylic Acid Derivatives as Electrophiles

- Because carbonyl groups are such good electrophiles, a wide variety of different nucleophiles can attack carboxylic acid derivatives.

- Consider the reaction between benzoyl chloride and methoxide:

tetrahedral intermediate

- Again, a **tetrahedral intermediate** is formed as the nucleophile attacks the electrophilic carbon, breaking the weakest bond (the C-O pi bond). The C-O pi bond reforms, regenerating the carbonyl group.

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Carboxylic Acid Derivatives as Electrophiles

- We can also see that this reaction would not have worked if we replaced the acid chloride with an amide. Why not?


NO REACTION!
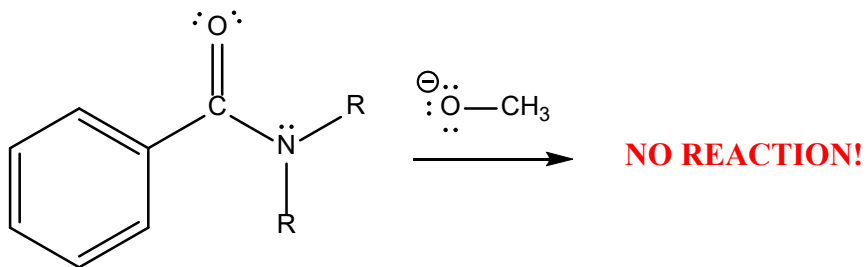
Interconverting Carboxylic Acid Derivatives

- We can use the leaving group's basicity as a measure of how reactive a carboxylic acid group is to this type of substitution:
  - Acid Chlorides (Cl⁻ leaves; pK_a of HCl is -7)
  - Anhydrides (RCO_2^- leaves; pK_a of RCO_2H is ~5)
  - Thioesters (RS⁻ leaves; pK_a of RSH is ~10)
  - Esters (RO⁻ leaves; pK_a of ROH is ~15)
  - Amides (R_2N^- leaves; pK_a of R_2NH is ~35)
  - Carboxylic Acids cannot undergo this type of reaction directly. Basic nucleophiles deprotonate them instead.
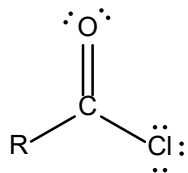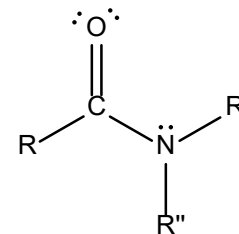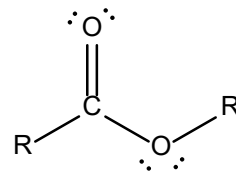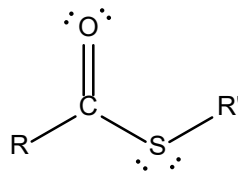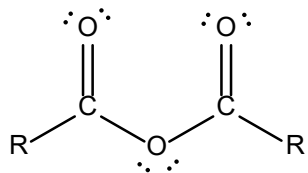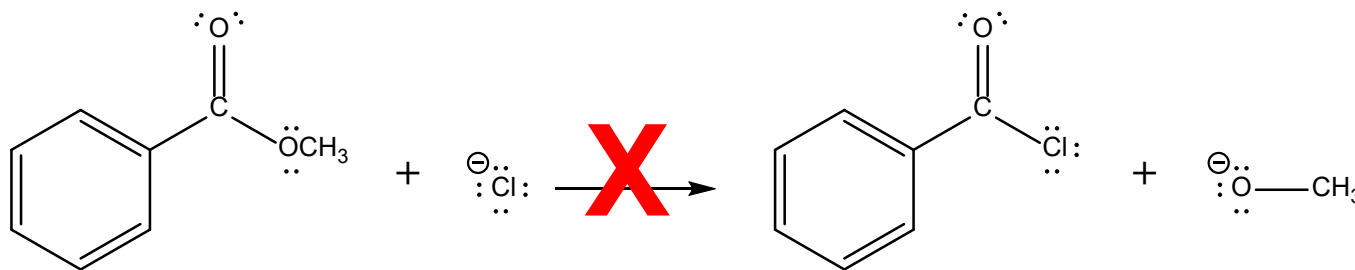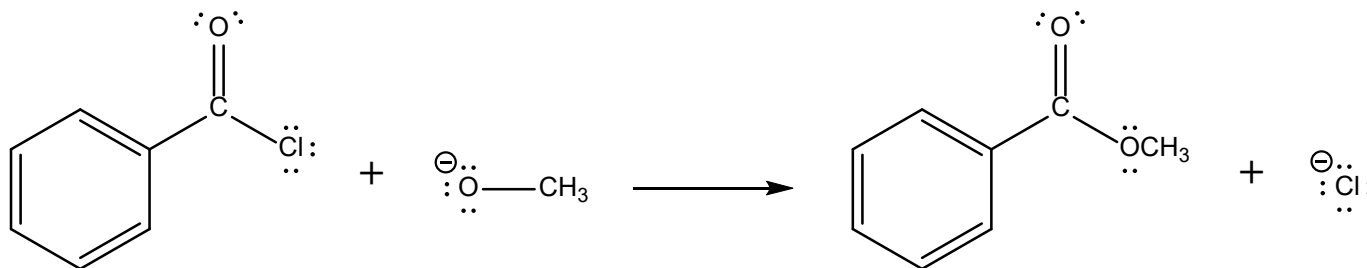
most electrophilic   least electrophilic
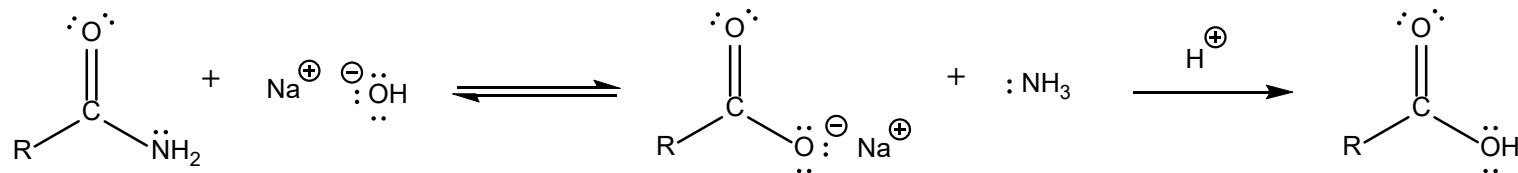
Interconverting Carboxylic Acid Derivatives

- As a general rule, we can only replace a better leaving group with a poorer leaving group. So, you can make an ester by reacting an acid chloride with RO^- but you cannot make an acid chloride by reacting an ester with Cl^-.
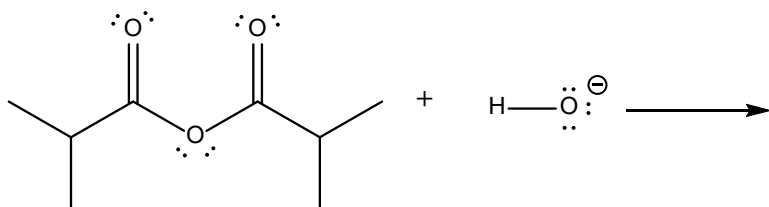
Interconverting Carboxylic Acid Derivatives

■ Carboxylic acids are a special case. The nucleophilicity of HO^- is similar to that of RO^- but if you add a lot of hydroxide and heat, you can use Le Châtelier's principle to push the reaction forward slowly. So, you can even react amides with HO^- to give the corresponding carboxylate salt (which can later be protonated to give the carboxylic acid):
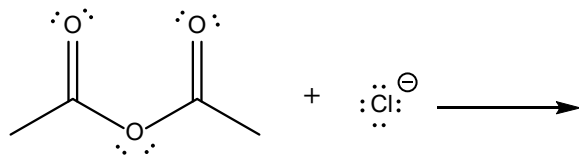

■ What pushes the equilibrium forward in the first step?

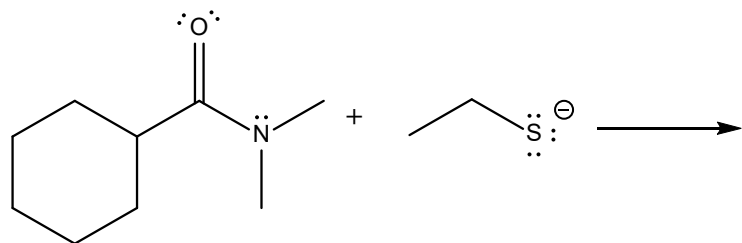# Interconverting Carboxylic Acid Derivatives

- Which of the following reactions would you expect to work <u>well</u>? For those that will, draw the products.
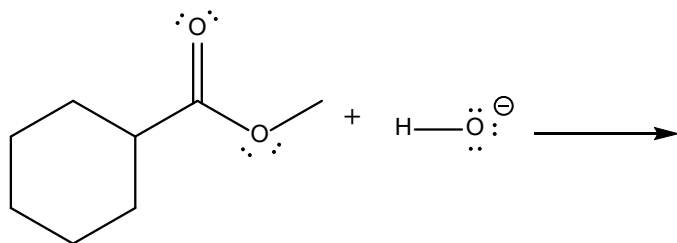
Making Acid Chlorides

- Since acid chlorides are among the most reactive carboxylic acid derivatives, they are popular choices as starting materials. They can be readily prepared from carboxylic acids and react with a wide variety of nucleophiles.

- To make an acid chloride from a carboxylic acid, just add thionyl chloride ($SOCl_2$):
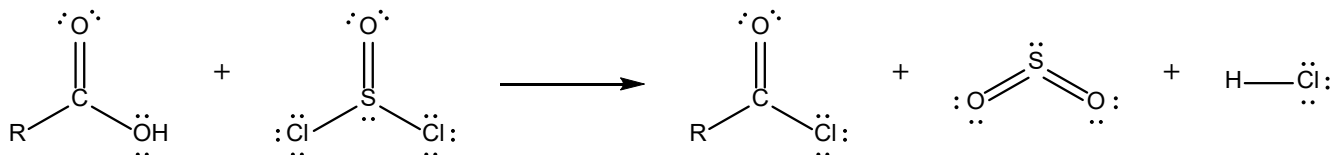
Similarly, thionyl bromide ($SOBr_2$) can be used to make acid bromides:
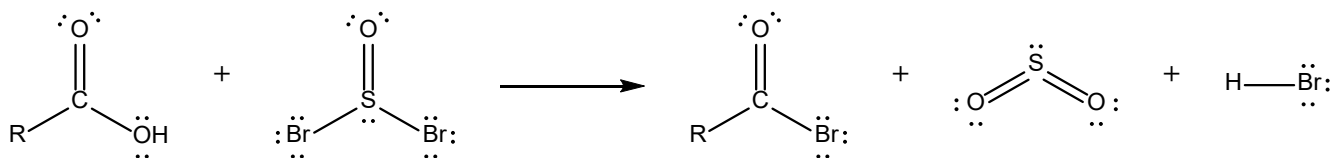
Making Acid Chlorides

- First, the carboxylic acid attacks the $SOCl_2$:

Making Acid Chlorides

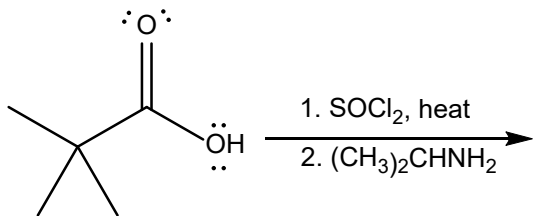- Then the chloride ion produced attacks the adduct:
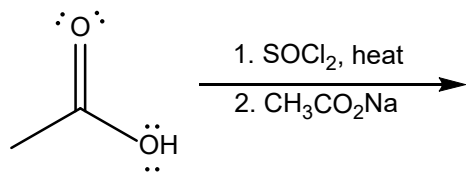
Making Acid Chlorides

- Finally, there is a rearrangement, breaking the adduct into the acid chloride and two gases (SO_2 and HCl):
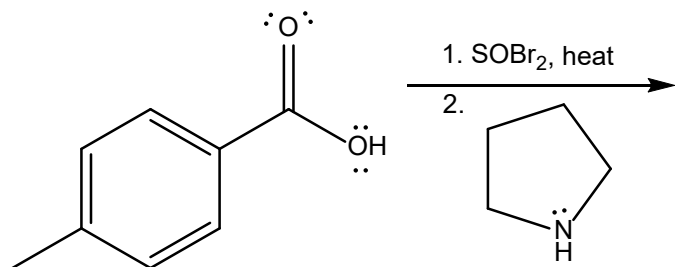
Making and Reacting Acid Chlorides

- Draw the products of each of the following reaction sequences:

1. SOCl$_2$, heat
2. (CH$_3$)$_2$CHNH$_2$

1. SOCl$_2$, heat
2. CH$_3$CO$_2$Na

1. SOBr₂, heat

2.

Making Carboxylic Acids from Esters

- Esters are less reactive than acid chlorides, but more abundant in nature. As such, they are important starting materials in organic synthesis. If necessary, an ester can be converted to a carboxylic acid – which can then be converted to the acid chloride.

- Reaction of an ester with hydroxide is called a **saponification** ("soap making") reaction:
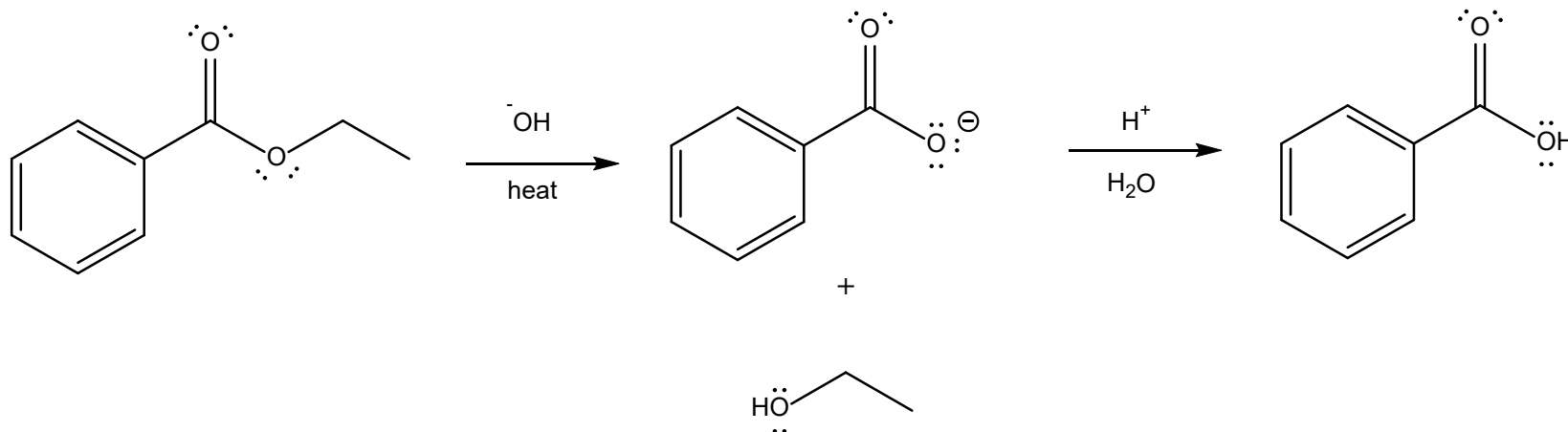
- Acidic work up is necessary if you wish to obtain the carboxylic acid rather than a carboxylate salt.

Making Carboxylic Acids from Esters

- If, on the other hand, you want to make soap, the carboxylate salt is your target:
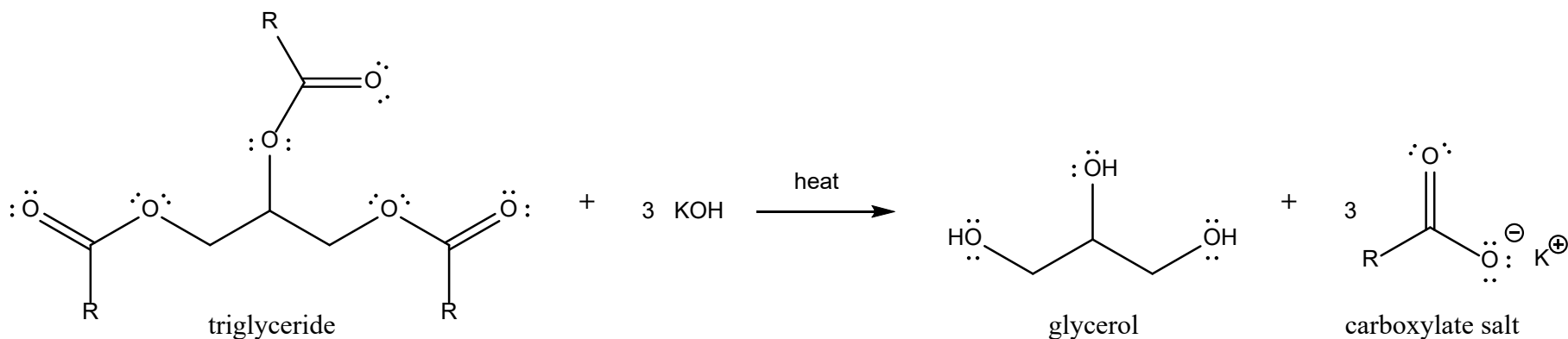
In soap making, R is an alkyl chain (typically 15-25 carbon atoms long). It may include double bonds (if an unsaturated fat was used).

Making Esters from Carboxylic Acids

- When making a carboxylic acid from an ester, we take advantage of the acidity of the carboxylic acid, deprotonating it to give an insoluble carboxylate salt. Since the salt precipitates out of solution, Le Châtelier's principle drives the reaction forward even though HO^- and RO^- are about equally basic.

- Unfortunately, that doesn't help us if we wish to do the reverse reaction: making an ester from a carboxylic acid. In fact, we cannot make an ester from a carboxylic acid under basic conditions. Why not?
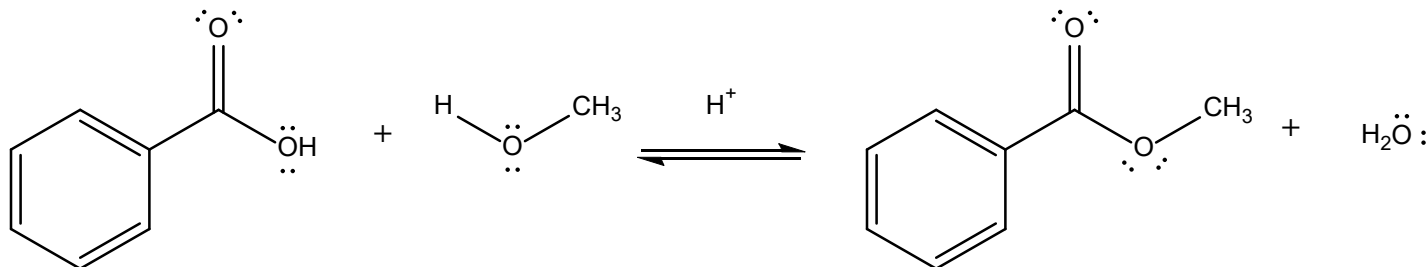
Making Esters from Carboxylic Acids

- We therefore have to use acidic conditions to make an ester from a carboxylic acid. Alcohols are not good enough nucleophiles to attack neutral carboxylic acid groups, so we need the acid to activate the carbonyl group in the carboxylic acid and make it more electrophilic before the alcohol will attack:
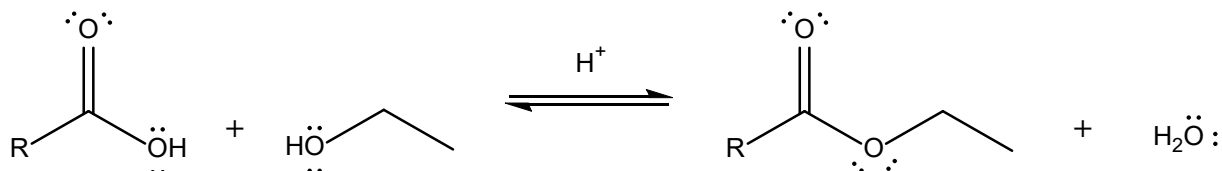
- This is known as a Fischer esterification.
- Since the alcohol and water are comparable nucleophiles, and the carboxylic acid and ester are comparable electrophiles, we must again use Le Châtelier's principle to drive the reaction forward. How?
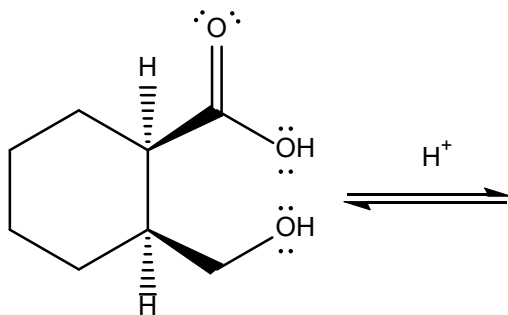
Making Esters from Carboxylic Acids

- A Fischer esterification may look like an ordinary substitution reaction, but it still goes through a **tetrahedral intermediate**. Remember that S_N2 reactions can only occur at tetrahedral carbon atoms; they CANNOT occur at carbonyl groups!
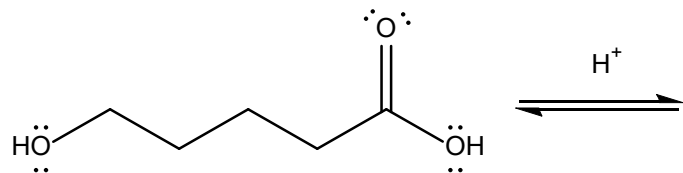
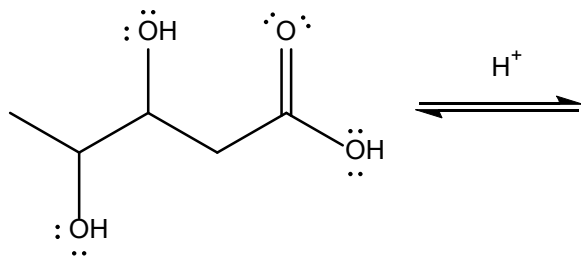# Making Esters from Carboxylic Acids

- If the alcohol and carboxylic acid are both in the same molecule, the product of an esterification will be a **lactone** (a cyclic ester). What are the products of the following reactions:

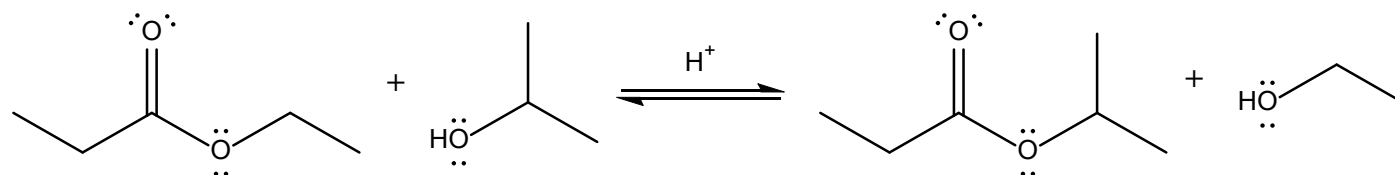# Making Esters from Carboxylic Acids
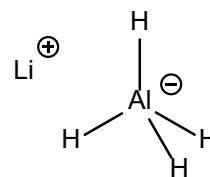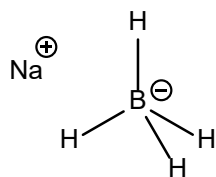
Making Esters from Other Esters

- We can perform **transesterification** reactions in a similar way:
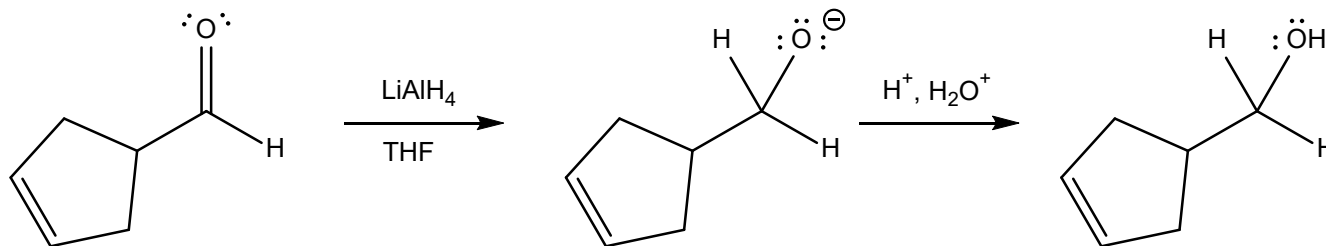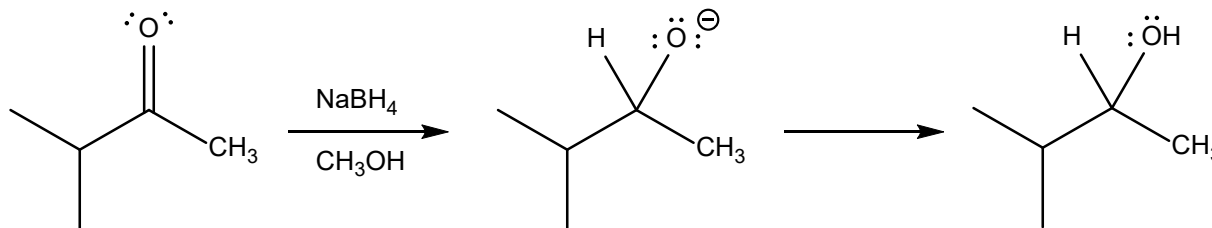

- Again, we need to promote the forward reaction over the reverse reaction. How can we do that?

Reduction of Carboxylic Acid Derivatives

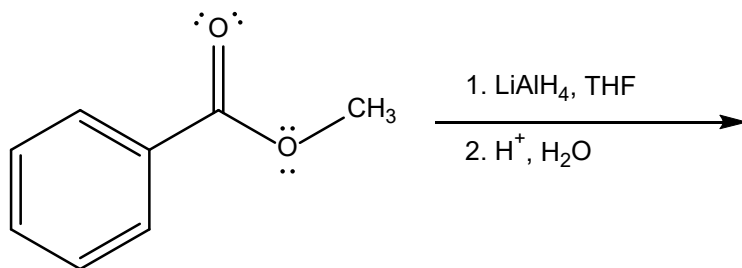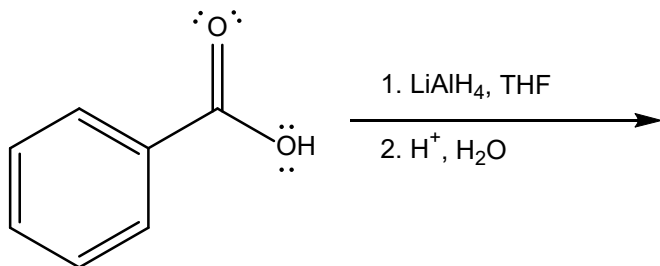- In CHEM 2500, you learned about nucleophilic hydride reagents like $LiAlH_4$ and $NaBH_4$:

- These reagents can add to the carbonyl group of an aldehyde or ketone, giving the corresponding alcohol:
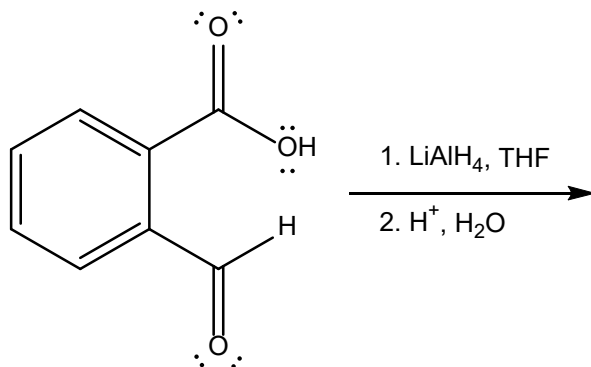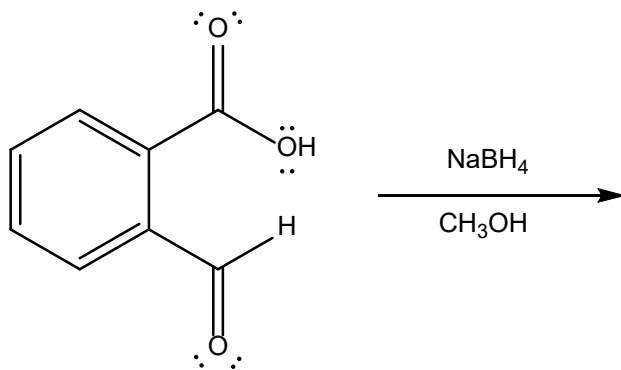
Reduction of Carboxylic Acid Derivatives

- $LiAlH_4$ can also reduce carboxylic acids and esters to the corresponding alcohols. $NaBH_4$ will not.

Reduction of Carboxylic Acid Derivatives

- In this way, $NaBH_4$ can be used to selectively reduce one type of carbonyl group in the presence of another.

Reduction of Carboxylic Acid Derivatives

- To get opposite selectivity (favour reduction of less electrophilic carbonyl groups), use an electrophilic reducing agent instead (reacts preferentially with more electron-rich carbonyl…).

- An electrophilic reducing agent requires activation before it can serve as a source of nucleophilic hydrogen. Common examples include BH_3 and $DIBAL$ (diisobutylaluminium hydride):
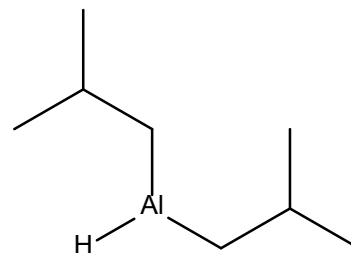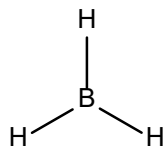
- What significant differences do you see between these reagents and $LiAl_4$ or $NaBH_4$?

Reduction of Carboxylic Acid Derivatives

- $DIBAL$ is a Lewis acid. As such, the first thing that happens when it reacts with a carbonyl is that the carbonyl donates a pair of electrons to it:
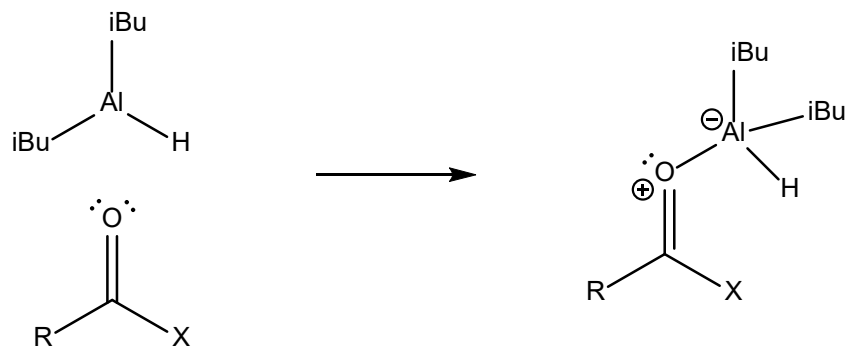
- This intermediate now more closely resembles $LiAlH_4$. It also has the advantage that the nucleophilic hydrogen atom is located very near the electrophilic carbon atom…
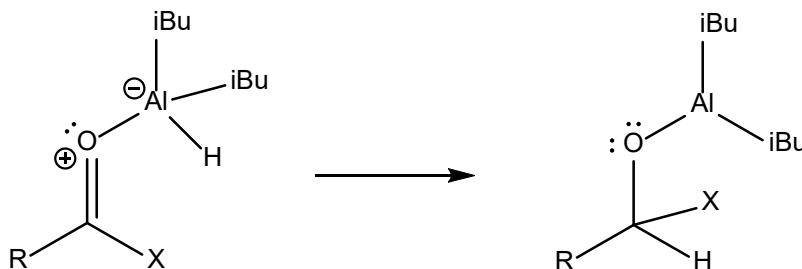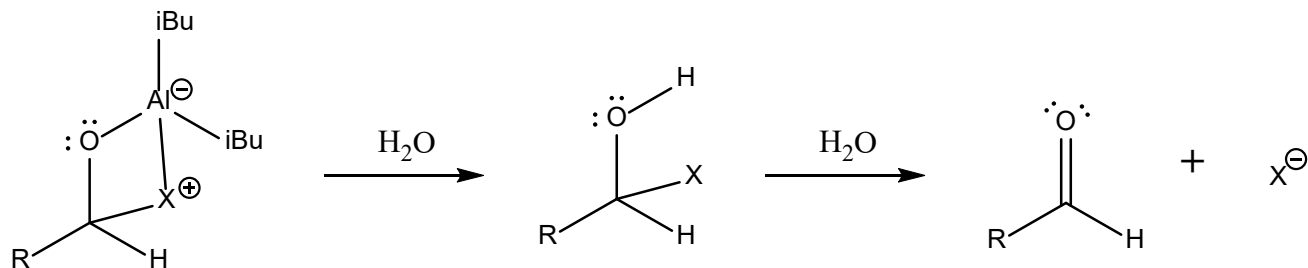
Reduction of Carboxylic Acid Derivatives

- If the "X" group has a lone pair (as it would in reduction of an ester or amide), that lone pair is donated to the aluminium atom in another Lewis acid-base reaction, giving an intermediate that is reasonably stable at low temperatures:
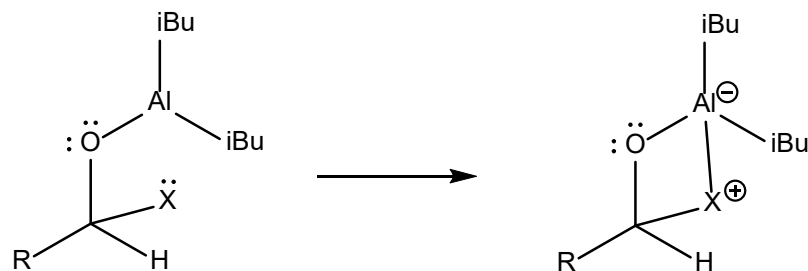
- Work-up with water hydrolyzes this intermediate, releasing the product of reduction:
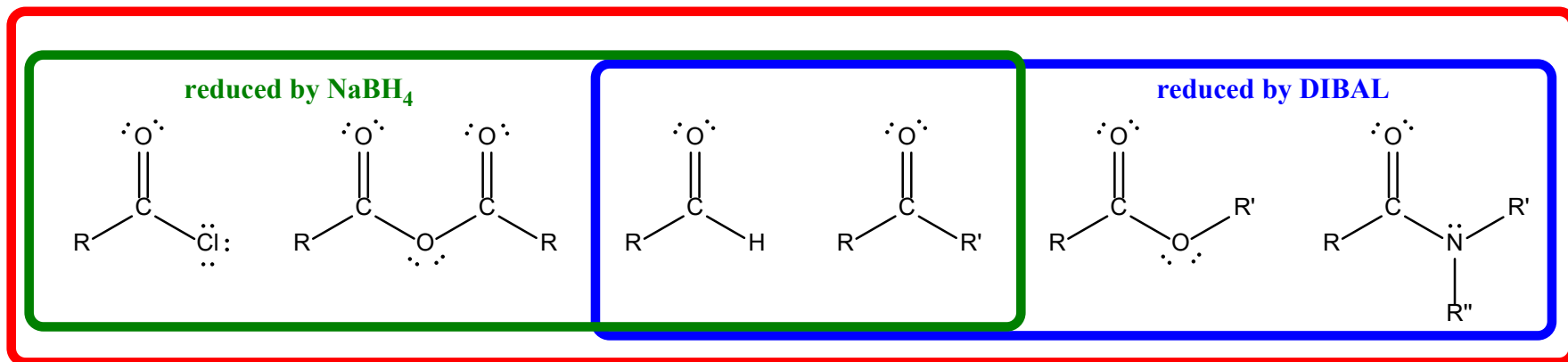
Reduction of Carboxylic Acid Derivatives

- If the intermediate is instead allowed to warm up before water is added, it collapses on its own. The resulting species can then be reduced by a second equivalent of $DIBAL$.

- Thus, $DIBAL$ can:
    - reduce an ester to an aldehyde (low temperature reaction followed by workup with aqueous acid)
    - reduce an ester to a primary alcohol (higher temperature reaction followed by workup with aqueous acid; $LiAlH_4$ also does this)
    - reduce an amide to an aldehyde (low temperature reaction followed by workup with aqueous acid)
    - reduce an amide to an amine (higher temperature reaction that allows amine to form before workup; $LiAlH_4$ also does this)
    - reduce a ketone to a secondary alcohol (typically, only done if the bulk of the of $DIBAL$ will allow you to favour one diastereomer of product over the other; otherwise, you could use $LiAlH_4$ or $NaBH_4$)
    - reduce an aldehyde to a primary alcohol (not a common application because it's usually cheaper to use $LiAlH_4$ or $NaBH_4$)

Reduction of Carboxylic Acid Derivatives

- The reactivity of different carbonyl compounds with $LiAlH_4$, $NaBH_4$ and $DIBAL$ is as follows:
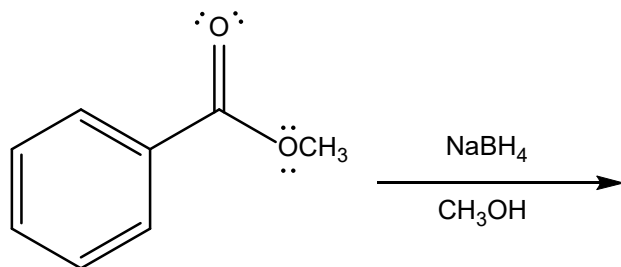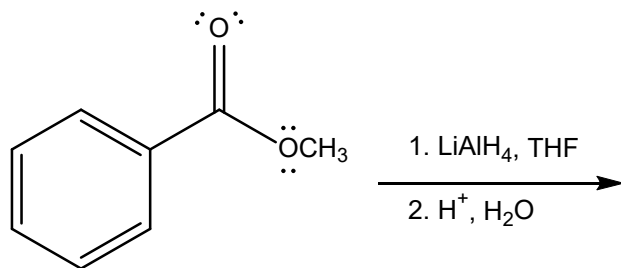

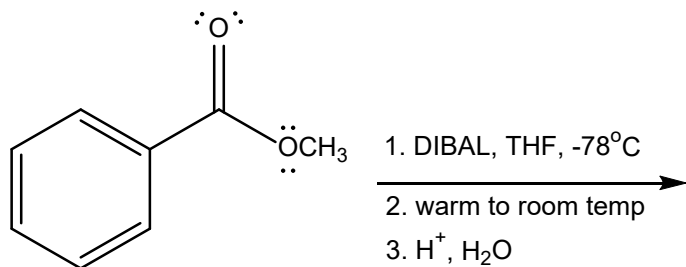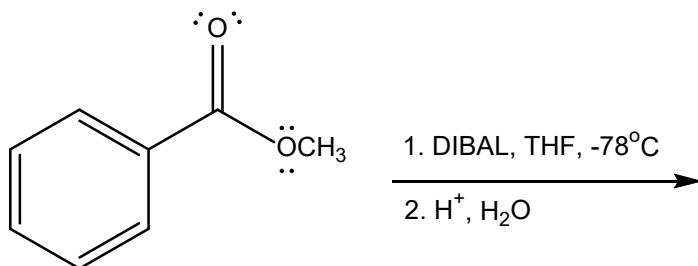most electrophilic carbonyl   least electrophilic carbonyl

Reduction of Carboxylic Acid Derivatives

■ For each of the following reactions, draw the organic product or write "no reaction" if that is the case.

1. DIBAL, THF, -78°C

2. H^+, H_2O

1. DIBAL, THF, -78°C

2. warm to room temp

3. H^+, H_2O

1. LiAlH$_4$, THF

2. H$^+$, H$_2$O

1. DIBAL, THF, -78°C

2. H$^+$, H$_2$O

1. DIBAL, THF, -78°C

2. warm to room temp

3. H$^+$, H$_2$O

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