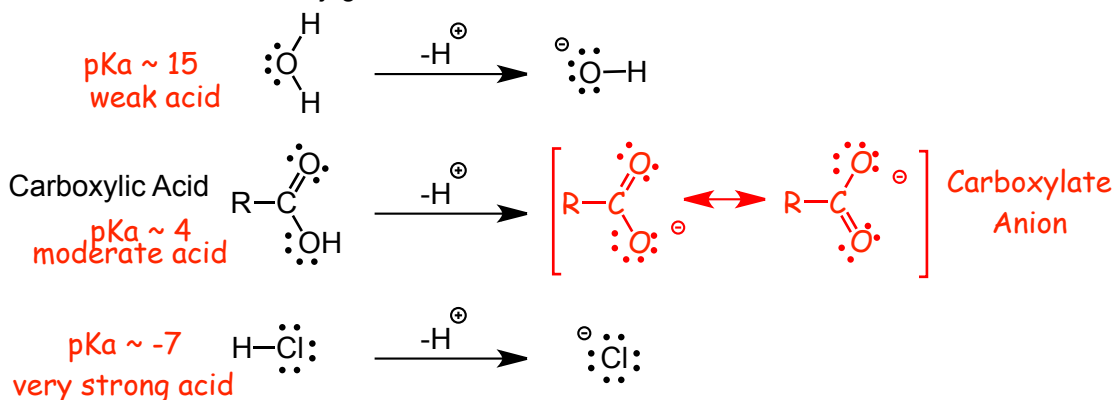


**Some Notation:** Acids and their conjugate bases



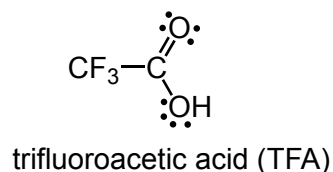
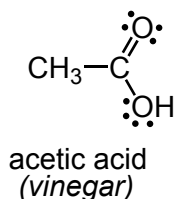
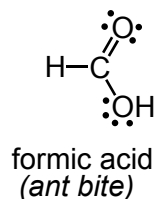
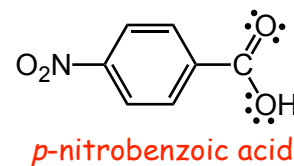
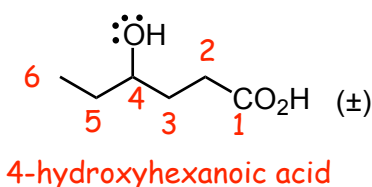
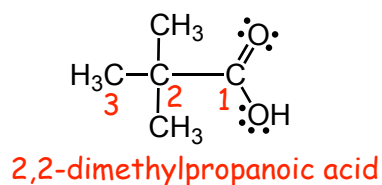
- Carboxylic acids are **moderate** acids, somewhere between the weak acid water and "real" acids such as hydrochloric (HCl).
- The conjugate base anion of a carboxylic acid is the **resonance stabilized** carboxylate anion.

## 1 Nomenclature

IUPAC priority: **acid** > aldehyde > ketone > alcohol > alkene > alkyne > halide

- Priority increases with increasing oxidation state, acids are the most oxidized functional group, they will always have the highest priority.
- The carbon carrying the  $-\text{CO}_2\text{H}$  is number 1.
- Acid use the suffix "**-oic acid**".

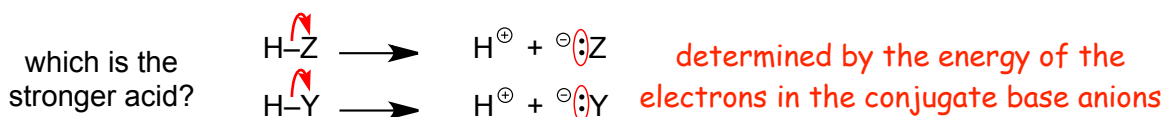
### Examples



You should know these, TFA is a common organic acid used in catalysis

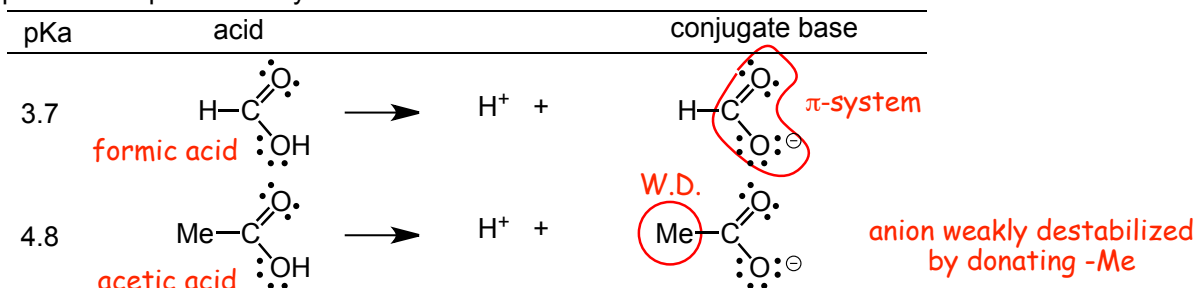
## 2 Factors Controlling Acidity

- When comparing acidity for carboxylic acids - think about the stability of the electrons in the conjugate base anion as usual. This always works except going down the periodic table, which we are not doing here.

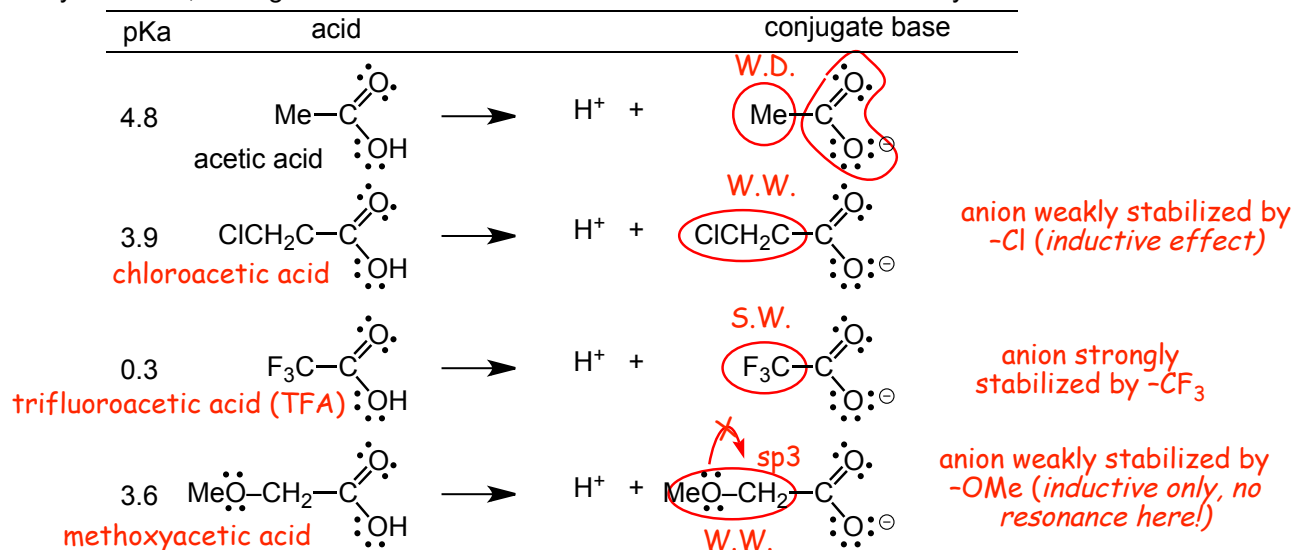


## Examples of pK<sub>a</sub>s

- Compare the simplest carboxylic acids.....

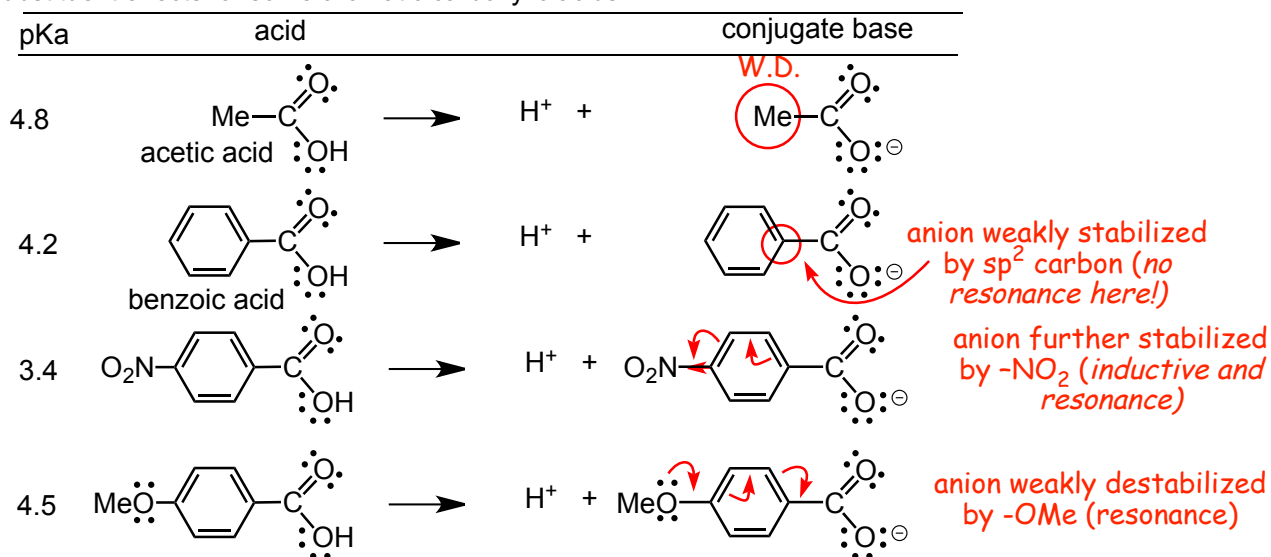


- For formic versus acetic acid (above), we can think of the -Me as a donating group that destabilizes the carboxylate anion, but higher solvation of the smaller formate anion almost certainly also contributes.



- Note: the methoxy substituent in the last example is not directly attached to the  $\pi$ -system, there is an sp<sup>3</sup> hybridized carbon atom in between, in this case it is not a donating group because there is no resonance donation, only a weak inductive effect of the electronegative oxygen.

- Substituent effects for some aromatic carboxylic acids.....

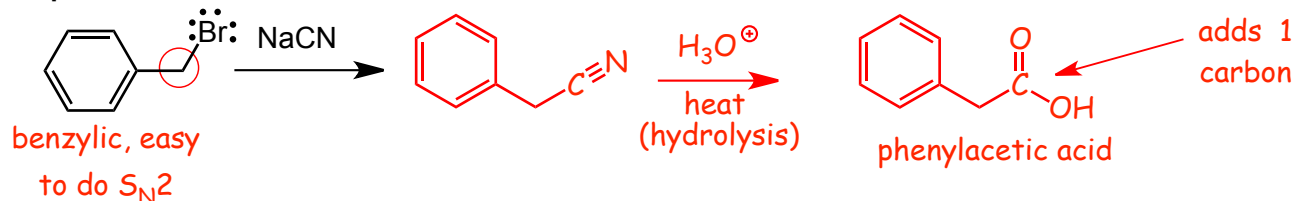


- Note: in the benzoate anion (conjugate base of benzoic acid), there is no possibility of delocalizing the non-bonding electrons into the benzene ring, the ring does not stabilize the electrons by resonance, there is only a very small stabilization due to the slightly stronger bonds attached to the  $\pi$ -system due to the sp<sup>2</sup> hybridized carbon of the ring.



- This is a standard acid catalyzed hydrolysis mechanism, but a **lot** longer, therefore we use  $+H^+/-H^+$  notation.
- Even though this is a **long** mechanism, it should be approached by analogy to previous hydrolysis mechanisms and using our knowledge of fundamental Bronsted/Lewis acid/base reactions and understanding how we break bonds from nitrogen to carbon by protonating.
- Note: **There are two steps in this mechanism that look odd**, the reprotonation step after the amide forms the same intermediate that deprotonated to form the amide, obviously formation of the amide could have been omitted from the mechanism and the mechanism would have been simpler.
- The purpose of this step, however, is to **show that an amide is a formal intermediate in the overall hydrolysis process**, and also to remind us that an amide can be hydrolyzed to form an acid.

#### Example

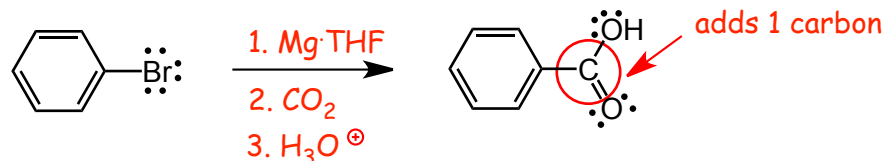


### 3.3 Carboxylic Acid Synthesis Strategies

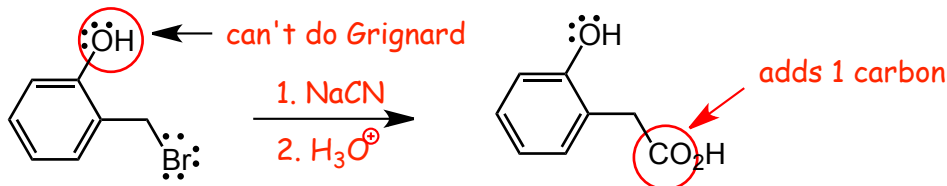
Starting with a bromide leaving group:

- Use the Grignard method for tertiary ( $3^\circ$ ) and aromatic halides (where the  $S_N2$  reaction is not possible).
- Use the nitrile method in presence of acidic protons (where no Grignard reaction is possible).

#### Examples



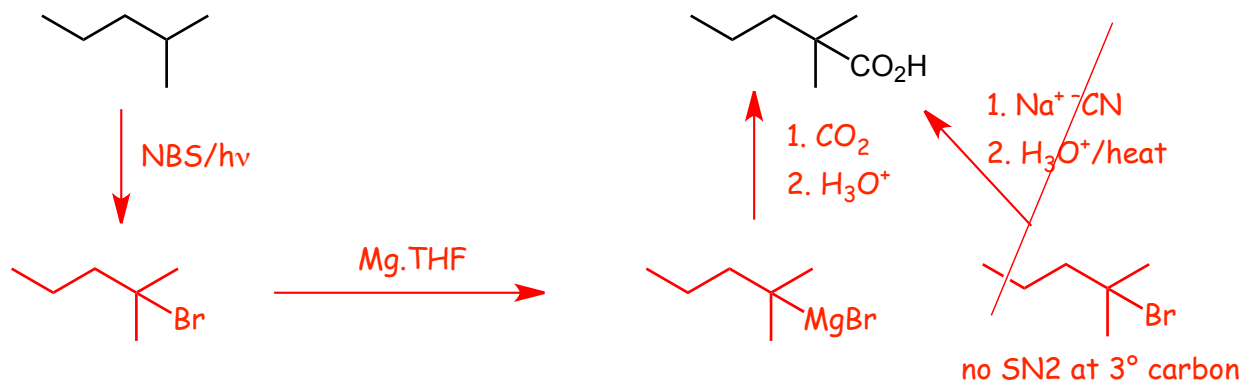
- We can't use the nitrile hydrolysis method above because we can't add the nitrile ( $NaCN$ ) because we can't do an  $S_N2$  at an  $sp^2$  hybridized carbon atom (above).



- The Grignard reaction is not possible above because of the  $-OH$  group, which would simply protonate the Grignard before it could do any other reaction. But formation of a nitrile followed by hydrolysis is possible here

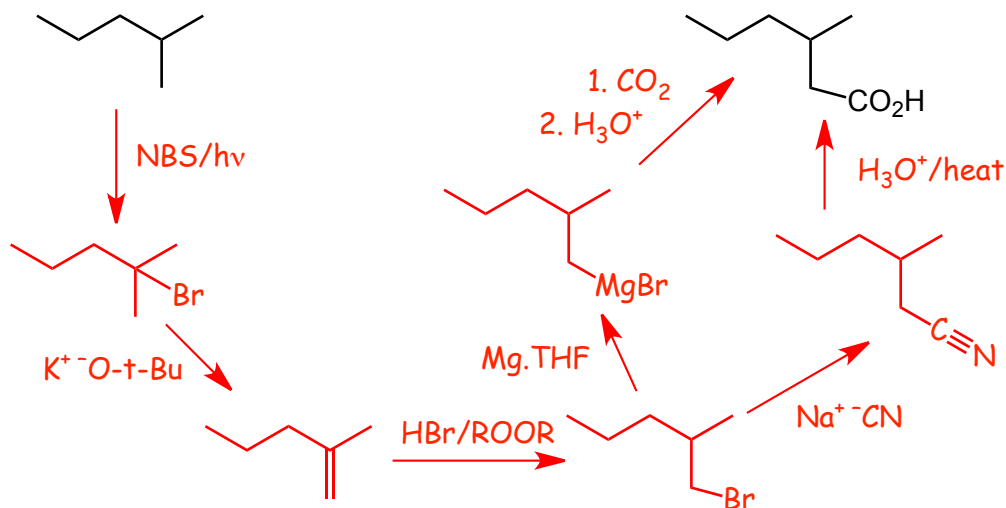
#### Multi-Step Synthesis Problem

Example 1: Give a synthesis of the target carboxylic acid on the right from the starting structure on the left:



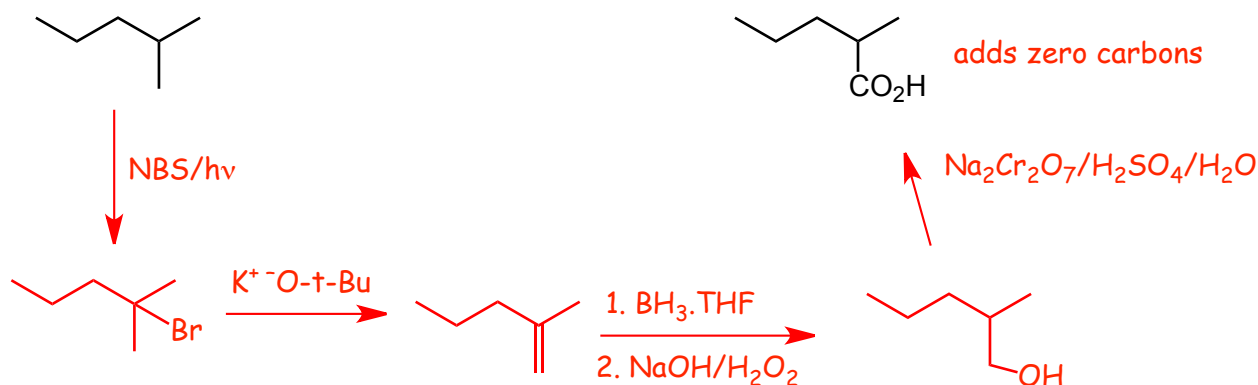
- We need to add 1 carbon atom to a tertiary carbon,  $S_N2$  will not work, this has to be a Grignard reaction.

**Example 2:** Give a synthesis of the target carboxylic acid on the right from the starting structure on the left:



• We need to add 1 carbon atom to a **primary** carbon, either the Grignard **or** the SN2 route with cyanide will work.

**Example 3:** Give a synthesis of the target carboxylic acid on the right from the starting structure on the left:



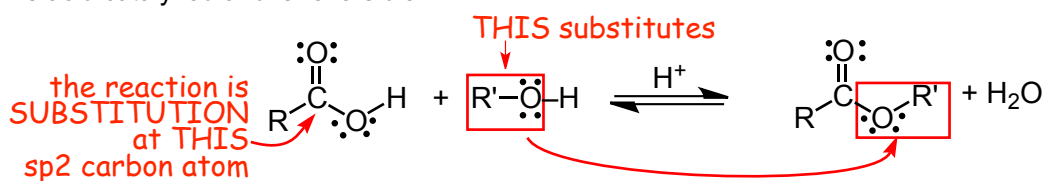
• Here we need to add zero carbon atoms, therefore we need to make the carboxylic acid by oxidation of a primary alcohol.

## 4 Reactions of Carboxylic Acids

### 4.1 Fischer Esterification

• It is mainly the mechanism that is important here since it introduces a **new principle**.

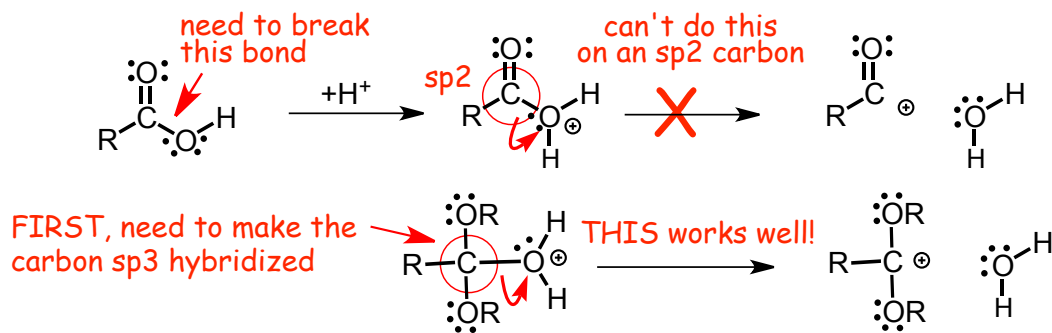
**The reaction** is acid catalyzed and is reversible:



• We can "push" the reaction towards the ester by using excess alcohol as the solvent, or adding a dehydrating agent to remove the water (**Le Chatelier's principle**).

• We **can't use  $\text{H}_3\text{O}^+$**  as the acid catalyst, because this would push the reaction "back" towards the acid due to ester hydrolysis in the presence of water (remember,  $\text{H}_3\text{O}^+$  is acid in water), use dry HCl gas that is bubbled into the alcohol solvent instead,

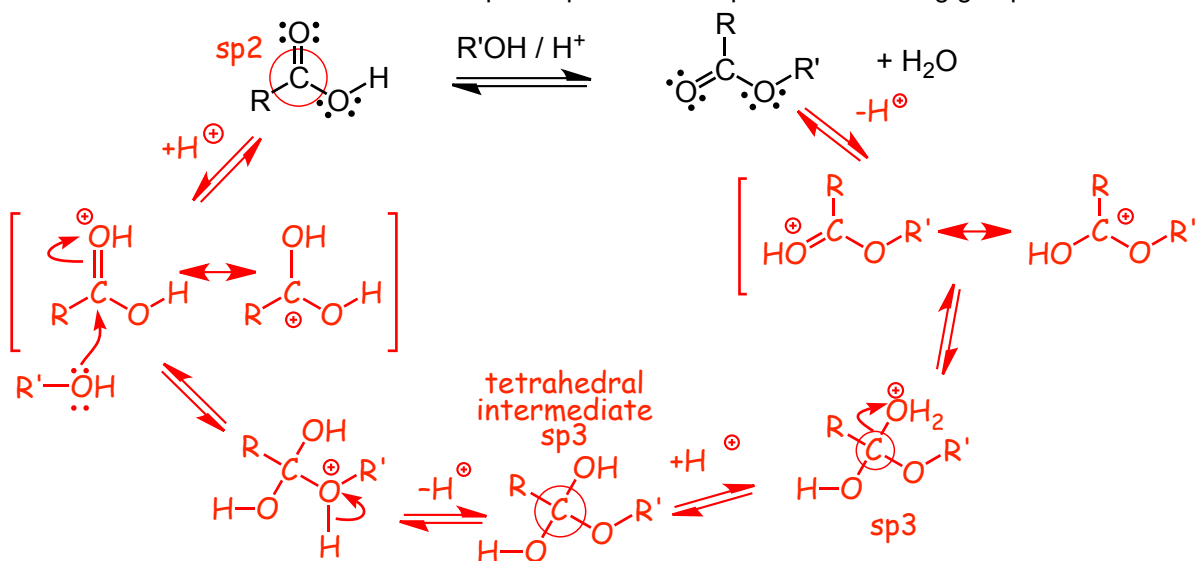
• The reaction is formally **substitution** at the  $\text{sp}^2$  hybridized carbon atom of the  $\text{C}=\text{O}$  carbonyl, **however, we can't do SN1 or SN2** even when the oxygen is protonated **because the carbon is  $\text{sp}^2$  hybridized!**



- The sp<sup>2</sup> hybridized C=O carbon **must be** transformed into an sp<sup>3</sup> hybridized carbon atom (tetrahedral intermediate), **then**, we can have the usual water leaving group.
- This is a **new mechanistic** principle.

### The Mechanism

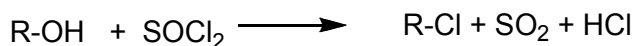
- It is similar to other mechanisms we have seen in aldehydes and ketones except that the substitution requires the transformation of the central carbon from sp<sup>2</sup> to sp<sup>3</sup> before the protonated leaving group can leave.



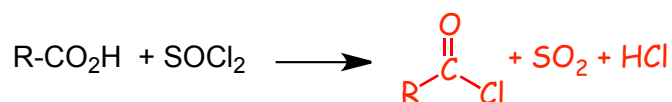
- Once the tetrahedral intermediate is formed, cleaving the C-OH bond can occur in the usual way because the carbon is now sp<sup>3</sup> hybridized, protonated the oxygen and have water as a good leaving group.
- We will learn a **much** better way of making esters in the next section.

## 4.2 Formation of Acid Chlorides

### Recall

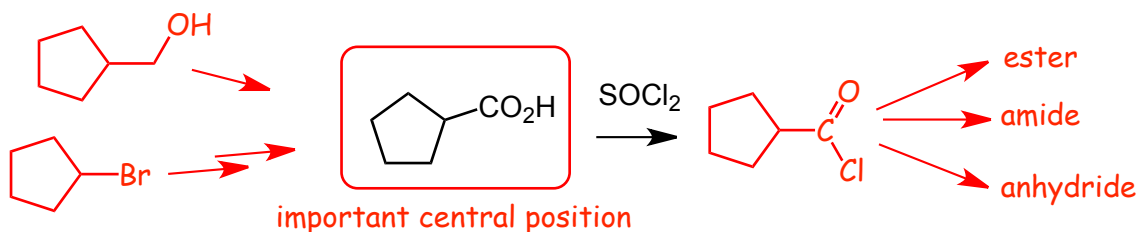


### Similarly



- The mechanism of this reaction is identical to that for formation of an alkyl chloride from an alcohol.
- **This is an important reaction**, because as we will soon see, conversion of an acid to an acid chloride allows synthesis of **all** carboxylic acid derivatives.

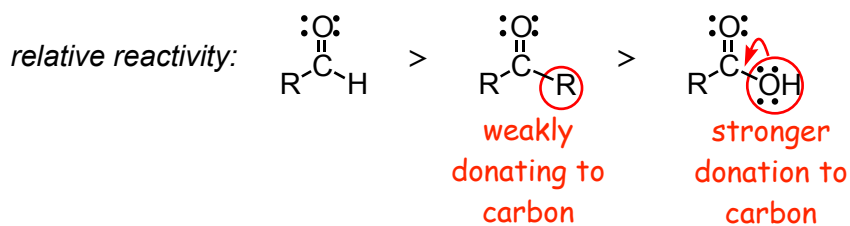
### Example



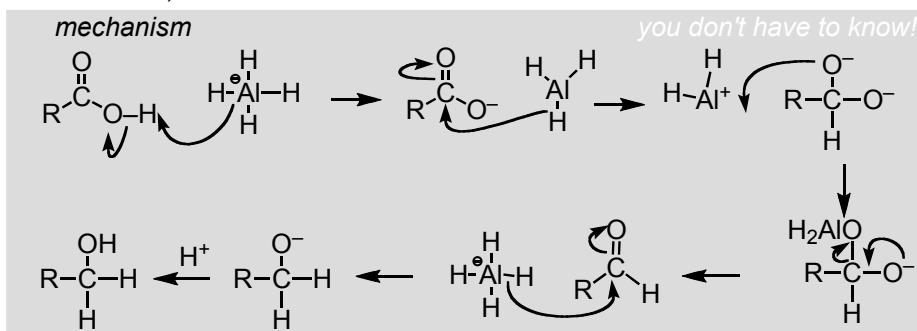
### 4.3 Reduction With Lithium Aluminum Hydride

Recall: R relative reducing ability:  $\text{H}^- > \text{LiAlH}_4 > \text{NaBH}_4$

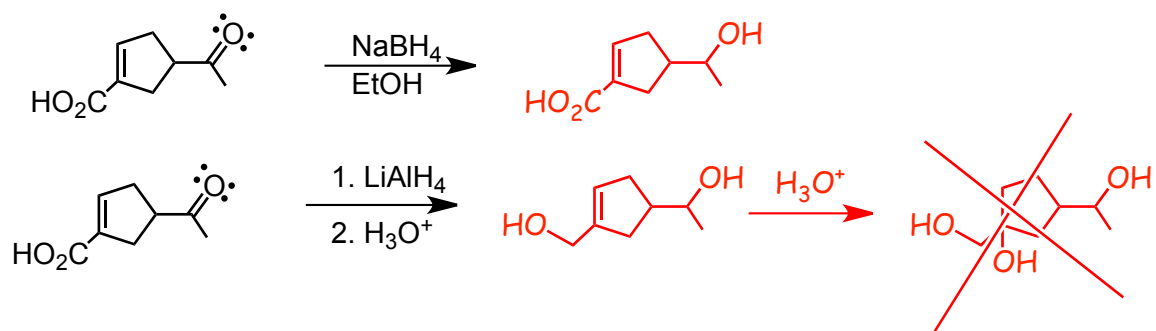
Also:



- $\text{NaBH}_4$  will not reduce an acid, but  $\text{LiAlH}_4$  will:



#### Examples



- **Note** that the  $\text{H}_3\text{O}^+$  that is used in the second step of the  $\text{LiAlH}_4$  reduction is in the form of an "acid workup", which means that enough acid is used to protonate any anions. Hydration of a  $\text{C}=\text{C}$  bond in an alkene usually requires heating in the presence of high concentrations of acid for extended periods, and so addition of water to the  $\text{C}=\text{C}$  bond in  $\text{LiAlH}_4$  reactions is unlikely to occur.

## 5 Summary of Reactions Involving Carboxylic Acids

