Week 2

More Nucleophiles and Carboxylic Acid Derivative Synthesis

2.1 Aldehydes and Ketones 2

4/5:

- Announcements:
  - PSet 1 is due Thursday 4/7.
    - Covers through today's content.
  - Midterm 4/21 during class.
    - No notes, no cheat sheets.
    - Shouldn't require stuff from last quarter.
    - Exams should be like problem sets but shorter and easier.
    - The practice exam and midterm are of identical structure.
    - PSet 1-2 material will be tested.
- Plan for today:
  - Hydride and carbide nucleophiles.
  - Finish Unit 1.
- You can't use acidic conditions in reactions with hydride and carbide nucleophiles.
  - The reason for this restriction is that hydrides and carbides are both strong bases and will preferentially react with any acids in solution instead of performing the chemistry that we want them to.
- Hydrogen nucleophiles.
- Levin reviews the reduction of carbonyls with $NaBH_4$ and $LiAlH_4$.
- Misc. notes.
  - The solvent for $NaBH_4$ is methanol, while adding $LiAlH_4$ requires a subsequent acidic workup.
  - BH_4^- is less reactive than AlH_4^- because boron is more electronegative than aluminum.
  - Mixing $LiAlH_4$ with methanol will cause an explosion, but $NaBH_4$ is mild enough that methanol is a feasible solvent.
- Mechanism ($NaBH_4$).
  - A concerted mechanism.

  - Herein, the $H-BH_3^-$ single-bond electrons attack the carbonyl carbon, the C=O π electrons attack the hydroxyl hydrogen on methanol, and the $H-OCH_3$ single-bond electrons retreat onto methanol's oxygen.

- Mechanism ($LiAlH_4$).
  - A stepwise mechanism.
  - AlH_4^- is a strong enough nucleophile to add into a carbonyl directly without needing the thermodynamic help of the methanol proton as in the $NaBH_4$ mechanism.
  - The alkoxide is then protonated by acid.
  - However, we have to beware of the alkoxide attacking AlH_3 in an unwanted side reaction.
    - The trapped form is the dominant form in solution, but overtime the alkoxide form protonates off.
    - AlH_3 also eventually reacts with enough acid to become **alumina**.
- **Alumina**: The complex ion $Al(OH)_4^-$.
- Carbon nucleophiles.
- **Lithiate**: An organolithium compound.
- Levin reviews the syntheses of both lithiates and Grigards.
- Recall that both of these can also only work in basic solution.
- Levin reviews the mechanism of a lithiate/Grignard attack on a ketone/aldehyde.
- Cyanide is another important carbon nucleophile.
  - It is formed from the reaction $H-CN \rightleftharpoons H^+ + CN^-$.
  - This is important because it's a rare carbanion with a reasonably acidic conjugate acid.
    - For instance, the H in $H-CR_3$ has $pK_a > 50$.
    - However, HCN has $pK_a \approx 9$.
    - The acidity arises from the C≡N triple bond and nitrogen functioning as an EWG.
- **Cyanohydrin**: The class of molecules resulting from the nucleophilic addition of HCN to a ketone or aldehyde. *Structure*

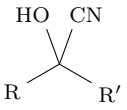
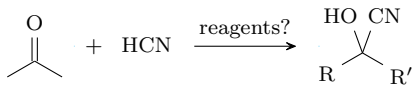


Figure 2.1: Cyanohydrin.

- General form.



  - The "reagents?" refers to the fact that this reaction *can* be accelerated by an acid or base catalyst, but no catalyst is necessary.
  - Acid catalysts are the most common, but anything works.
- Mechanism (neutral).
  - Similar to Figure 1.8a, but with no final deprotonation step necessary.

- We now transition to the problem of replacing carbonyls with vinyl groups.
  - We could do this by alkylating the carbonyl and then dehydrating. However, this leads to several possible products since acid-catalyzed dehydration does not select any alkene in particular.
  - A cleaner form exists using a new carbon nucleophile, a **phosphorous ylide**.
- **Phosphorus ylide**: The class of molecules having a P−C bond with a negative charge on C and a positive charge on P. *Structure*

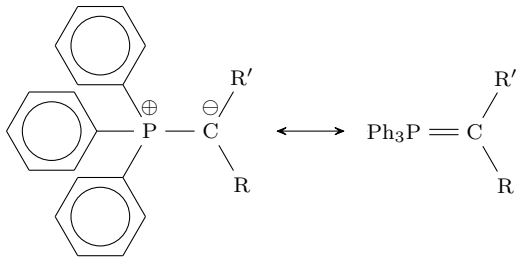


Figure 2.2: Phosphorous ylide.

  - The reactivity of phosphorous ylides is dominated by the left resonance structure in Figure 2.2.
- Synthesis of phosphorous ylides.

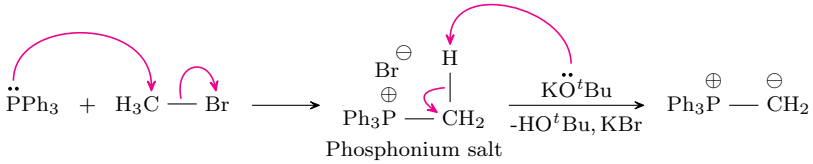
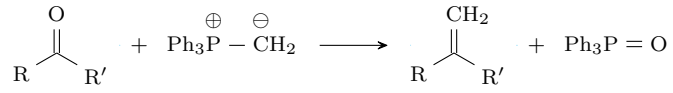


Figure 2.3: Synthesizing phosphorous ylides.

  - The first step is proceeds through an S_N2 mechanism.
  - The second step is aided by the fact that there is only one site with α-hydrogens. Additionally, the protons are mildly acidic because of the positive charge.
  - Note that we can use n-butyl lithium in place of KO^tBu if we want.
- A nice thing about PPh_3 is that it's air stable, so we can measure it out on the lab bench. (PMe_3 is pyrophoric, for instance).
- The Wittig[1] olefination.
- General form.



  - The creation of $Ph_3P{=}O$ (a very stable compound) is the thermodynamic driving force for the reaction.
    - Making this compound as a driving force is actually a common trick in organic chemistry.
- Mechanism (wrong).
  - Follows the model we've been using. Only recently disproven. We may use either this one or the correct one on exams.

[1] "VIT-tig"

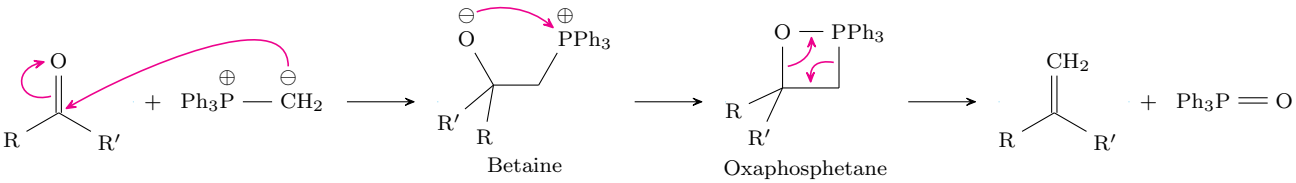
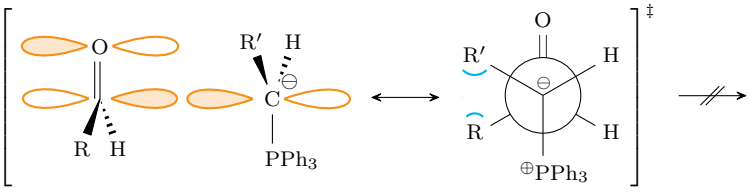


Figure 2.4: Wittig olefination mechanism (stepwise).

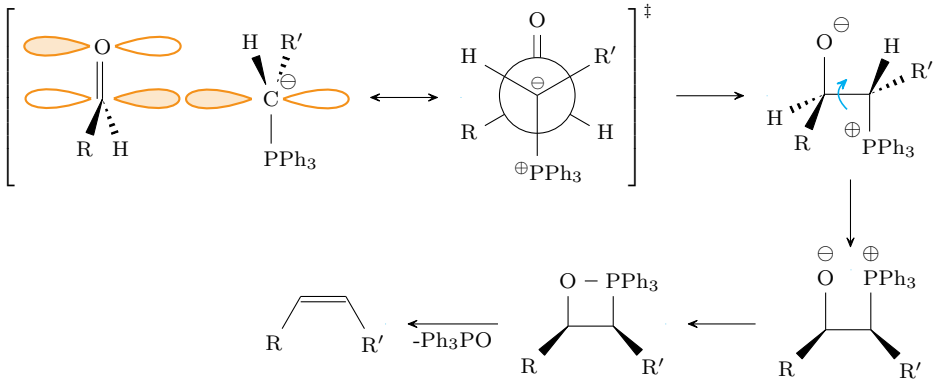
  - The Newtonian mechanics of OChem; we can get the right answer by using the wrong model.
  - The modern understanding is that the betaine never forms.
- This is a **retro-pericyclic mechanism**.
- The last step is a **retro-[2 + 2]**.
  - Note that the arrows may be drawn either of the two ways between adjacent bonds.

- The Wittig olefination is stereoselective for the *cis*-product.
  - This is strange since the *cis*-product is the less thermodynamically stable one.

- Three-dimensional intuition for the stereoselectivity.



(a) Unsuccessful collision.

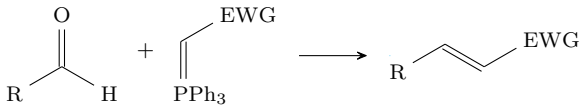


(b) Successful collision.

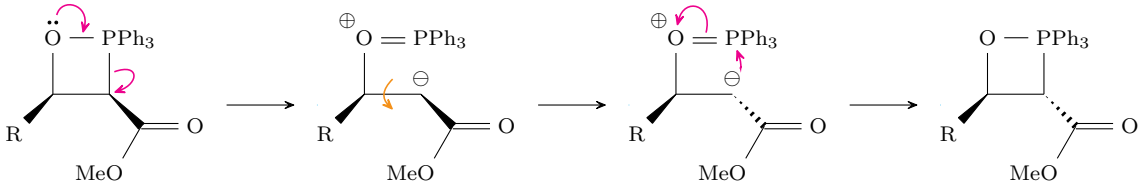
Figure 2.5: Wittig olefination stereoselectivity.

- We break the π C=O bond by filling the π^* C=O orbital. Thus, our carbanion p orbital collides end-on with the C=O π^* orbital.
- A gauche clash (as in Figure 2.5b) is higher energy and is not the favored collision.
- Thus, Figure 2.5a is the transition state that forms.
  - But we need to form a P–O bond, so after forming the *trans* imtermediate, we need to rotate the bond.
  - Once you form the *cis* product, you can't go back, so we'll go ahead and rotate to get the P–O bond.

- Stabilized ylides.



(a) General form.



(b) Intermediate rearrangement.

Figure 2.6: Stabilized ylides.

  - If the ylide has an EWG, the *trans* alkene will be formed.
  - In particular, the EWG stabilizes a carbocation formed from the oxaphosphetane EWG. We can then rotate and rebond before proceeding to the *trans* product.
  - Note that if the EWG on the aldehyde, we still form the *cis* product.

- Mechanism (correct).

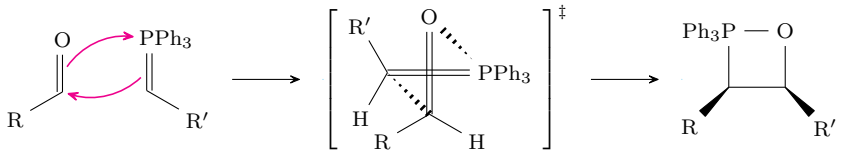


Figure 2.7: Wittig olefination mechanism (modern).

  - A $[2+2]$ followed by a retro $[2+2]$. We also have a T-shaped transition state that puts them far away. Then they rotate into *cis* position for the oxyphosphatane.

- Ketone Wittigs.
  - Slower but still proceed.
  - The biggest groups always end up *cis*.
- **α, β unsaturated carbonyl**: A carbonyl conjugated with an alkene spanning the α to β positions.
- The two possible nucleophilic additions to α, β unsaturated carbonyls are **1,2-additions** and **1,4-additions**.
- **1,2-addition**: A nucleophilic addition to the carbonyl carbon (numbered 2^{nd} atom from the carbonyl oxygen, which is 1 in turn).
- **1,4-addition**: A nucleophilic addition to the β position (numbered 4^{th} atom from the carbonyl oxygen, which is 1 in turn).
- $NaBH_4$.
  - The mechanism is similar to that in Figure 9.3a of Labalme (2022). However, Levin shows the the complete formation of an enol (after 1,2-addition) that then tautomerizes to a normal carbonyl before being attacked again.

- $LiAlH_4$.
  - The mechanism is similar to that in Figure 9.3b of Labalme (2022). However, Levin shows a single nucleophilic attack that can't proceed to a second until reductant is added into solution, but this inactivates the $LiAlH_4$.
- The pure 1,2-addition product is the major product for both $NaBH_4$ and $LiAlH_4$, but you get a mix of products?
- Organolithiums are highly selective for the 1,2-addition product, however.
  - Lithium is small and hard and favors bonding with the oxygen.
- Grignards still give a mixture.
  - Magnesium is happy to coordinate both the oxygen and the alkene (it's of intermediate hardness/softness).
- Hard-hard interactions are preferred because of Coulombic attraction; soft-soft interactions are preferred because of van der Waals forces.
- **Cuprate**: A compound containing an anionic copper complex.
  - The cuprates relevant to us are dialkyl cuprates, which have the form $LiCuMe_2$.
  - These are formed via the reaction

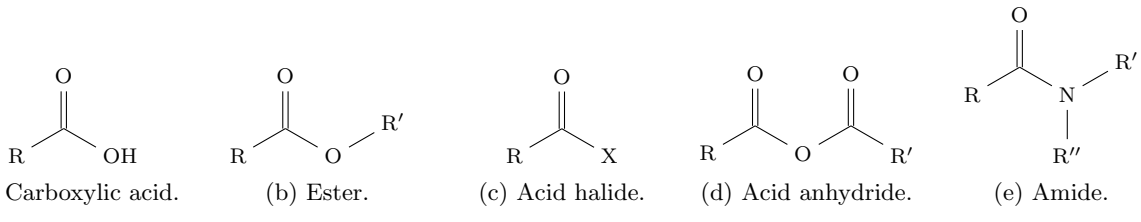
$$2\,\mathrm{MeLi} \xrightarrow[-\mathrm{LiI}]{\mathrm{CuI}} \mathrm{LiCuMe_2}$$

  - Cuprates are soft and yield exclusively 1,4-addition.
- Levin goes over some practice problems.

2.2 Carboxylic Acids and Derivatives 1

4/7:

- We now consider compounds that have heteroatoms where the α carbon of the carbonyl used to be.
  - The heteroatoms can be oxygen (esters), nitrogen, etc.
- Today, we will do oxygen and nitrogen nucleophiles but in this context.
  - Next Tuesday, we will do carbon and hydrogen nucleophiles in this context.
- Carboxylic acid derivatives.



(a) Carboxylic acid. (b) Ester. (c) Acid halide. (d) Acid anhydride. (e) Amide.

(f) Nitrile. (g) Carbonate. (h) Carbamate. (i) Urea.

Figure 2.8: Carboxylic acid derivatives.

  - Once again, we will not be tested on nomenclature, but it's good to know.
  - Acid anhydrides are so named because it is two carboxylic acids, minus a water molecule.
  - Nitriles are still a carbon bonded to three heteroatoms; it's just the same heteroatom.

- A key property of carboxylic acids is that they're... acidic.
- Acidity.
  - Gives the pK_a's of benzoic acid, benzyl alcohol, and phenol to demonstrate that resonance is king.
    - Benzoic acid is more acidic than phenol, which is more acidic than benzyl alcohol.
  - Inductive effects (changes to the α carbon) play a smaller role.
  - EWGs on arene rings when present play an even smaller role.
  - These latter two effects allow us to fine-tune acidity.
- Methods of carboxylic acid synthesis.
  1. Overoxidation.
  2. Carboxylation of Grignards or lithiates.
  3. Nitrile hydrolysis.
- Overoxidation.
- General form.

$$\mathrm{CRH(OH)} \xrightarrow[\mathrm{H_2O}]{\mathrm{CrO_3,\, H_2SO_4}} \mathrm{RCOOH}$$

  - Note that the reagents constitute Jones reagent.
- Mechanism.
  - Virtually identical to that from Labalme (2022).
- Carboxyliation of Grignards and lithiates.
- General form.

$$\mathrm{RLi} \xrightarrow[\mathrm{2.\, H_3O^+}]{\mathrm{1.\, CO_2}} \mathrm{RCOOH}$$

  - Note that we may use either lithiates (RLi) or Grignards (RMgBr), even though only an organolithium compound is shown above.
- Mechanism.

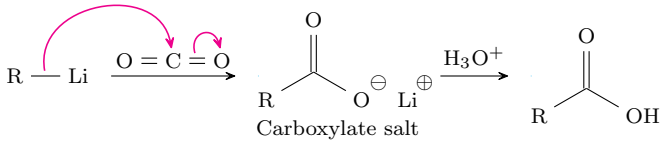
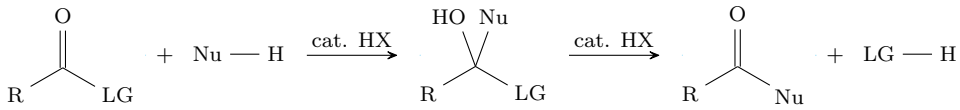
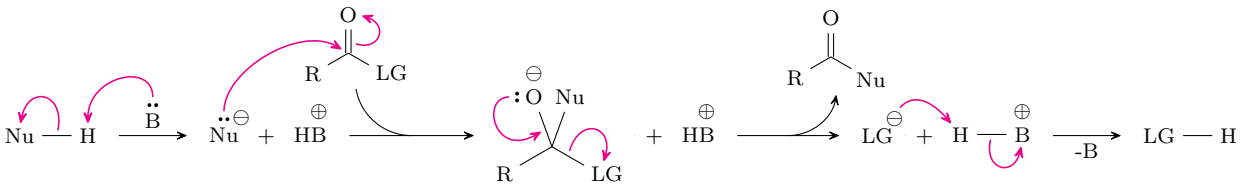


Figure 2.9: Carboxylation of lithiates mechanism.

- Mechanistic interlude: Nucleophilic acyl substitution.



(a) Acid-catalyzed reactivity.

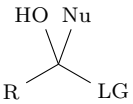


(b) Base-catalyzed reactivity.

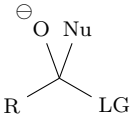
Figure 2.10: The typical reactivity of carboxylic acid derivatives.

- This mode of reactivity is the one that is most typical of carboxylic acid derivatives.
  - It is so-named because the portion of a carboxylic acid derivative that is not the leaving group is called an **acyl group**, and we are substituting one group on the acyl for another.
- Think of all of the carboxylic acid derivatives (see Figure 2.8) as containing a leaving group on one of their sides.
  - When these compounds react nucleophiles, the nucleophile replaces the leaving group.
- These reactions are either acid- or base-catalyzed.
  - In the acid-catalyzed version (Figure 2.10a), the first step proceeds exactly as in Figure 1.8a, except that $R' = LG$. The second step proceeds exactly as in Figure 1.8b, except that it is the leaving group that is protonated/removed instead of the nucleophile we just added in.
  - The basic mechanism is related to Figure 1.9, but rather than being a straight replication, the alkoxide species produced in Figure 1.9a proceeds straight to the reactivity of the alkoxide in Figure 1.9b (see Figure 2.10b).

- **Acyl group**: A moiety derived from the removal of the leaving group in a carboxylic acid derivative. *Not to be confused with* **acetyl group**.
- **Acetyl group**: A moiety derived from the removal of the hydroxyl group in acetic acid (for example). *Denoted by* **Ac**.
- **Tetrahedral intermediates**: The nucleophilic acyl substitution intermediates (of both the acidic and basic pathways) that have four groups attached to the central carbon.



(a) Acidic intermediate.



(b) Basic intermediate.

Figure 2.11: The tetrahedral intermediates.

- Historically, the name arose when scientists were arguing about whether or not an sp^3 carbon could be in this reaction. Some scientists supported the theory that these tetrahedral intermediates existed, while others disagreed.

- Nitrile hydrolysis.
- General form.

$$RCN + H_3O^+ \longrightarrow RCOOH + NH_4{}^+$$

  - Note that here we're using a stoichiometric full equivalent of acid, not just catalytic acid, because we are liberating ammonia which mops up our acid, forming $NH_4{}^+$ as a byproduct.
  - The existence of this reaction is the reason we consider nitriles to be carboxylic acid derivatives (i.e., because we can interconvert them with carboxylic acids).

- Mechanism.

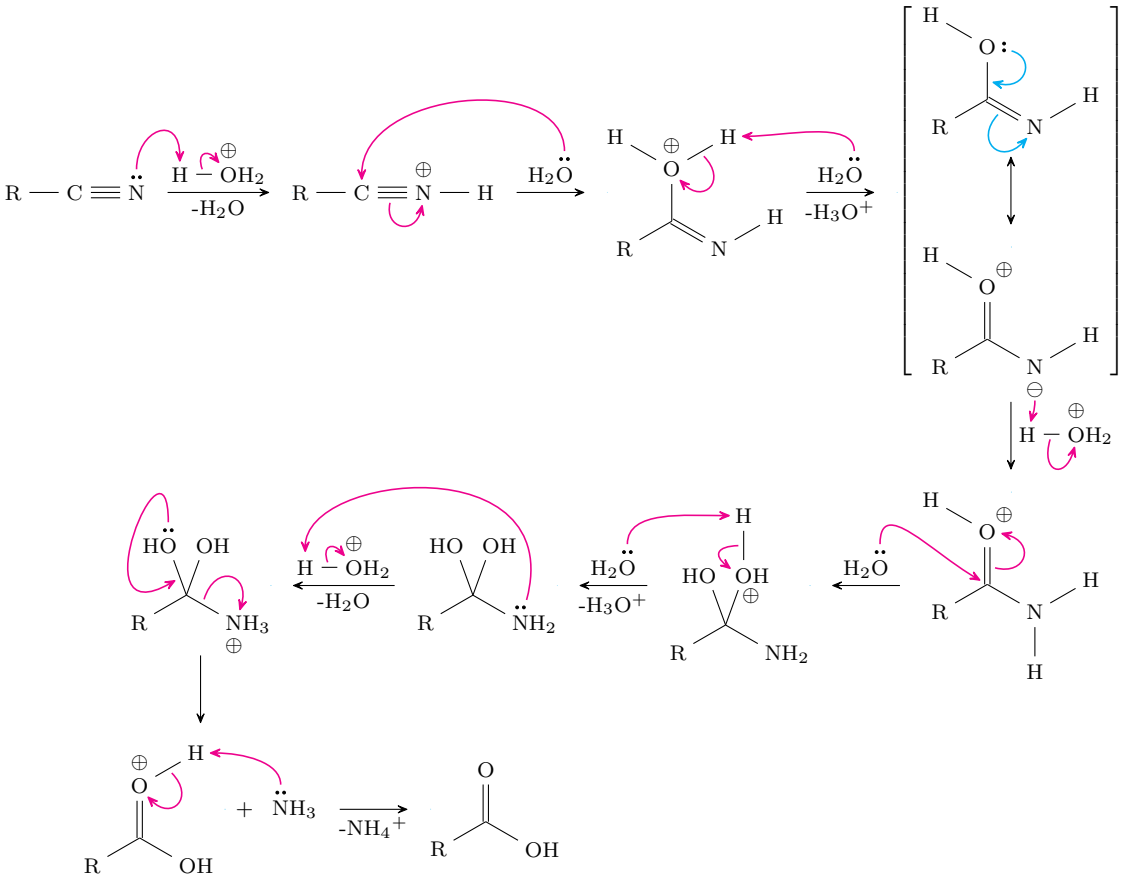


Figure 2.12: Nitrile hydrolysis mechanism.

  - Note that the fourth intermediate is one deprotonation away from being an amide.
    - However, the reaction conditions continue as drawn to a carboxylic acid because in general, the amide oxygen is more basic than the nitrile nitrogen, so if the conditions are such that the nitrile will begin the reaction, the amide will certainly finish it.
  - Note that there are some enzymes that can stop at the amide through various mechanisms that recognize one species as substrate but not another.
  - Every once in a while, people will claim that they've isolated the amide in this mechanism, but these results are hard to reproduce because of the above facts.
  - If we do add up all of the equivalents of water and acid added, we can see that only one equivalent of acid is added, overall (and two equivalents of water).
  - Observations: (1) it's almost always the most nucleophilic and electrophilic atoms that react next in solution, and (2) electronegative $\neq$ electrophilic as electronegative atoms often make adjacent atoms more electrophilic by withdrawing their electron density.

- Dehydration of amides.
- General form.

$$\mathrm{RCONH_2} \xrightarrow[\Delta]{\text{reagents}} \mathrm{RCN}$$

  - This is the reverse reaction to nitrile hydrolysis.
  - Reagents is either $\mathrm{SOCl_2}$ or $\mathrm{POCl_3}$ (which are both **dehydrating agents**).

- **Dehydrating agent**: A chemical that drives conversions in which water is lost from a molecule.
  - Notice how the amide overall loses two hydrogens and an oxygen (i.e., a water molecule overall) in Figure 2.13.
- Mechanism.

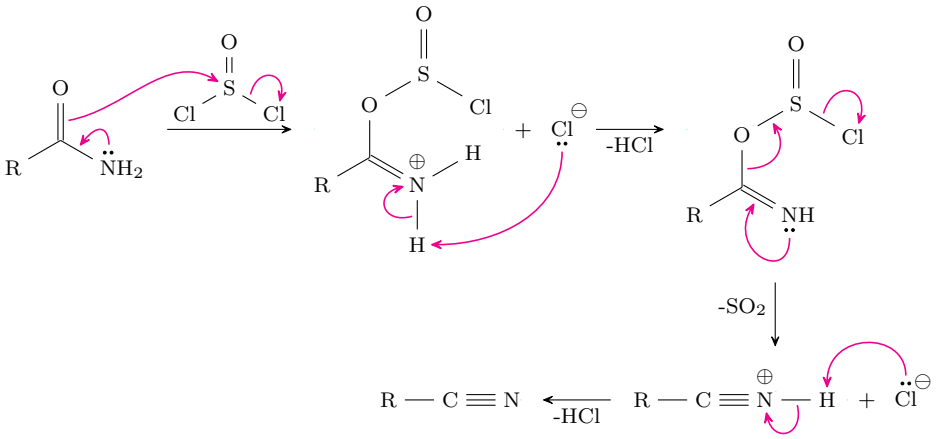


Figure 2.13: Dehydration of amides mechanism.

  - Part of the reason the amide oxygen is such a good nucleophile is because the nitrogen can participate, as in step 1 above.
  - Driving force: Kicking out a gas (SO_2) and chloride.
  - Note that the mechanism implies that we must have an amide with two H's (esp., we cannot have one or two R groups in their place).
  - Although only the mechanism for $SOCl_2$ is illustrated, the mechanism is virtually identical for $POCl_3$.
- Comparing methods 2 and 3 of synthesizing carboxylic acids.

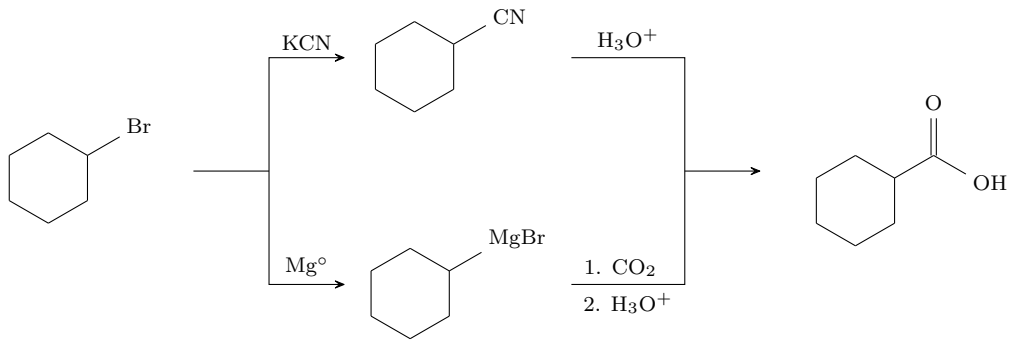
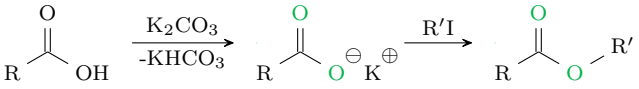


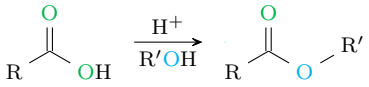
Figure 2.14: Two ways to synthesize a carboxylic acid from an alkyl halide.

  - Both carboxylation and nitrile hydrolysis achieve the same end result from the same starting material, begging the question of why both are necessary.
  - The answer lies in the fact that both suit different types of reaction conditions.
  - Carboxylation is strongly basic, so we can't use molecules with free H's.
  - Nitrile hydrolysis proceeds through S_N2 to start, so we can't use tertiary bromides.
    - This is important on part of PSet 1!

- Methods of ester synthesis.
  1. Nucleophilic.
  2. Fischer esterification.
- Nucleophilic.
- General form.



  - We deprotonate the carboxylic acid using a relatively weak base.
    - K_2CO_3 is often the weak base of choice because it's insoluble in most solvents but will react in a biphasic mixture.
    - Additionally, since $KHCO_3$ is usually insoluble and the carboxylate is typically soluble in the organic solvent in which the reaction is being carried out, it's really easy to separate the two.
  - The second step proceeds via an S_N2 mechanism, so methyl or primary alkyl halides are best.
  - Note that the two initial oxygens (green) proceed through the whole of the process and end up in the product.
- Fischer esterification.
- General form.



  - The acid is a catalyst, and we need an excess of the alcohol, which we typically just use as our solvent.
  - Reasons we need an excess of the alcohol.
    - This is essentially a thermoneutral reaction; there's not a great thermodynamic driving force between the carboxylic acid and ester.
    - Thus, the only way to get the reaction to go forward is to overwhelm it with an excess of the alcohol so that Le Châtelier's principle comes into play.
  - Removing water can also help drive the reaction.
  - H_3O^+ (i.e., excess water) reverses the reaction.
  - Note that the mechanism here is a nucleophilic attack, and it is the *methanol* oxygen (blue) that gets incorporated into the final ester (whose initial oxygens are colored green).
- **Saponification**: Subjecting an ester to a single equivalent of KOH (or any other hydroxide base) to form the carboxylate and the alcohol.
  - This is very old chemistry.
  - Sapon- is the Latin prefix for soap.
  - Ancient peoples discovered that combining and heating animal fat, wood ash, and a bit of water creates soap.
  - Combining triglycerides with pot ash yields glycerol soap and long-chain fatty acid carboxylates.
    - Pot ash is where we get the name for potassium, because the ashes from a wood stove are rich in potassium hydroxide.
    - Fatty acid carboxylates serve to solublize grease in water because the lipid end interacts with the grease and the carboxylate end interacts with the water. This is how all soaps work!

- General form.

$$\mathrm{RCOOR'} \xrightarrow{\mathrm{KOH}} \mathrm{RCOOK} + \mathrm{R'OH}$$

  - The carboxylate is an end-stage product. Resonance delocalizes the negative charge over the carbon atom, significantly decreasing its electrophilicity and hence its capacity to participate in future reactions.
  - The presence of basic conditions make it so that this reaction is not reversible.
    - Indeed, if we mix a base with RCOOH, we will just deprotonate the acid and return to the carboxylate form.

- Mechanism.

  - Hydroxide attacks the ester as a nucleophile, and $\mathrm{OR^-}$ leaves to form a carboxylic acid. But $\mathrm{OR^-}$ (a strong base) will then deprotonate RCOOH (a strong acid) to form the carboxylate and alcohol.

- Acid chloride synthesis.

- General form.

$$\mathrm{RCOOH} \xrightarrow[\mathrm{Py}]{\mathrm{SOCl_2}} \mathrm{RCOCl} + \mathrm{[PyH]Cl} + \mathrm{SO_2}$$

  - Pyridine is not strictly necessary, but it greatly increases the reaction rate.
  - Driven in a similar way to the dehydration of amides; we release $\mathrm{SO_2}$ gas, expel a water molecule, and mop up the extra $\mathrm{Cl^-}$ with pyridine.

- Mechanism.

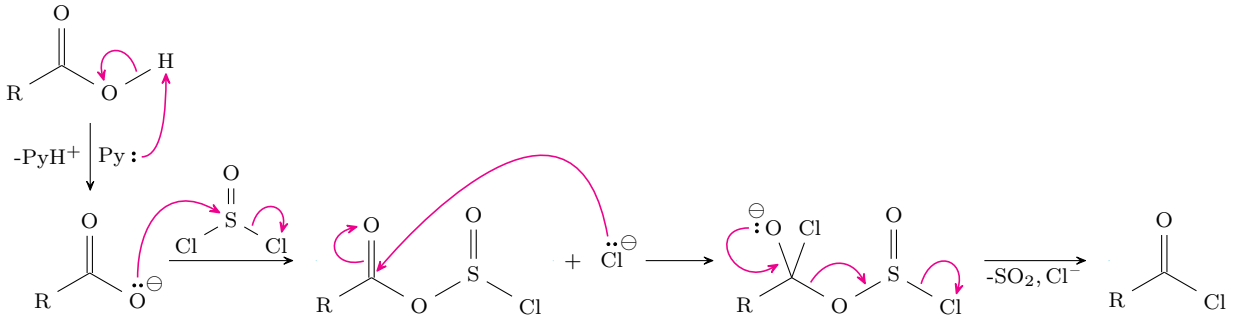


Figure 2.15: Acid chloride synthesis mechanism.

  - Since chloride is a fairly week nucleophile, its addition in step 3 takes a while and is reversible.
    - However, this step is driven in the forward direction by releasing $\mathrm{SO_2}$ gas from the resulting tetrahedral intermediate (Le Châtelier's principle).

- Anhydride synthesis.

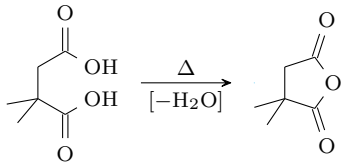
- General form (standard).

$$2\,\mathrm{RCOOH} \xrightarrow[\mathrm{[-H_2O]}]{\Delta} \mathrm{RCOOCOR}$$

  - High heat is required.
  - If you use two different carboxylic acids, you will get a statistical mixture of products. Importantly, you will not get any real selectivity.

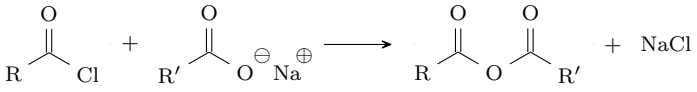
- You can selectively create 5-6 membered rings containing anhydrides because this reaction proceeds intramolecularly as well as intramolecularly.

- General form (intramolecular).



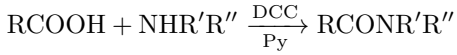
  - In particular, if you have a single molecule with two different carboxylic acid groups 2-3 carbons apart, then heating a sample of said molecule while removing water will result in a ring-closing anhydridization.
  - If we want to make a ring with another number of carbons, we should go through acid chlorides (see below).

- A way to selectively create anhydrides is via acid chlorides and sodium carboxylates.
- Mixed anhydride synthesis.
- General form.



  - This reaction proceeds via nucleophilic substitution.

- Amide synthesis.
- General form.



- Mechanism.

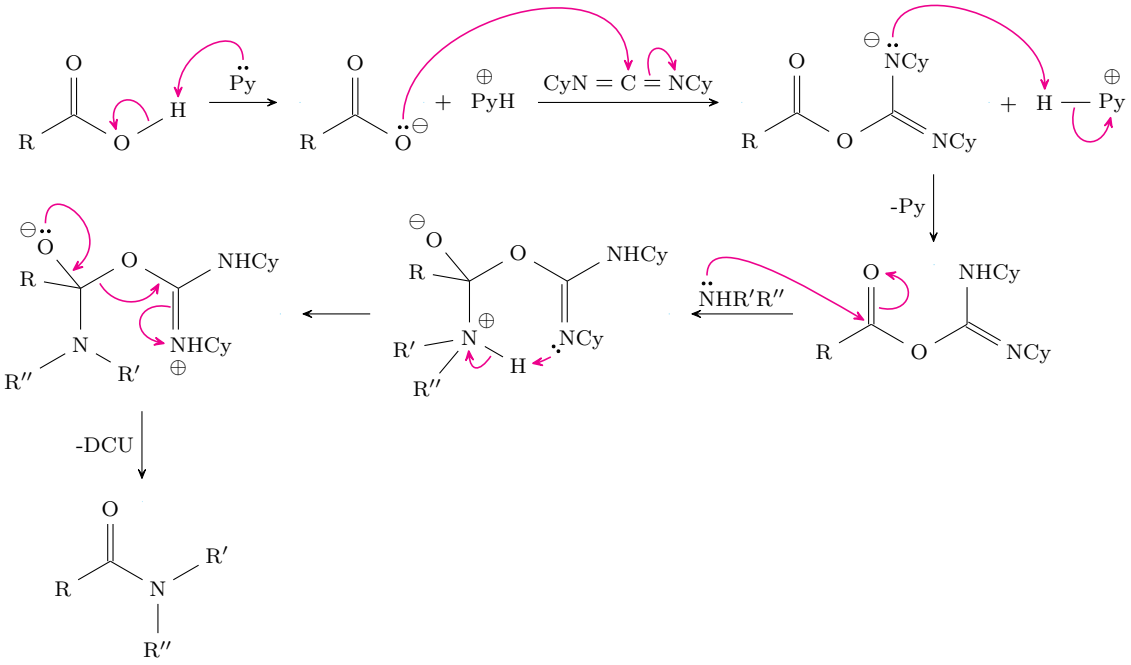


Figure 2.16: Amide synthesis mechanism.

  - Note that as in other mechanisms, DCC eventually transforms into a type of leaving group.

  - Normally, we use external reagents for proton transfers because doing an internal one would in most cases involve a transition state with a 4-membered ring, which is highly strained.
    - However, in step 5 here, we can do an internal proton transfer because the transition state's conformation is that of a 6-membered ring.

- **DCC**: Dicyclohexylcarbodiimide, a dehydrating reagent key to amide synthesis. *Structure*

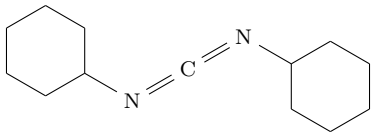


Figure 2.17: Dicyclohexylcarbodiimide (DCC).

- DCC reacts with water as follows.

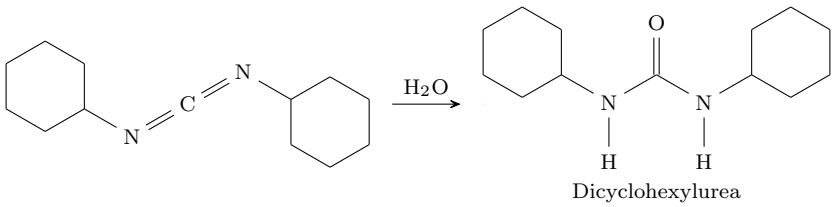


Figure 2.18: DCC and water.

- **DCU**: Dicyclohexylurea, the product of the reaction of DCC and water.
- Reactivity scale.

  acid chloride > anhydride > ester > amide > carboxylate

  - It should make intuitive sense that acid chlorides are the most reactive carboxylic acid derivatives and carboxylates are the least.
    - Acid chlorides have an electronegative group on the already electrophilic carbon, exacerbating the molecular dipole.
    - Carboxylates delocalize their negative charge over the carbon (as discussed earlier), greatly reducing or eliminating the molecular dipole.
    - A good rule of thumb is that the compound with the best leaving group and worst nucleophile (an acid chloride) is the most reactive, and vice versa in that the compound with the worst leaving group and the best nucleophile (a carboxylate) is the most reactive.
  - What we mean by "reactivity" is that compounds higher on the reactive scale can react with an appropriate nucleophile to become compounds lower on the scale.
    - For instance, we can take an acid chloride to an anhydride, ester, amide, or carboxylate (and we have reactions to do that), but we cannot take all (or any) of these molecules back to an acid chloride without forcing conditions.
    - Some things that qualify as forcing conditions are the use of acidic conditions and dehydrating reagents.
    - In other words, this reactivity scale is for the compounds in basic media with no dehydrating reagents present.

- MCAT comments.
- Trialkyl amines and pyridines.

  - According to our reactivity scale, we should be able to react NEt_3 with RCOCl to yield an amine, for example.
    - However, this leads to a positively charged nitrogen in the amine that cannot be quenched (e.g., by deprotonation). Thus, this is a highly reversible reaction that favors the reactants.
  - Similarly, we should be able to react an anhydride with pyridine.
    - But since pyridine cannot be deprotonated either, the reactants are favored in this reversible reaction once again.

- However, this implies that pyridines can be used to catalyze nucleophilic acyl substitutions.
- **DMAP**: Dimethylaminopyridine, which is one of the best catalysts for nucleophilic acyl substitutions. *Structure*

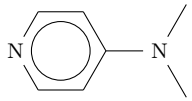


Figure 2.19: Dimethylaminopyridine (DMAP).

  - Levin gives an example synthesis using DMAP, namely nucleophilic addition to an anhydride.
    - In essence, DMAP adds to the carbonyl, kicks out the leaving group, and then the nucleophile adds to the carbonyl and kicks out DMAP.
  - Adding DMAP can accelerate a reaction that would take overnight to taking only a few minutes.

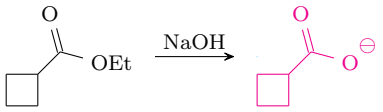
- Acid chlorides, anhydrides, and esters all create the same product (an amide) when reacting with an amine.
  - But, you need only one equivalent of the amine for esters while you need two equivalents for the first two.
  - This is because of the pK_a's.
    - In order of increasing pK_a, we have HCl < RCOOH < $NR_2H_2^+$ < ROH.
    - Thus, the first two byproducts (HCl and RCOOH) protonate amines in solution, whereas ROH does not.

2.3 Discussion Section

4/8:

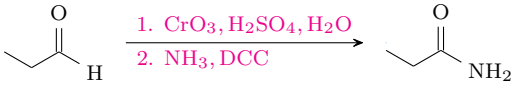
- We will be working with hot sand baths in the next lab, so just leave them to cool and do not dispose of the contents unless you're sure they're cool.
- Practice problems.

1.

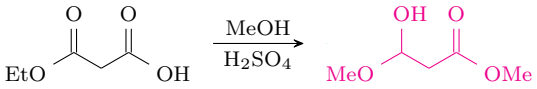


  - We form a COO^- ion instead of the carboxylic acid because we are in basic solution.
  - The mechanism is a nucleophilic attack on the carbonyl, the oxygen electrons swinging back down and kicking out EtO^-, and then deprotonation of the acid.

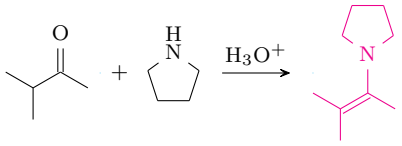
2.



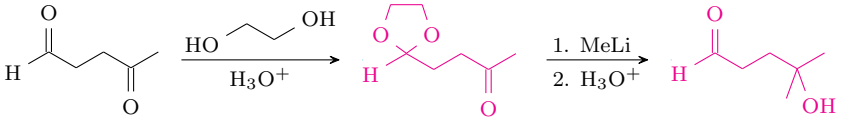
- The intermediate after step 1 is the carboxylic acid, as we have used aqueous Jones reagent.

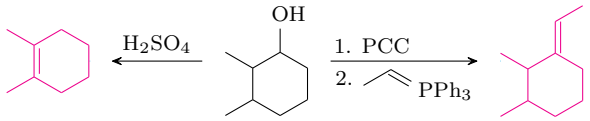
3. 

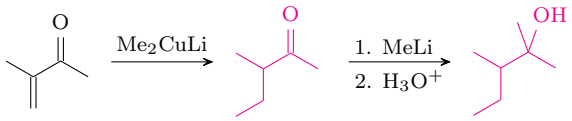
   - The reaction of the ester (left) is called **transesterification**; the reaction of the carboxylic acid (right) is called ether formation.
   - It's important to know that you can get ester formation in both of these cases.
   - This is a common problematic side reaction in synthetic chemistry.
   - Mechanism: Methanol attacks each carbonyl, the other group leaves, and then deprotonation.

4. 

   - We choose this enamine as the major product by Zaitsev's rule.

5. 

6. 

7. 

2.4 Chapter 17: Carboxylic Acids and Their Derivatives

From Solomons et al. (2016).

- Naming carboxylic acids.
  - Drop the final -e of the name of the alkane corresponding to the longest chain in the acid and add -oic acid.
    - Common names include formic acid (methanoic acid), acetic acid (ethanoic acid), butyric acid (butanoic acid), valeric acid (pentanoic acid), caproic acid (hexanoic acid), stearic acid (octadecanoic acid)[2].
  - The carboxyl carbon is numbered 1.
- Naming esters.

[2]Solomons et al. (2016) discusses the origins of these names, too.

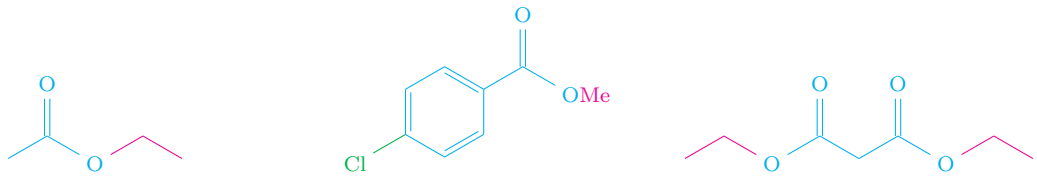


Figure 2.20: Ester nomenclature.

  - Take the name of the alcohol (ending with -yl) and the name of the carboxylic acid (ending with -ate or -oate).

- Naming anhydrides.

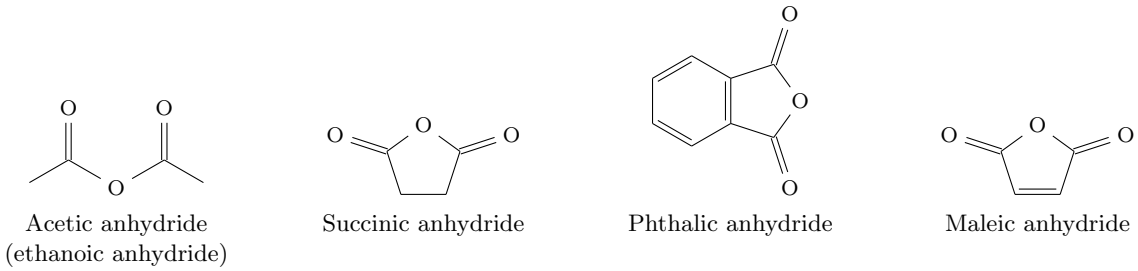


Figure 2.21: Special anhydrides.

  - "Most anhydrides are named by dropping the word acid from the name of the carboxylic acid and adding the word anhydride" (Solomons et al., 2016, p. 766).

- Naming acyl chlorides.
  - Drop -ic acid from the name of the acid and then add -yl chloride.
    - Examples include acetyl chloride (ethanoyl chloride), propanoyl chloride, and benzoyl chloride.

- Naming amides.

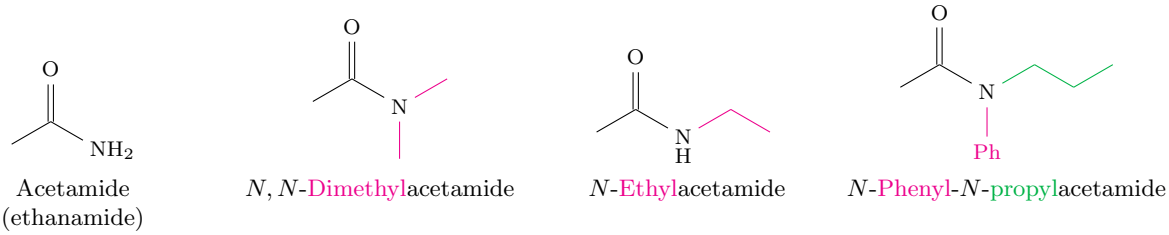
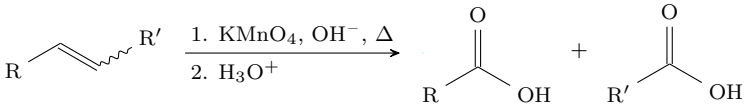


Figure 2.22: Amide nomenclature.

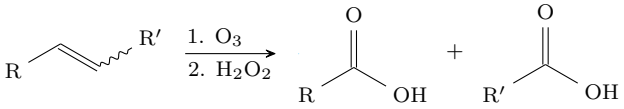
  - Drop -ic acid from the name of the acid and then add -amide.
  - "Alkyl groups on the nitrogen atom of amides are named as substituents, and the named substituent is prefaced by N- or N,N-" (Solomons et al., 2016, p. 767).

- Amides with nitrogen atoms bearing one or two hydrogen atoms are able to form strong intermolecular bonds.

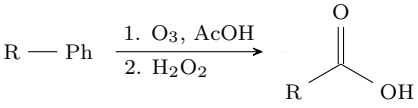
- Nitrile nomenclature.
  - Add the suffix -nitrile to the name of the corresponding hydrocarbon.
    - Examples include ethanenitrile (acetonitrile [abbrev. ACN]) and propenenitrile (acrylonitrile).
- New methods of carboxylic acid synthesis.



(a) Oxidation of alkenes 1.



(b) Oxidation of alkenes 2.



(c) Oxidation of benzene.

Figure 2.23: More methods of carboxylic acid synthesis.

- The ordering of carbons away from a carbon of interest is α, β, γ, δ, and continuing on in Greek alphabetic order.
- We can open a lactone with base and water, followed by an acidic workup.
  - We can close a γ- or δ-lactone from a γ- or δ-alcohol carboxylic acid and acid.
- Solomons et al. (2016) discusses lactams and alkyl chloroformates.
- Carbamates are also known as urethanes.
- Solomons et al. (2016) discusses decarboxylatoin, polyesters, polyamides.