CHEM 22200 (Organic Chemistry III) Notes

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April 28, 2022

Contents

List of Figures

Chapter 16

Aldehydes and Ketones

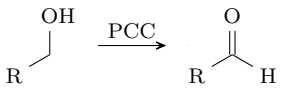
16.1 Electron Pushing

3/28:

- Levin and Weixin[1] are teaching.
- Problem sets are based on lecture content.
- Levin took the class just 13 years ago.
- We're gonna learn a lot about carbonyls this quarter.
- Unit 1: Additions to carbonyls.
- Defines carbonyls, ketones, aldehydes, and formaldehyde.
  - Formaldehyde is the most electrophilic carbonyl compound due to electronics and sterics: Carbons are both electron-donating and bulky.
  - Note that sterics are the primary factor.
- Carbonyls are electrophilic at the carbon (Levin draws the resonance structure).
- Reviews curved arrow formalism.
  - You should be able to write a full English sentence to describe each arrow.
    - In the formaldehyde resonance structure, for example, we can write, "The C=O π bond breaks and the electrons become a lone pair on the oxygen."
    - As another example, consider Et_3N attacking acetic acid, leaving behind the acetate ion. In this case, we can write the two sentences, "The nitrogen lone pair makes a new bond to the hydrogen" and "The O–H bond breaks and the electrons become a lone pair on oxygen."
  - You can draw arrows from negative charges; this notation is assumed to imply there's a lone pair on the negatively charged atom that actually does the attacking.
- Ways to make carbonyls.
  1. Oxidation of alcohols.
  2. Friedel-Crafts acylation.
  3. Ozonolysis.
  4. Diol cleavage.
  5. Alkyne hydration.
  6. Alkyne hydroboration.

[1] WAY-shin

- Oxidation of alcohols.
- General form.



- Mechanism.

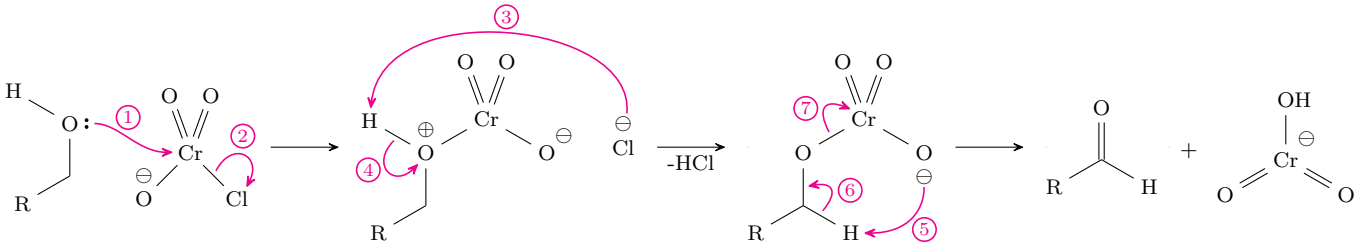
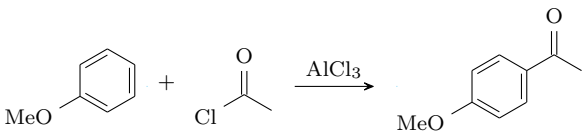


Figure 16.1: Oxidation of alcohols mechanism.

  - We could also draw a resonance structure of the CrO_2OH product that puts the negative charge on one of the previously double-bonded oxygens.
  - The mechanism of this reaction is hotly debated, and the above is only the most likely case.
    - One contested point of this mechanism is what the role of pyridinium is. Some mechanisms show it doing the third-step deprotonation, for example.
  - Note that the numbering of the curved arrows identifies them with the following sentences.
    1. Oxygen lone pair makes Cr–O bond.
    2. Cr–Cl bond breaks; becomes Cl l.p.
    3. Cl l.p. makes H–Cl bond.
    4. O–H bond breaks; becomes O l.p.
    5. O l.p. makes new OH bond.
    6. CH bond breaks and electrons make a new C=O π bond.
    7. O–Cr bond breaks; becomes a Cr l.p.

- Friedel-Crafts acylation.
- General form.



- Mechanism.

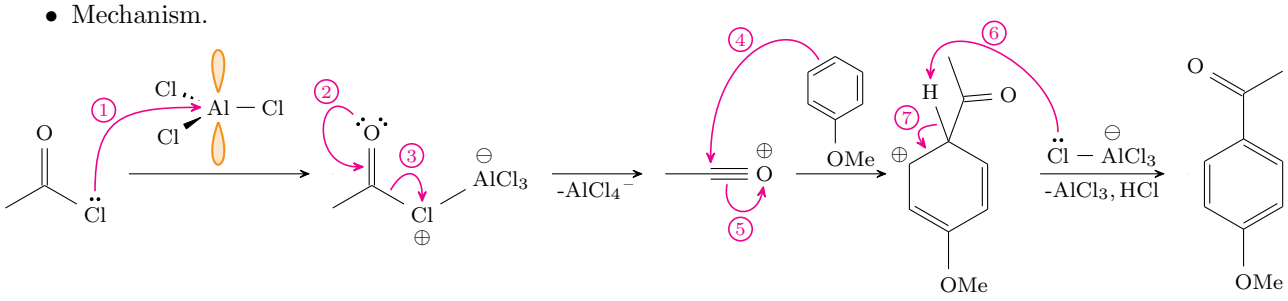
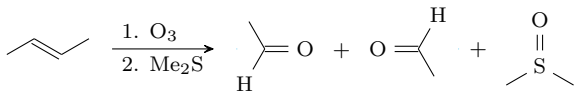


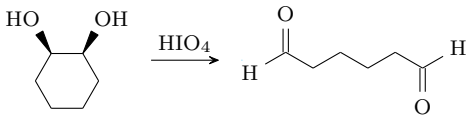
Figure 16.2: Friedel-Crafts acylation mechanism.

  - Note that the charge on aluminum in $AlCl_4^-$ is a *formal* charge; it is not indicative of the presence of a lone pair.
  - Remember that we form the ortho/para product because those dearomatized intermediates benefit more greatly from resonance stabilization.
  - Sentences.
    1. Cl l.p. makes a bond to aluminum.
    2. O l.p. makes C=O π bond.
    3. C–Cl bond breaks; becomes Cl l.p.
    4. C–C π bond breaks, and makes a new C–C bond.
    5. C≡O π bond breaks; makes O l.p.
    6. Cl l.p. makes a bond to H.
    7. C–H bond breaks; becomes a C=C π bond.

- We will not show any sentences hereafter, but it's a good idea to write them if you're still unclear on what the arrows are doing.
- Ozonolysis.
- General form.



- Mechanism.
  - Nearly identical to Dong's first quarter (Figure 7.3 of Labalme (2021)), but a few steps are combined and a few others are separated.
  - If you don't add Me_2S, you can isolate the ozonide intermediate. Use caution, however, as ozonides are explosive.
- Diol cleavage.
- General form.



  - Cis-diols react faster, but aren't necessarily required.
- Mechanism.

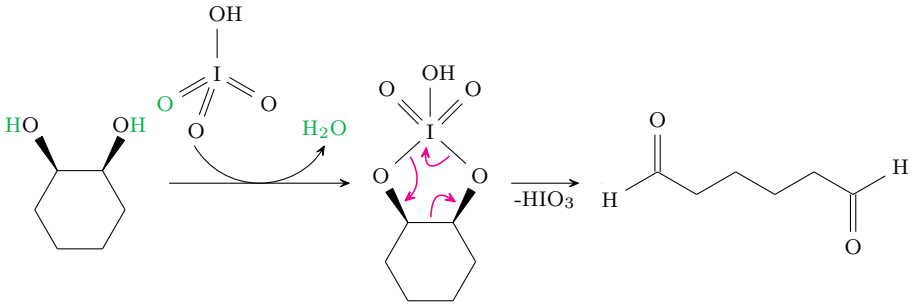
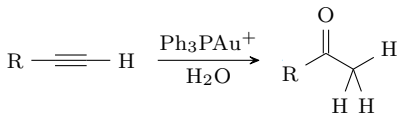


Figure 16.3: Diol cleavage mechanism.

- Alkyne hydration.
- General form.



  - Every place gold is we can use mercury instead, but since gold is less toxic and more active, we prefer to use it (even though it's more expensive). Any of the soft Lewis acid transition metals in the bottom-right corner island will work, though.

- Mechanism.

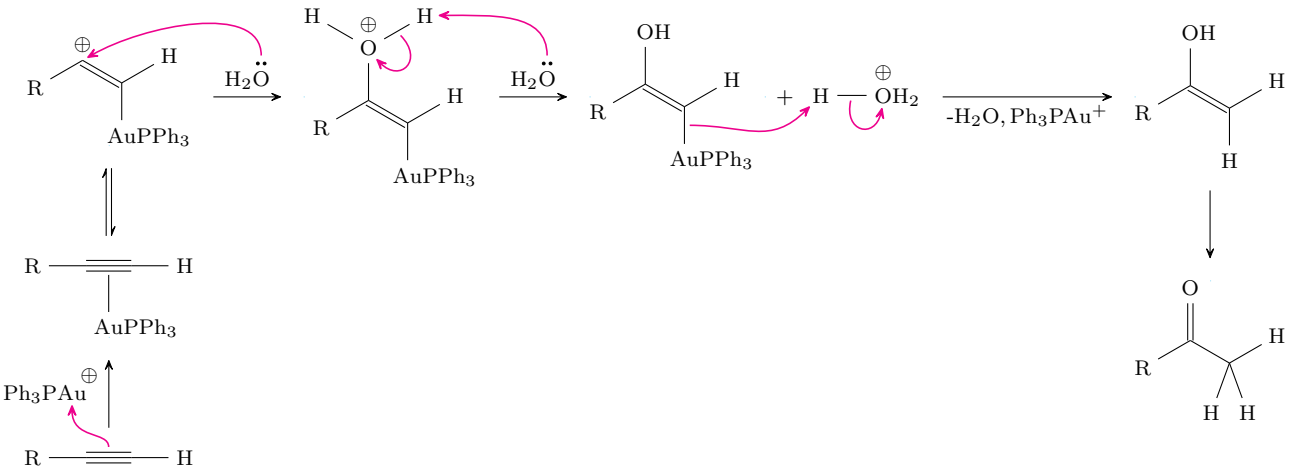
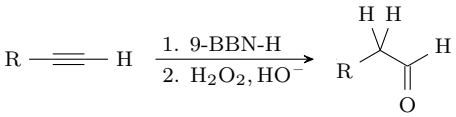


Figure 16.4: Alkyne hydrogenation mechanism.

  - We won't need to know the arrow-pushing mechanism for the tautomerization until Unit 3.

- Alkyne hydroboration.
- General form.



- **9-BBN-H**: 9-Borabicyclo[3.3.1]nonane, a source of R_2B-H with really big R groups, just like $(sia)_2BH$.
  Structure

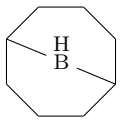


Figure 16.5: 9-Borabicyclo[3.3.1]nonane (9-BBN-H).

- Mechanism.
  - The **enol boronate** undergoes another kind of tautomerization (which, again, we'll see in Unit 3) to yield the final product.

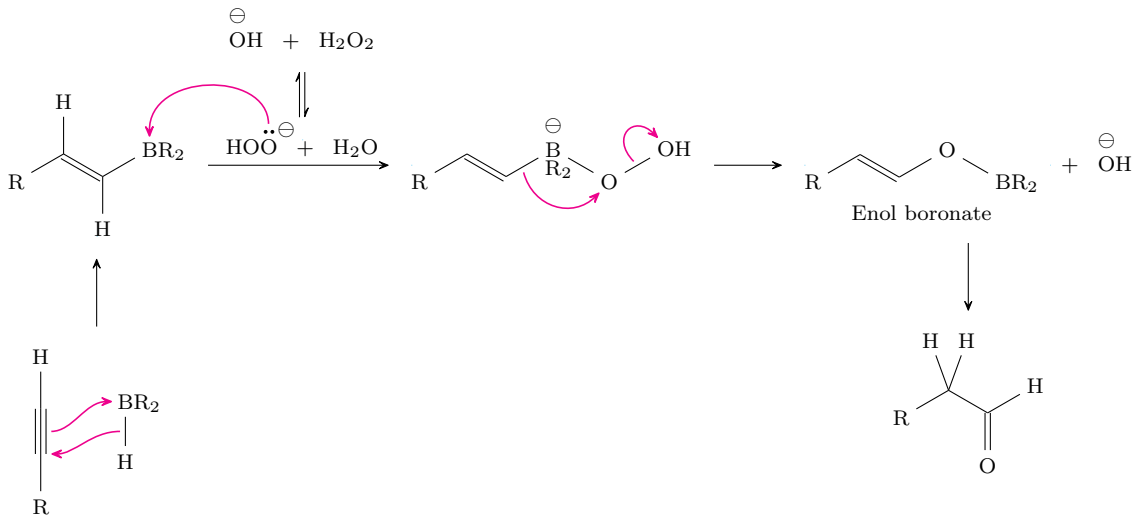


Figure 16.6: Alkyne hydroboration mechanism.

- The two(-ish) most important mechanisms in CHEM 222 are Figure 16.7 promoted either by acid or base.

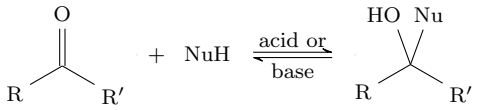
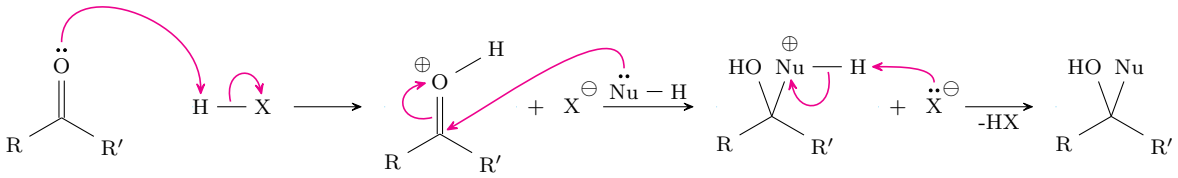
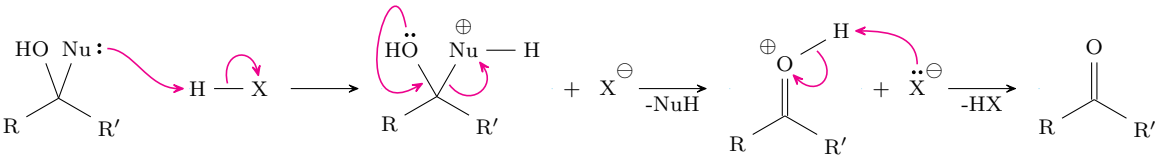


Figure 16.7: The key mechanism in CHEM 22200.

- Acidic mechanism.



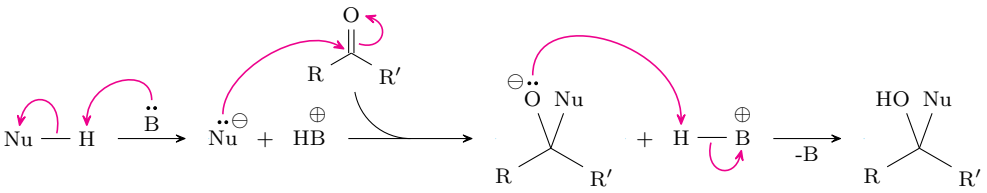
(a) Forward direction.



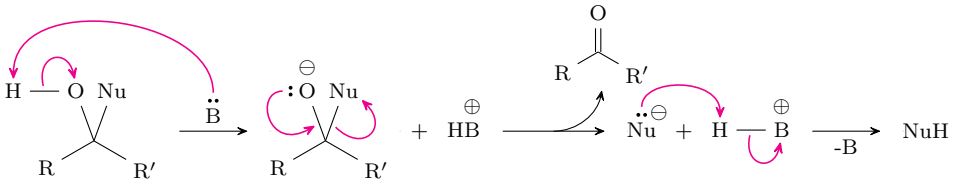
(b) Reverse direction.

Figure 16.8: Nucleophilic addition/elimination with carbonyls (acid-promoted).

  - The forward and reverse mechanisms are the same.
- **Principle of microscopic reversibility**: The lowest energy path in the forward direction must be the lowest energy path in the reverse direction.
- Basic mechanism.
  - B: means base, not boron.



(a) Forward direction.



(b) Reverse direction.

Figure 16.9: Nucleophilic addition/elimination with carbonyls (base-promoted).

16.2 Aldehydes and Ketones 1

3/31:

- Final exam: Tuesday, May 31 from 8-10 PM. A few different rooms; more on that later.
- Picking up from last time with acid- and base-catalyzed nucleophilic addition to carbonyls (Figures 16.8 and 16.9).
  - Today: Specific nucleophiles and mechanisms.
- **Carbonyl hydrate**: The class of molecules resulting from the nucleophilic addition of H_2O to a carbonyl group. *Structure*

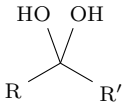
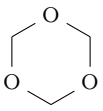
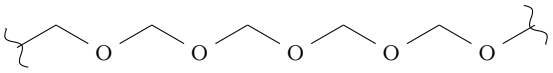


Figure 16.10: Carbonyl hydrate ($R' = H, C$).

- Carbonyl hydrate formation constants in aqueous solution.
  - $COMe_2 \rightleftharpoons C(OH)_2Me_2$: $K = 1.4 \times 10^{-3}$.
  - $COMeH \rightleftharpoons C(OH)_2MeH$: $K \approx 1$.
  - $COH_2 \rightleftharpoons C(OH)_2H_2$: $K = 2.2 \times 10^{3}$.
    - This means that in aqueous solution, formaldehyde largely exists as a diol.
  - $COPhH \rightleftharpoons C(OH)_2PhH$: $K = 8.3 \times 10^{-3}$.
    - Conjugation stablilizes the aldehyde; when you go to the hydrate, you break that conjugation.
  - $CO^iPrH \rightleftharpoons C(OH)_2{}^iPrH$: $K = 0.6$.
    - Sterically bulky aldehydes favor the carbonyl form because the diol is bulkier and thus less thermodynamically stable (more steric clashing).
- Aside: Formaldehyde's state at STP is gaseous.
  - Outside of the gas phase (and aqueous solution), formaldehyde is very unstable; it will either exist as **trioxane** or **paraformaldehyde** (see Figure 16.11).



(a) Trioxane.



(b) Paraformaldehyde.

Figure 16.11: Anhydrous nongaseous formaldehyde forms.

- Hydrate formation.
  - Occurs under both acidic and basic conditions.
- Mechanism.
  - The mechanisms are identical to Figures 16.8a and 16.9a with Nu−H = HO−H and H−X = H−OH_2^+ or B = OH^-, respectively.
  - Note that it is not necessary to show the first step of Figure 16.9a (deprotonation of the nucleophile by the base) in this case because this is just the reaction $HO{-}H + OH^- \longrightarrow HO^- + H{-}OH$.
- Note that H_3O^+ or H^+ is an abbreviation for some strong acid in solution, but there is always a counterion present; if there were even a couple of excess positive molecules, you would generate a huge static field.
- **Ketal**: The class of molecules resulting from the nucleophilic addition of an alcohol (ROH) to a ketone. *Structure*

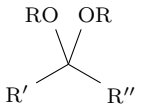


Figure 16.12: Ketal.

- **Acetal**: The class of molecules resulting from the nucleophilic addition of an alcohol (ROH) to an aldehyde. *Structure*

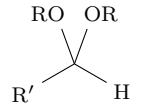
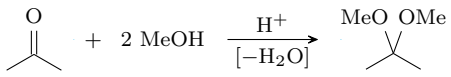


Figure 16.13: Acetal.

- General form.



  - We have an acid catalyst, and we are *removing water* in the process.
    - Water is generated as a byproduct during the course of the reaction, and removing it drives the reaction in the forward direction by Le Châtelier's principle.
  - The formation of ketals and acetals incorporates two molecules of ROH.
  - Ketals and acetals can only form under acidic conditions.

- Mechanism.

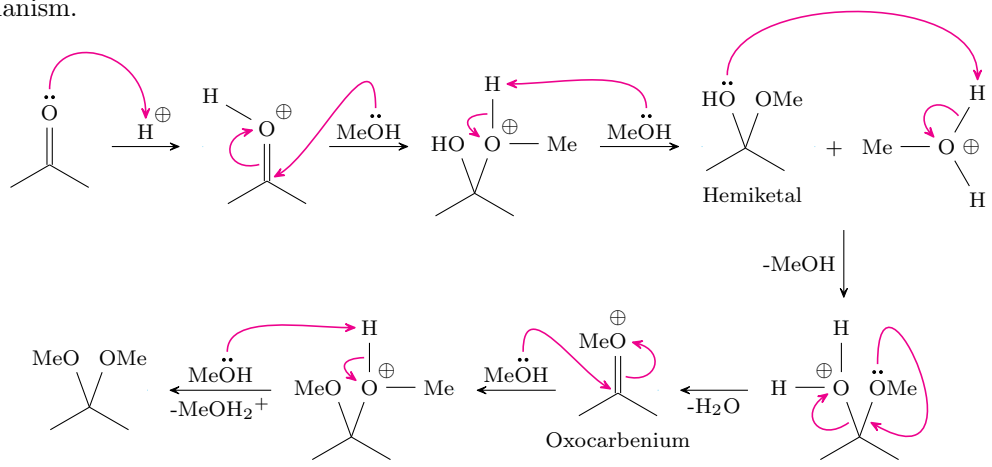


Figure 16.14: Ketal formation mechanism.

  - Basic conditions don't work because we need water as a good leaving group; OH^- is a terrible leaving group, so if we were to try to run this reaction in basic media, we would get stuck at the hemiketal.
  - Energetically, this is not always the most favored mechanism. This is why removing water is important if we want to form a ketal.
    - Indeed, if we have a ketal and add an excess of water and acid, we will recover the original ketone.
  - Note that just like there are hemiketals, there are hemiacetals.
  - We should know both the forward and reverse direction for ketal formation, even though Levin only showed the forward mechanism explicitly. (Know that microscopic reversibility still holds here.)

- **Dean-Stark apparatus**: An experimental setup that removes water during the course of a reaction.

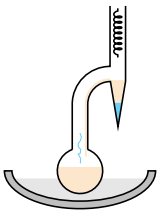
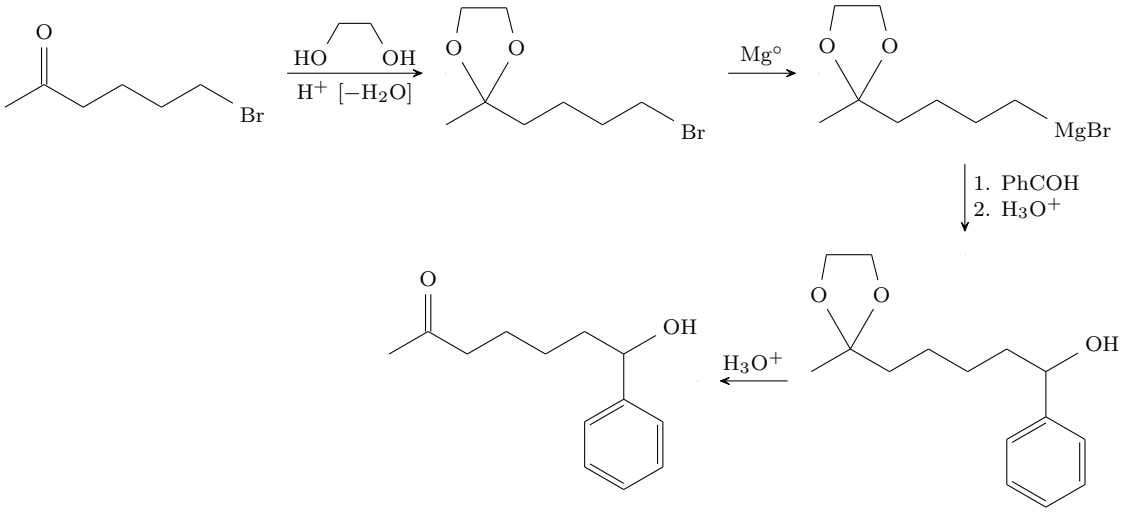


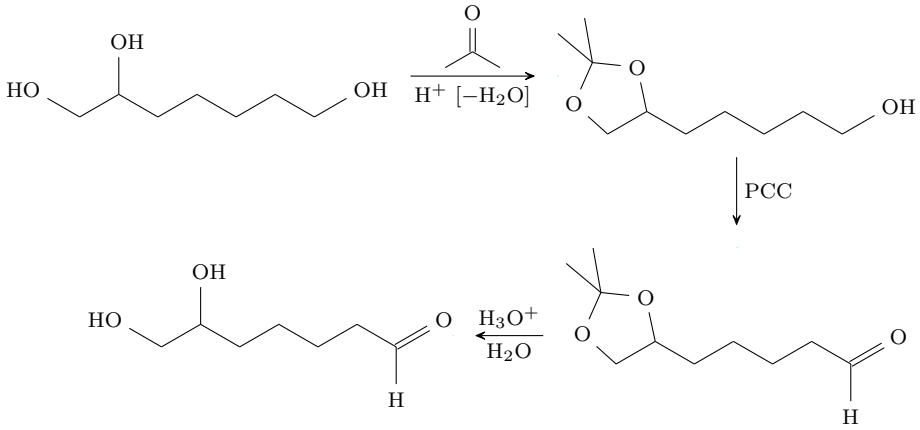
Figure 16.15: Dean-Stark apparatus.

  - The bowl at the bottom of Figure 16.15 is a heat bath. The orange solvent is toluene, and we can see water evaporating from the mixture as it is formed during the reaction and then boiled off.
  - As water evaporates, it moves upward to the reflux condenser, where it condenses and falls into the bath of toluene below.
  - Toluene is not miscible with water and it floats above water. Thus, droplets that fall off of the condenser sink to the bottom of the toluene bath to be trapped and displace more toluene back into the reaction flask at the same time.
    - Note that the immiscibility with and lower density than water are the two key properties we look for in the solvent we use for such a reaction. Toluene is a common choice, but it's not the only possible one.

- The Dean-Stark apparatus is a *physical* method for removing water.
- An example of a *chemical* method would be using a drying agent.
  - Although we could use Na_2SO_4 or $MgSO_4$ as we have in lab, these materials tend to get a bit clumpy, hindering the reaction.
  - As such, the substance of choice is a 3 Å molecular sieve (an aluminosilicate).
  - Aluminsilicates have pores so small that they can selectively absorb very tiny molecules, such as water, even at the exclusion of methanol.
- Note that we will not be asked names on exams, but it's good to know them for continuing studies in chemistry as well as knowing what he's talking about in class.
- Since ketals are stable through basic conditions and their formation is reversible, we can use them as protecting groups.
- Example syntheses using ketals as protecting groups.



(a) Protecting carbonyls.



(b) Protecting alcohols.

Figure 16.16: Using ketals as protecting groups.

- Using a ketal to protect a carbonyl (Figure 16.16a).

  - If we convert 1-bromo-5-hexanone (the starting material in Figure 16.16a) to a Grignard directly, we can't prevent the intramolecular attack.
  - However, we can first add an alcohol under acidic conditions while removing water.
    - Chemists usually use ethylene glycol, which forms a cyclic diol.
    - Ethylene glycol is cheap, provides a more stable ring, and forms faster due to increased local concentration.
  - Now that no part of the molecule is electrophilic, we are free to make it into a Grignard and carry out our desired Grignard-based synthesis.
  - As a last step, we can remove the alcohol.
    - Note that adding H_3O^+ for a few seconds quenches the alkoxides, yielding the fourth molecule in Figure 16.16a. If we let that molecule sit with the acid for a few hours, though, then the alcohol will come off, and we can isolate the fifth molecule in Figure 16.16a.

- Using a ketal to protect a 1,2-diol (Figure 16.16b).
  - The initial reaction selectively forms the five-membered rings because five- and six-membered rings have extra stability.
    - This implies that we can also use this method to protect 1,3-diols.
    - For the purposes of this class, medium sized rings will not form.
  - Once we have protected our alcohols, we can react the rest of the molecule, finally removing our protecting group with $H_3O^+ + H_2O$.
  - We'd need methods beyond the scope of this class to convert the other alcohols to aldehydes.

- Hemiacetals and hemiketals are rarely isolable.
  - Exception: Hemiacetals in ring systems.
  - For example, glucose contains a hemiacetal.
  - Hemiketals are almost never observed.

- **Imine**: The class of molecules containing a C=N double bond. *Structure*

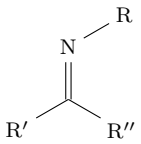
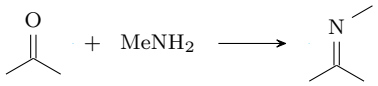


Figure 16.17: Imine.

  - Note that all three R groups can be carbon, hydrogen, or another heteroatom such as oxygen (see the below discussion of oximes and hydrazones, for instance).

- General form.



  - Can form under acidic, basic, and neutral conditions.
  - The mechanism is pretty complicated with a lot of variations, but we are only responsible for the one described below.
    - Others are provided in the notes posted on Canvas.

- Nitrogen is tricky.

  - Electronegativity: C = 2.55, N = 3.04, and O = 3.44.
  - Methylamine is more basic and more nucleophilic than methanol.
    - Water and methanol both have $pK_a \approx 15$, whereas methylamine has $pK_a \approx 40$.
    - Similarly, methylammonium has $pK_a \approx 10$, while $MeOH_2^+$ has $pK_a \approx -4$ and a protonated carbonyl has $pK_a \approx -6$.

- Further equilibrium constants.
  - $CMe_2(OH)^+ + MeOH \rightleftharpoons COMe_2 + MeOH_2$: $K \approx 100$.
    - This equilibrium is related to ketal formation (Figure 16.14).
    - In particular, it shows that even though only one out of every hundred molecules of acetone will exist in the protonated form (on average), that is enough to proceed with ketal formation.
  - $CMe_2(OH)^+ + MeNH_2 \rightleftharpoons COMe_2 + MeNH_3^+$: $K \approx 10^{16}$.
    - Thus, acid catalysis is far slower for amines than for alcohols.

- Mechanism (acidic conditions).
  - The mechanism is entirely analogous to Figure 16.14 up until the formation of the **iminium** ion. This intermediate is simply deprotonated at the nitrogen to yield the final imine.
  - Note that it proceeds through a **hemiaminal** intermediate as opposed to a hemiketal/hemiacetal.

- **Hemiaminal**: The functional group consisting of a hydroxyl and amine group bound to the same carbon. *Structure*

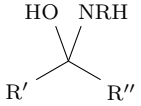


Figure 16.18: Hemiaminal.

- Regeneration of the acid catalyst in both Figure 16.14 and the acid imine formation mechanism.
  - It is correct to depict MeOH and $MeNH_2$, respectively, taking off the proton in the last step.
  - However, neither $MeOH_2^+$ nor $MeNH_3^+$ sticks around long.
  - Indeed, there is a background proton transfer equilibrium between the strong acid and the alcohol/amine. Such equilibria are typically established much more quickly than other kinds of equilibria and serve to quickly replenish the quantity of free acid in solution.

- **Hydroxylamine**: The compound $H_2N–OH$.

- **Oxime**: The class of molecules resulting from the nucleophilic addition of hydroxylamine to a carbonyl group. *Structure*

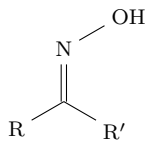
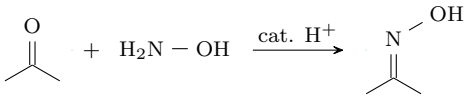


Figure 16.19: Oxime.

- General form.



- **Hydrazine**: The compound H_2N-NH_2.
  - Hydrazine is used as rocket fuel.
  - It is highly explosive as a reduced (and thus less stable) form of dinitrogen (one of the most stable molecules in existence) that can, in addition, release hydrogen gas.
- **Hydrazone**: The class of molecules resulting from the nucleophilic addition of hydrazine to a carbonyl group. *Structure*

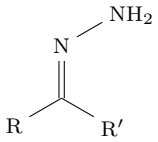
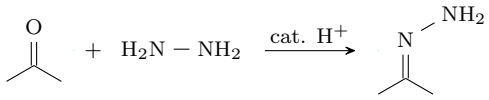
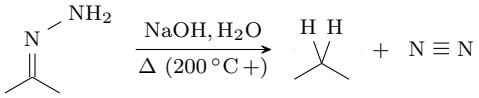


Figure 16.20: Hydrazone.

- General form.



- Imine stability.
  - Imines are sensitive; they are prone to hydrolysis and can convert back to carbonyls easily.
  - Oximes and hydrazones are much more stable.
- Reasons why oximes and hydrazones are more stable.
  - Oximes.
    - The starting material (hydroxylamine) is destabilized by the ***α*-effect**.
    - There is increased *s*-character in the nitrogen lone pair of an oxime, which stabilizes the product.
  - Hydrazones.
    - Resonance lends stability (we can push the lone pair of the terminal nitrogen toward the N–N single bond, and push the N=C double bond toward the carbon to form a carbanion).
- ***α*-effect**: The destabilizing effect of the repulsion of lone pairs across a chemical bond.
- The Wolff-Kirshner reduction.
  - Again, we won't need to know names for tests ("the old white men who developed these reactions get enough credit"), but we will need them as we more forward in chemistry.
- General form.



  - The driving force is the creation of N_2, which is a huge thermodynamic sink.

- Mechanism.

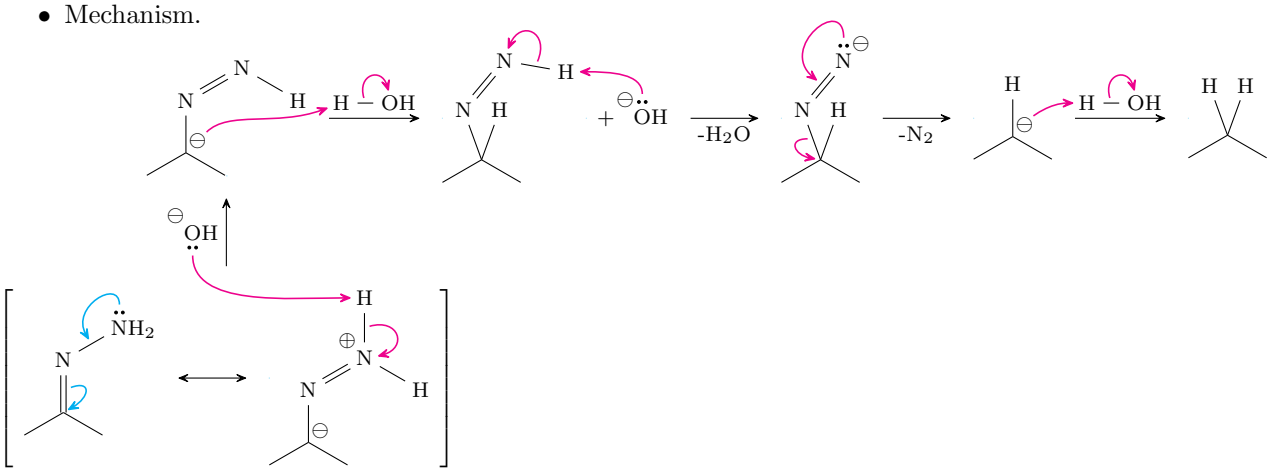


Figure 16.21: Wolff-Kirshner reduction mechanism.

  - Essentially, what we do is we return the hydrazone to a carbonyl, and then we remove the carbonyl.

- **Enamine**: The class of molecules resulting from the nucleophilic addition of dialkyl amines (R_2NH) to a ketone or aldehyde. *Structure*

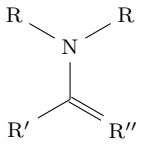
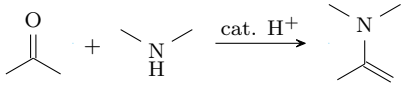


Figure 16.22: Enamine.

- General form.



- **Iminium**: The class of ions containing a $C{=}N^+$ double bond. *Structure*

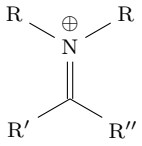


Figure 16.23: Iminium.

- Mechanism.
  - As with the formation of imines, we get to an iminium intermediate.
  - After that, however, we deprotonate at the α-carbon and rearrange into our final enamine.
- Summary of today: Acetone can combine with...
  1. Water to form a hydrate;
  2. Alcohols to form a ketal;
  3. Primary amines to form imines;
  4. Secondary amines to form enamines.

16.3 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 $\mathrm{H{-}CN} \rightleftharpoons \mathrm{H^+ + CN^-}$.
  - This is important because it's a rare carbanion with a reasonably acidic conjugate acid.
    - For instance, the H in $\mathrm{H{-}CR_3}$ has $\mathrm{p}K_\mathrm{a} > 50$.
    - However, HCN has $\mathrm{p}K_\mathrm{a} \approx 9$.
    - 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*

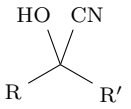
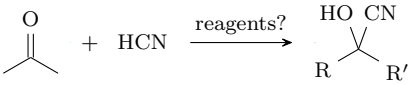


Figure 16.24: Cyanohydrin.

- 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 16.8a, 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*

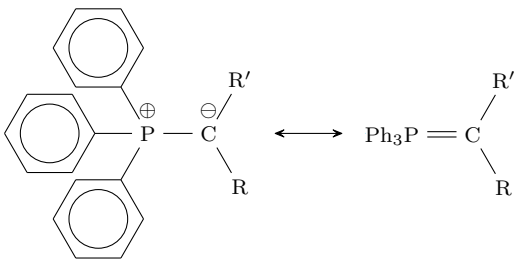


Figure 16.25: Phosphorous ylide.

- The reactivity of phosphorous ylides is dominated by the left resonance structure in Figure 16.25.

- Synthesis of phosphorous ylides.

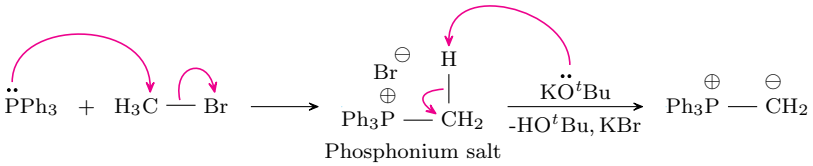


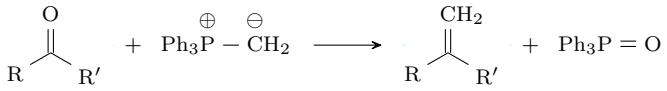
Figure 16.26: Synthesizing phosphorous ylides.

  - 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^{t}Bu 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[2] 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).

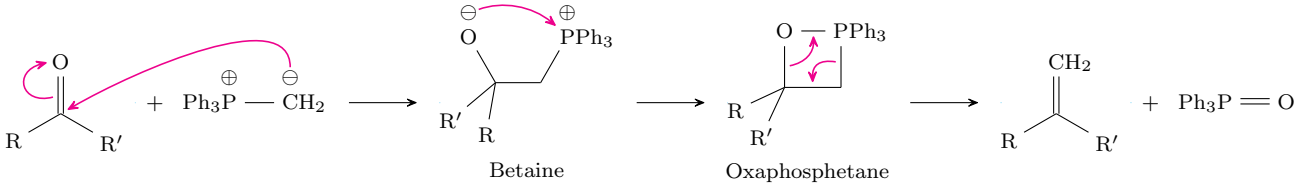


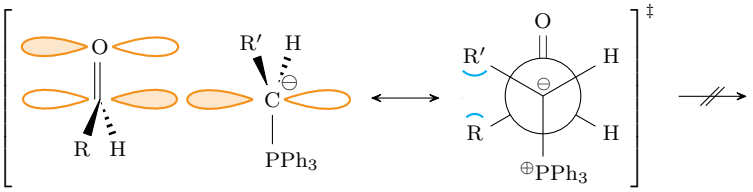
Figure 16.27: Wittig olefination mechanism (stepwise).

  - Follows the model we've been using. Only recently disproven. We may use either this one or the correct one on exams.
    - 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.

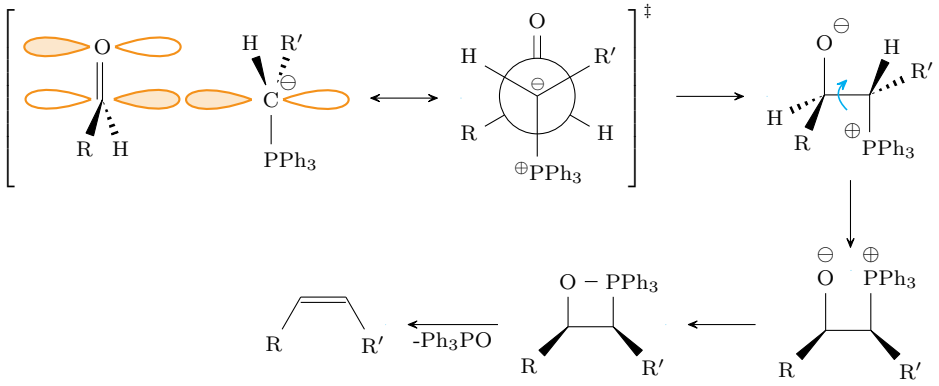
- The Wittig olefination is stereoselective for the *cis*-product.
  - This is strange since the *cis*-product is the less thermodynamically stable one.

[2] "VIT-tig"

- Three-dimensional intuition for the stereoselectivity.



(a) Unsuccessful collision.

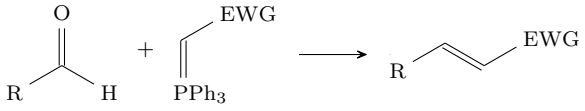


(b) Successful collision.

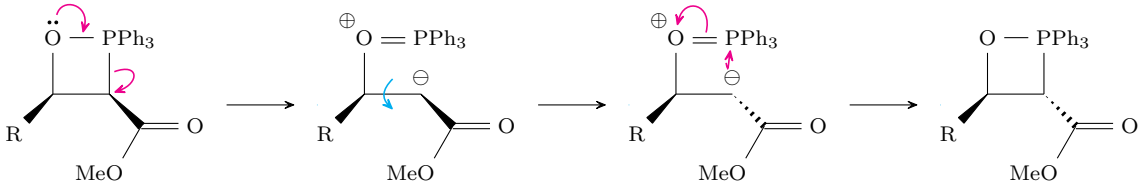
Figure 16.28: Wittig olefination stereoselectivity.

  - 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 16.28b) is higher energy and is not the favored collision.
  - Thus, Figure 16.28a 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 16.29: 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).

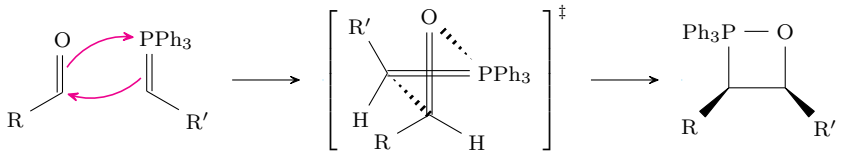


Figure 16.30: Wittig olefination mechanism (modern).

  - 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 β position (numbered 4^{th} atom from the carbonyl oxygen, which is 1 in turn).

- **1,4-addition**: A nucleophilic addition to the carbonyl carbon (numbered 2^{nd} 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

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

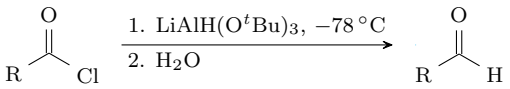
  - Cuprates are soft and yield exclusively 1,4-addition.
- Levin goes over some practice problems.

16.4 Chapter 16: Aldehydes and Ketones

From Solomons et al. (2016).

4/20:

- Naming aldehydes.
  - Aliphatic aldehydes are named in the IUPAC system by replacing the final -e of the name of the corresponding alkane with -al.
    - Common names include formaldehyde, acetaldehyde (ethanal), propionaldehyde (propanal), and naming ethanal-derivatives as acetaldehyde derivatives.
  - The aldehyde is assigned position 1 when other substituents are present (remember that it's always at the end of the chain).
  - Aldehydes in which the CHO group is attached to a ring system are named substitutively by adding the suffix carbaldehyde.
    - For example, benzaldehyde is formally benzenecarbaldehyde.
- Naming ketones.
  - Aliphatic ketones are named in the IUPAC system by replacing the final -e of the name of the corresponding alkane with -one.
    - Ketones are commonly named by the two groups to their sides (e.g., ethyl methyl ketone instead of butanone, or methyl propyl ketone instead of 2-pentanone).
    - Common names that have been retained: Acetone (propanone), acetophenone (1-phenylethanone), and benzophenone (diphenylmethanone).
  - The carbonyl is assigned the lowest possible position.
- Ketone and alkene groups as prefixes.
  - An aldehyde bonded at the carbonyl carbon to something else is a methanoyl (or formyl) group.
  - Ethanone bonded at the carbonyl carbon is an ethanoyl (or acetyl [abbrev. Ac]) group.
  - A ketone other than ethanone bonded at the carbonyl carbon is an alkanoyl or acyl group.
- For example, we might encounter 2-methanoylbenzoic acid (o-formylbenzoic acid).
- Aluminum hydride derivatives less reactive than $LiAlH_4$ include DIBAL-H and lithium tri-*tert*-butoxyaluminum hydride.
- An additional, useful aldehyde-forming reaction is



- Synthetic technique: To add on an extra carbon, create a bromide and then hit it with KCN. Then create your carboxylic acid derivative of choice.
- Nucleophilic addition to carbonyl compounds is promoted by the flat sp^2 geometry about the carbonyl carbon (the attack site), and by protonation of the carbonyl oxygen under acidic conditions (for weak nucleophiles).
- Many nucleophilic additions to carbonyls are reversable; this stands in sharp contrast to previously-discussed C–C bond forming reactions, which are essentially irreversible.
- Aldehydes are more reactive than ketones.
  - They are favored by both steric (hydrogen is smaller) and electronic (alkyl groups electronically saturate the carbonyl carbon) factors.
- Aldehyde hydrates are also known as *gem*-diols (short for geminal diols).
- Discusses thioacetals (acetals but with sulfur instead of oxygen).

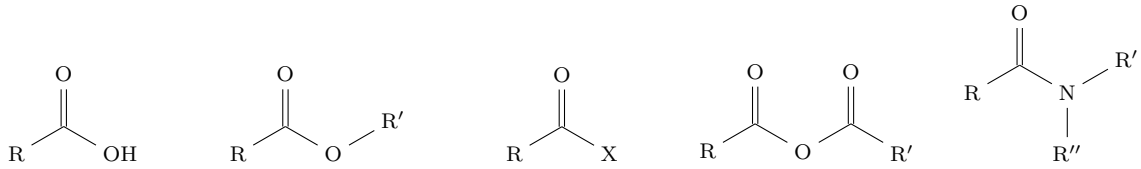
Chapter 17

Carboxylic Acids and Derivatives

17.1 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 17.1: 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 in determining acidity.
    - 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.

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

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

- Mechanism.

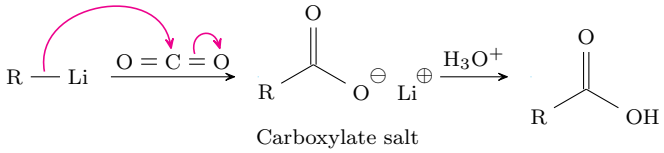
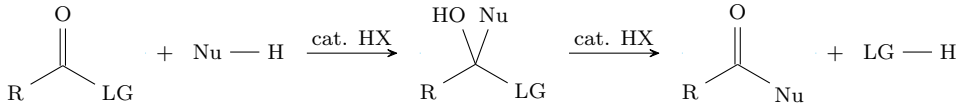
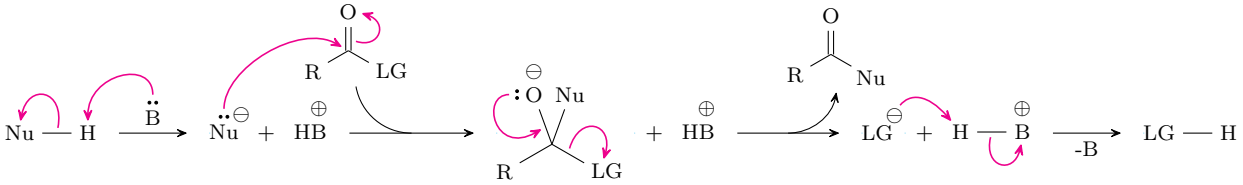


Figure 17.2: Carboxylation of lithiates mechanism.

- Mechanistic interlude: Nucleophilic acyl substitution.



(a) Acid-catalyzed reactivity.



(b) Base-catalyzed reactivity.

Figure 17.3: 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 17.1) 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 17.3a), the first step proceeds exactly as in Figure 16.8a, except that R′ = LG. The second step proceeds exactly as in Figure 16.8b, except that it is the leaving group that is protonated and kicked out instead of the nucleophile we just added in.
    - The basic mechanism is related to Figure 16.9, but rather than being a straight replication, the alkoxide species produced in Figure 16.9a proceeds straight to the reactivity of the alkoxide in Figure 16.9b (see Figure 17.3b).

- **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 17.4: 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.
  - Note that the fourth intermediate is one deprotonation away from being an amide.
    - However, the reaction conditions do not produce an amide but continue as drawn to a carboxylic acid.
    - This is 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).

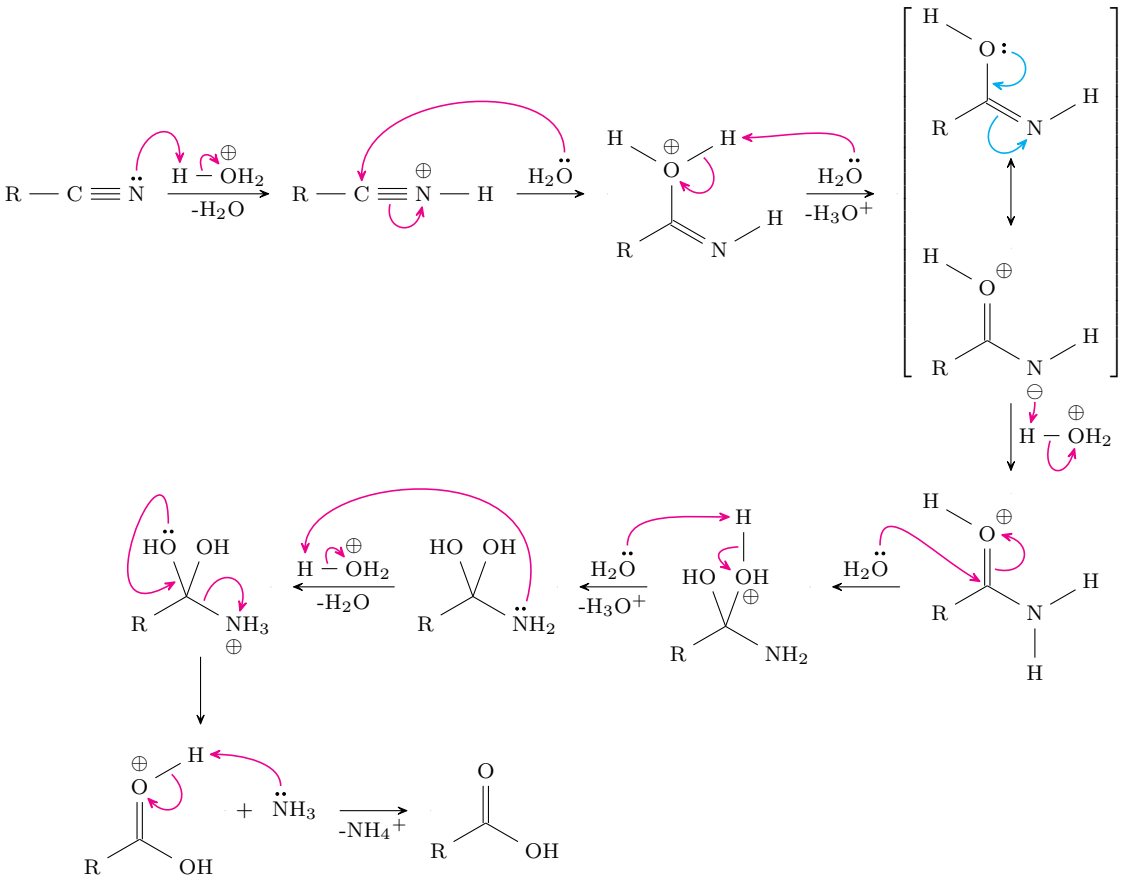


Figure 17.5: Nitrile hydrolysis mechanism.

- 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 $SOCl_2$ or $POCl_3$.
  - $SOCl_2$ and $POCl_3$ are **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 17.6.
- 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 $POCl_3$.

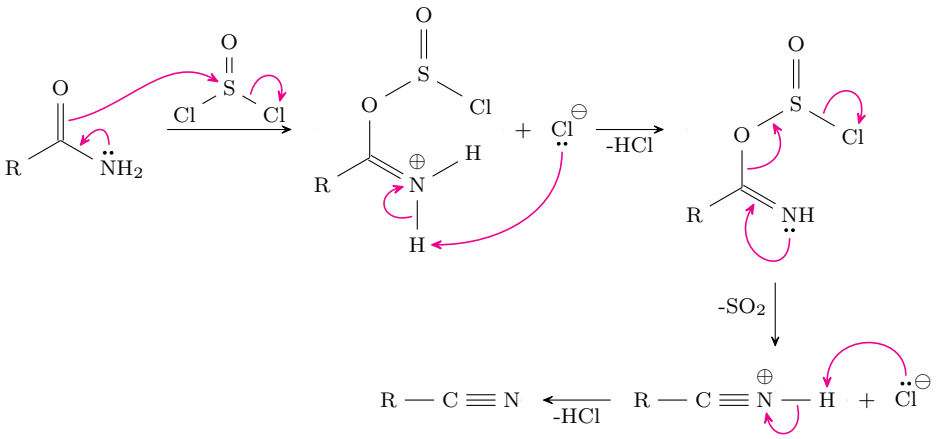


Figure 17.6: Dehydration of amides mechanism.

- Comparing methods 2 and 3 of synthesizing carboxylic acids.

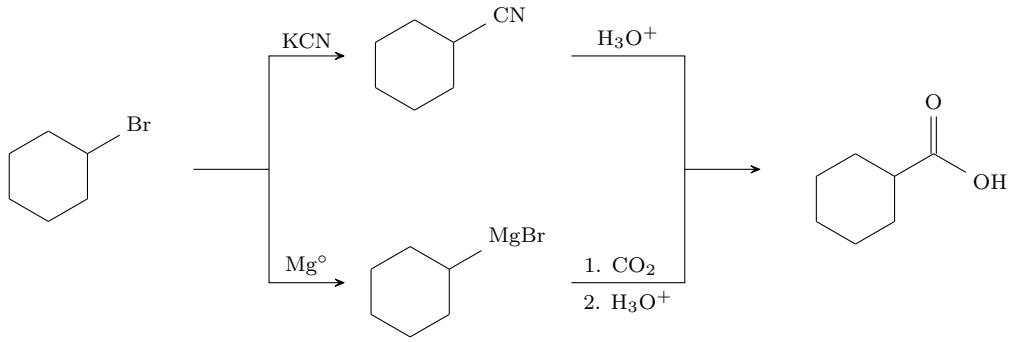


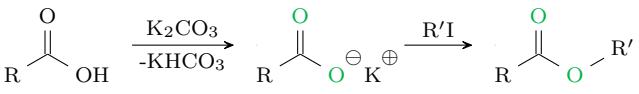
Figure 17.7: Two ways to synthesize a carboxylic acid from an alkyl halide.

  - 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.

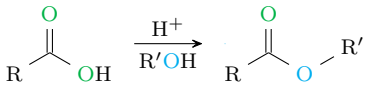
- General form.



  - 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 OR^- leaves to form a carboxylic acid. But OR^- (a strong base) will then deprotonate RCOOH (a strong acid) to form the carboxylate and alcohol.

- Acid chloride synthesis.
- General form.

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

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

- Mechanism.

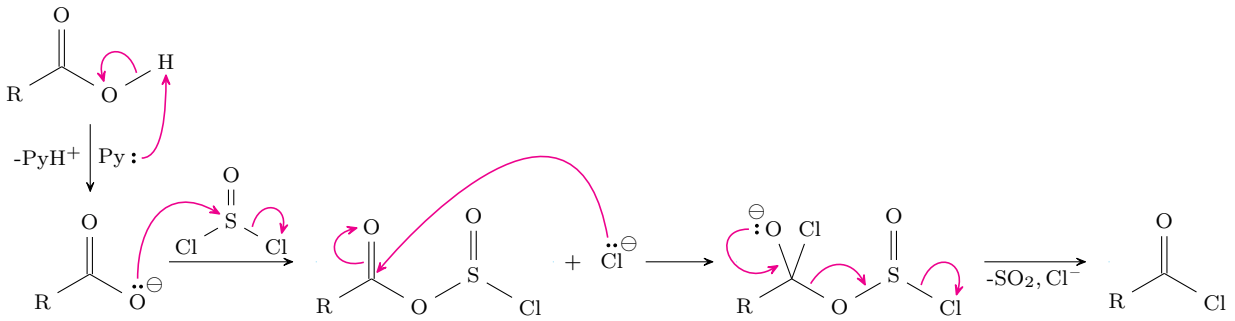


Figure 17.8: Acid chloride synthesis mechanism.

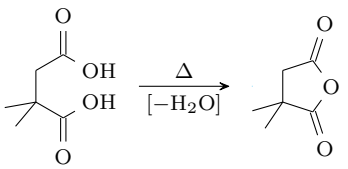
  - Since chloride is a fairly week nucleophile, it's addition in step 3 takes a while and is reversible.
    - However, this step is driven in the forward direction by releasing SO_2 gas from the resulting tetrahedral intermediate (Le Châtelier's principle).

- Anhydride synthesis.
- General form (standard).

$$2\,RCOOH \xrightarrow[[-H2O]]{\Delta} RCOOCOR$$

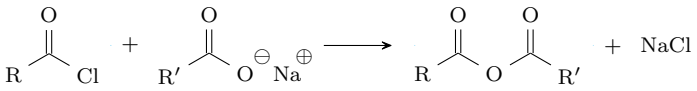
  - High heat is required.
  - If you use two different carboxylic acids, you will get a statistical mixture (no real selectivity).

- 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.

$$\mathrm{RCOOH + NHR'R''} \xrightarrow[\mathrm{Py}]{\mathrm{DCC}} \mathrm{RCONR'R''}$$

- Mechanism.

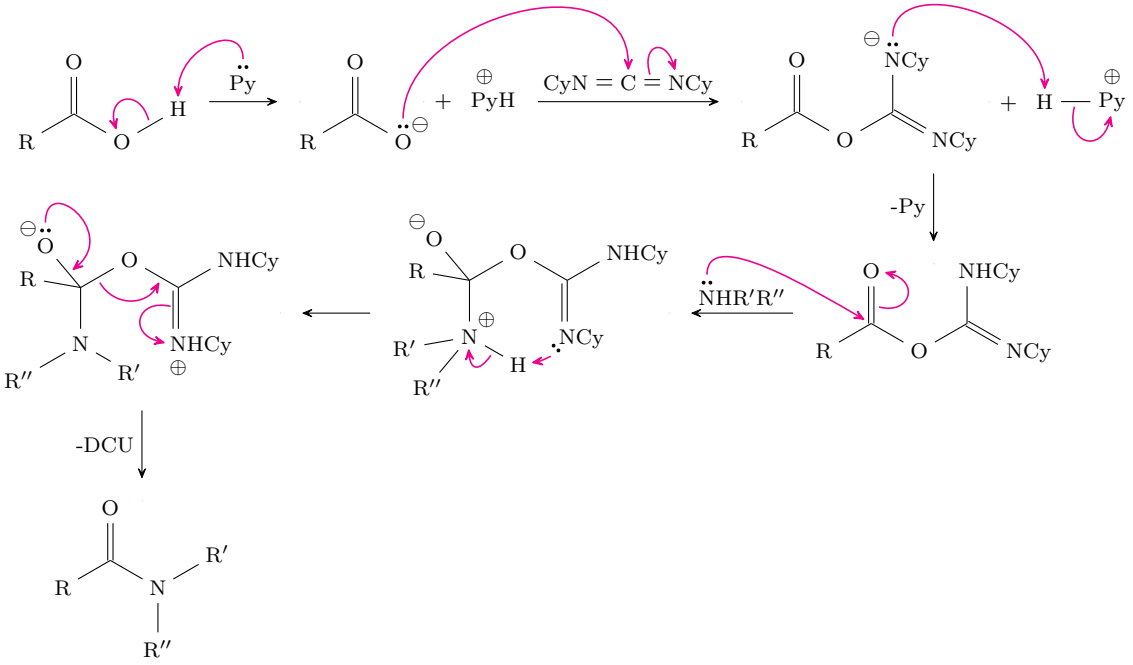


Figure 17.9: Amide synthesis mechanism.

  - 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*

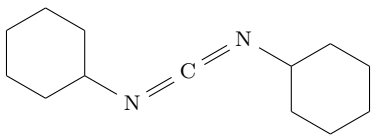
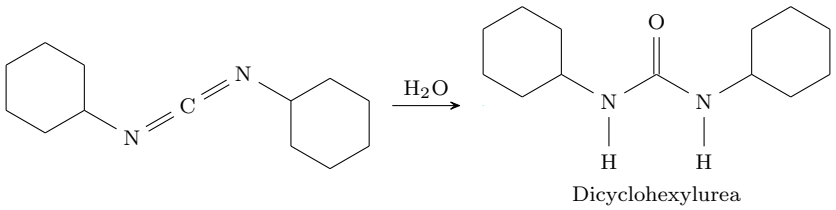


Figure 17.10: Dicyclohexylcarbodiimide (DCC).

- DCC reacts with water as follows.



Dicyclohexylurea

Figure 17.11: 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*
  - Levin gives an example synthesis using DMAP, namely nucleophilic addition to an anhydride.

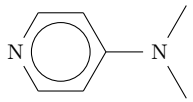


Figure 17.12: Dimethylaminopyridine (DMAP).

- In essence, DMAP adds to the carbonyl, kicks out the leaving group, and then the nucleophile adds to the carbonyl and kicks out DMAP.

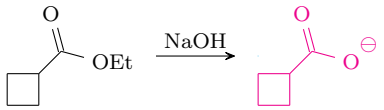
– Adding DMAP can accelerate a reaction that would take overnight to taking only a few minutes.

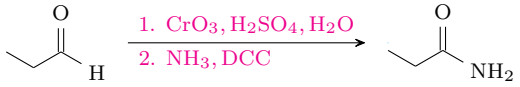
- Acid chlorides, anhydrides, and esters all create the same product (an amide) when reacting with an amine.
  - But, you need only one equivalent of the amine for esters while you need two equivalents for the first two.
  - This is because of the pK_a's.
    - In order of increasing pK_a, we have HCl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

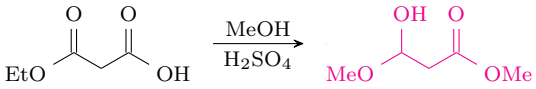
17.2 Discussion Section

4/8:

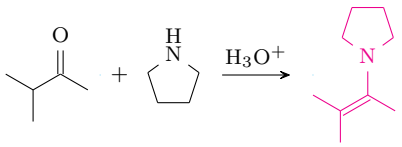
- We will be working with hot sand baths in the next lab, so just leave them to cool and do not dispose of the contents unless you're sure they're cool.
- Practice problems.

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. 

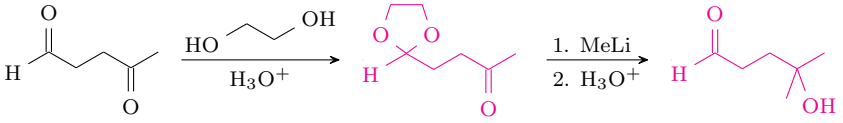
   - The intermediate after step 1 is the carboxylic acid, as we have used aqueous Jones reagent.
3. 

   - 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.



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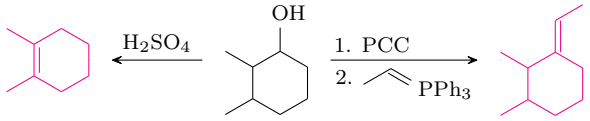

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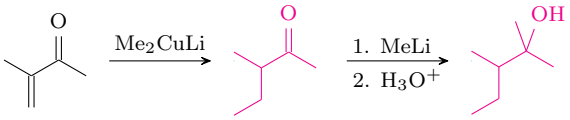
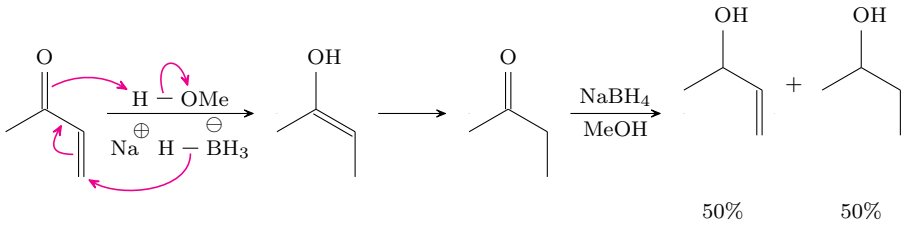


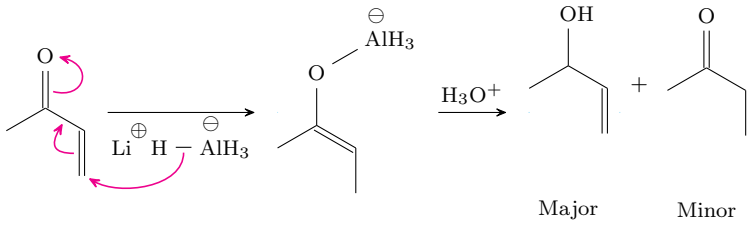
17.3 Office Hours (Levin)

4/11:

- α, β-unsaturated carbonyls?



(a) $NaBH_4$.



(b) $LiAlH_4$.

Figure 17.13: Reduction of α, β unsaturated compounds.

– Levin's predictions basically line up with those from Labalme (2022), although he has a different way of deriving them.

– The 1,2-reduction product is the same in both. But for the $NaBH_4$, you get full reduction as the other major byproduct.

– We will never be asked to use this reaction synthetically because it is not selective.

  - We're most likely to encounter alkyllithiums or cuprates. The thing to keep in mind with the messy ones is that they're messy. We're more just interested in introducing enolate chemistry with these.

- Problem Set 1, Question 3a: We form one bond with the best stereochemistry and then do an S_N2 to simultaneously form the epoxide and kick out SPh_2.
- Problem Set 1, Question 2f: Cyclic systems are one of the only places you see hemi-acetals.
- Problem Set 1, Question 3b: The transition state has too much ring strain, so show proton transfers as being mediated by solvent molecules.
- n-butyl lithium stands for "normal"-butyl lithium; s-butyl lithium is sec-butyl lithium.

17.4 Carboxylic Acids and Derivatives 2

4/12:

- Last time:
  - We discussed the reactivity of compounds of the form $RCOOXR'$ where X is a heteroatom.
  - We looked at nucleophilic addition to such compounds under acidic and basic conditions, which more often than not proceeds through a nucleophilic acyl substitution mechanism.
  - Certain classes can be taken to others by the addition of a nucleophile.
  - Reviews adding amines to acid chlorides, anhydrides, and esters, and the amount of amine needed for each.
- Today: How carboxylic acid derivatives interact with hydrides and carbides.
  - Most of the early lecture content is straight outta CHEM 221. Highlights will follow.
- Carbide addition to...
  1. Ketones and aldehydes.
  2. Carboxylic acids.
  3. Esters.
- Ketones and aldehydes.

$$\mathrm{RCOR'} \xrightarrow[2.\ \mathrm{H_3O^+}]{1.\ \mathrm{R''Li}} \mathrm{CRR'R''(OH)}$$

  - We can use lithiates or Grignards.
- Carboxylic acids.

$$\mathrm{RCOOH} \xrightarrow{\mathrm{R'Li}} \mathrm{RCOOLi} + \mathrm{R'H}$$

  - We protonate the lithiate, yielding a carboxylate with a lithium countercation and an aliphatic species.
- Esters.

$$\mathrm{RCOOR'} \xrightarrow[2.\ \mathrm{H_3O^+}]{1.\ \mathrm{R''Li}} \mathrm{CR(R'')_2(OH)}$$

  - Two equivalents of the lithiate add in, the OR' group leaves, and the alcohol is reduced.
  - See Figure 9.2 of Labalme (2022) for the mechanism.
  - The fact that we observe double addition means that the **overaddition product** is the major product.
  - If you only add one equivalent of lithiate, the major products will be the overaddition product and unreacted ester; the ketone will only be a very minor product.

    - This is because esters are less electrophilic due to donation from the ether oxygen, so the lithiate will selectively go for the ketone as soon as it becomes available.
    - Ester resonance essentially partially protects it from nucleophilic addition.

- **Overaddition product**: A nucleophilic addition product in which the nucleophile adds more than once.
    - So named because we typically only want monoaddition.
- Hydride addition to...
    1. Esters ($NaBH_4$, $LiAlH_4$, and DIBAL-H).
    2. Amides ($LiAlH_4$ and DIBAL-H).
- Esters ($NaBH_4$).
    - $NaBH_4 + MeOH$ does not react with esters (for the purposes of this class).
- Esters ($LiAlH_4$).

$$\mathrm{RCOOR'} \xrightarrow[2.\ \mathrm{H_3O^+}]{1.\ \mathrm{LiAlH_4}} \mathrm{RCH_2OH + R'OH}$$

    - See Figure 9.2 of Labalme (2022) for the mechanism.
    - Mechanistically, the aldehyde intermediate is much more reactive than the ester, once again.
    - Is it the lithium cation that bonds to the alkoxide or the AlH_3 species?
- Selecting for addition to the ester instead of addition to the aldehyde intermediate.
    - We are going to change the structure of our reducing agent.
    - We want to continue using aluminum since $NaBH_4$ is not strong enough, but we can play with the ligands.
    - Thus, we change from the tetracoordinate AlH_4^- to **DIBAL-H**.
- **DIBAL-H**: Diisobutylaluminum hydride, a neutral, tricoordinate aluminum species with an empty p orbital that is useful for selecting the mono-hydride addition product in cases where overaddition is common. *Also known as* **DIBAL**. *Structure*

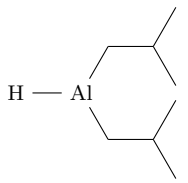


Figure 17.14: Diisobutylaluminum hydride (DIBAL-H).

- Esters (DIBAL-H).
- General form.

$$\mathrm{RCOOR'} \xrightarrow[2.\ \mathrm{H_3O^+}]{1.\ \mathrm{DIBAL-H}} \mathrm{RCOH + R'OH}$$

- Mechanism.
    - We might commonly expect to see the second intermediate (the zwitterion) decompose back into the initial reactants. However, it reacts to form a charge-neutral species that will not dissociate, as doing so would create an aluminum cation (highly unstable) in addition to the alkoxide.

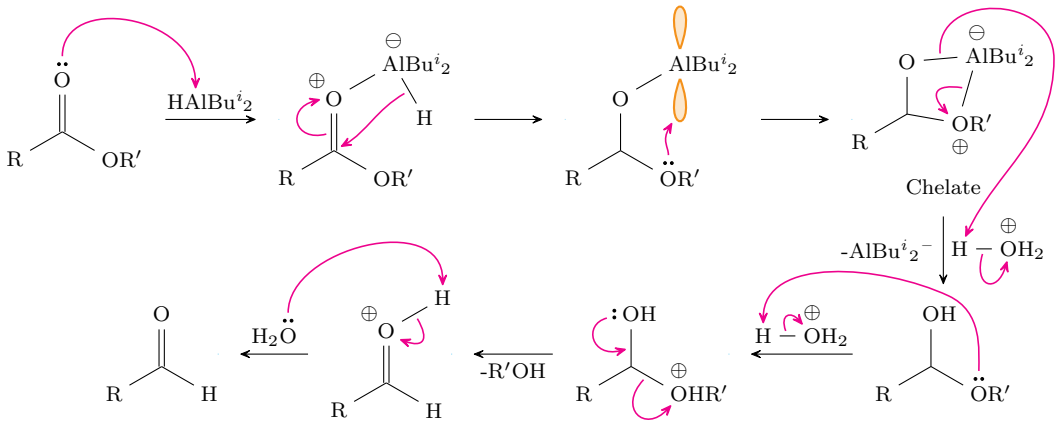


Figure 17.15: Monoreducton of esters mechanism.

- Aluminum's empty p orbital plays a key role in the third step as a Lewis acid/electron acceptor for the electrons of the ether oxygen.
- The chelate is extra stable.
  - Even though there are only four atoms in its ring (as opposed to five or six), aluminum is a *third*-row main group element, meaning that it forms longer, more flexible bonds. Thus, aluminum-containing rings can tolerate smaller number of atoms than normal organic ring systems.
  - The implication is that it will not break down to kick out the alkoxide $\mathrm{OR'}^-$. This stability is what most directly favors the monoaddition product.
- The last several steps (after the addition of the acid) constitute the decomposition of a hemiacetal under acidic conditions.
- In practice, this reaction is really difficult to pull off.
  - The chelate is only stable at $-78\,^\circ\mathrm{C}$. If it warms up much beyond that, it will decompose into the aldehyde.
  - The reaction of DIBAL-H with the ester is exothermic, so you have to keep it really cold and do the addition really slowly. Otherwise, the internal exotherm will raise the temperature and ruin the reaction.
  - Thus, you will often see in the literature chemists circumventing this reaction via a reduction ($\mathrm{LiAlH_4} + \mathrm{H_3O^+}$) followed by PCC/Swern.
  - However, for the purposes of this class, we can treat the DIBAL-H method as if it works perfectly in every case, i.e., as if we're just laying out a synthetic plan and the person performing the reactions will do everything perfectly. In other words, we should definitely feel free to use this method (as written from a naïve perspective) in any synthesis questions we encounter.

- Amides ($\mathrm{LiAlH_4}$).
- General form.

$$\mathrm{RCONR'R''} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{RCH_2NR'R''}$$

  - We don't *need* an aqueous workup, but it's often performed anyway to remove excess alumina.
- Mechanism.

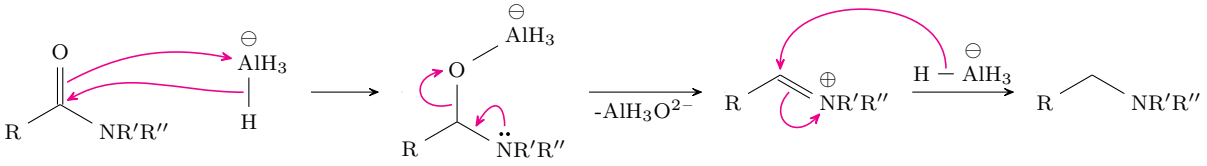


Figure 17.16: Reduction of amides mechanism.

  - Unlike with esters, nitrogen is a stronger donor than the oxygen atom, so it will kick it out in the second step.

- Amides (DIBAL-H).
- General form.

$$\mathrm{RCONR'R''} \xrightarrow[2.\ \mathrm{H_3O^+}]{1.\ \mathrm{DIBAL-H}} \mathrm{RCOH + NHR'R''}$$

- Mechanism.

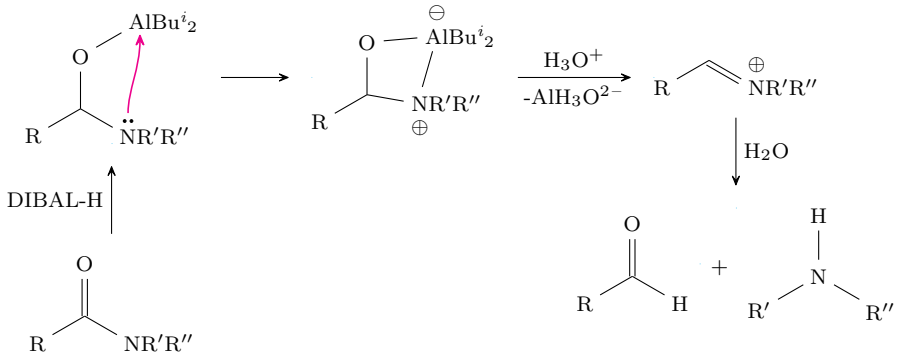


Figure 17.17: Monoreducton of amides mechanism.

  - Amides coordinate with DIBAL much more easily than esters.
  - Note that in the last step, the acid destroys any remaining DIBAL-H and then reduces the final species.
    - This likely proceeds analogously to the steps in the latter parts of Figure 17.5.

- Note that the role, stability, and structure of the tetrahedral intermediates are what determines the reactivity of amines with both sets of reagents.
- Reactions of nitriles.
- Nitriles (R′Li).
- General form.

$$\mathrm{RCN} \xrightarrow[2.\ \mathrm{H_3O^+}]{1.\ \mathrm{R'Li}} \mathrm{RCOR'}$$

  - Useful for generating a ketone from a carboxylic acid derivative.
  - No overaddition.

- Mechanism.

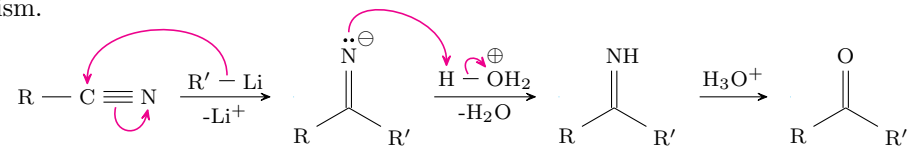


Figure 17.18: Nitrile alkylation mechanism.

  - Explaining the lack of overaddition.
    - Unlike with esters, there is no good leaving group in the first intermediate.
    - Indeed, adding another lithiate would kick out an N^{2-} species (highly unstable), but this would never happen.

    - Additionally, since the acid destroys the $LiAlH_4$, even though we end up producing a ketone (an electrophilic carbonyl), there is no further reactivity.
  - The last step is imine hydrolysis, which Levin mentioned in Aldehydes and Ketones 1 is reactivity to which imines are prone.

- Nitriles (DIBAL-H).
- General form.

$$\mathrm{RCN} \xrightarrow[2.\ \mathrm{H_3O^+}]{1.\ \mathrm{DIBAL-H}} \mathrm{RCOH}$$

- Mechanism.
  - As in Figure 17.15, the heteroatom (nitrogen) attacks the aluminum of DIBAL-H to start. We then undergo the same proton rearrangement to get to a stable species. However, instead of forming a chelate, the acid takes us to the same imine as in Figure 17.18, and then further to the aldehyde (also as in Figure 17.18).
- Nitriles ($LiAlH_4$).
- General form.

$$\mathrm{RCN} \xrightarrow[2.\ \mathrm{H_3O^+}]{1.\ \mathrm{LiAlH_4}} \mathrm{CH_2RNH_2}$$

- Mechanism.

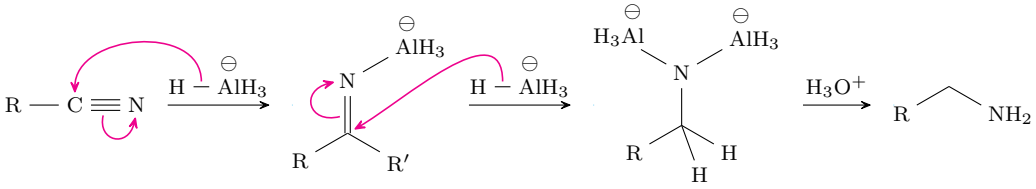


Figure 17.19: Nitrile reduction mechanism.

  - Why does this work here but not with R′Li?
- This nitrile reactivity allows two important types of transformations.
  - From an alkyl halide precursor, use KCN to take it to a nitrile, and then transform it to your carboxylic acid derivative of choice.
  - From a ketone, use HCN to take it to a cyanohydrin, and then move to a carboxylic acid derivative.
    - Watch out for acidic protons on the alcohol here, though!
    - Because of it, we can reduce to an amine with $LiAlH_4$ with ease, but we have to play with the concentrations to get the others to work (for example, by using a huge excess of the reagent in comparison to a lithiate).
- Transforming carboxylates to ketones.
- General form.

$$\mathrm{RCOOH} \xrightarrow[2.\ \mathrm{H_3O^+,\ time}]{1.\ \mathrm{R'Li},\ \Delta} \mathrm{CORR'}$$

  - Grignards won't work here; we do need the stronger lithiates.
  - We need an excess of R′Li and high heat ($\sim 100\,^\circ\mathrm{C}$).

- Mechanism.

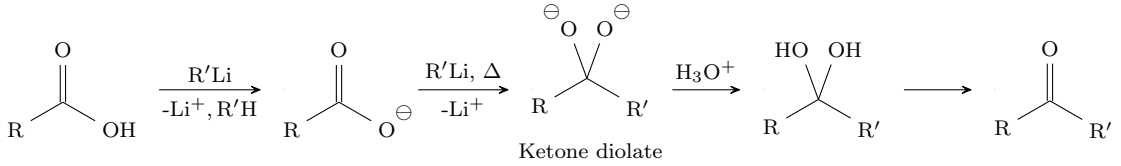
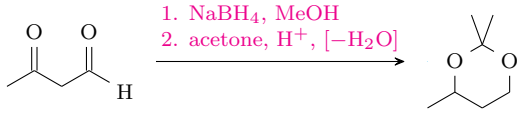


Figure 17.20: Carboxylic acid to ketone mechanism.

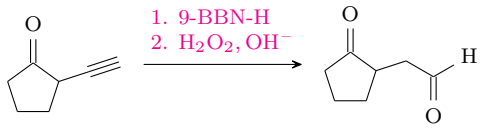
  - The excess lithiate is used to both deprotonate the carboxylic acid and alkylate the carboxylate that gets formed.
  - The heat is used to overcome the low electrophilicity of the carboxylate.

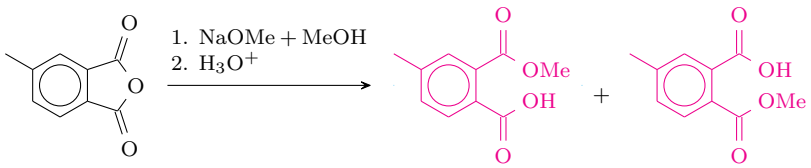
17.5 Problem Session

- Practice problems.

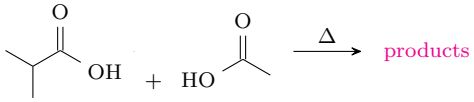
1. 

   - Sulfuric acid is a dehydrating acid.

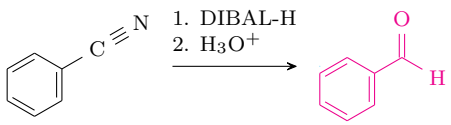
2. 

3. 

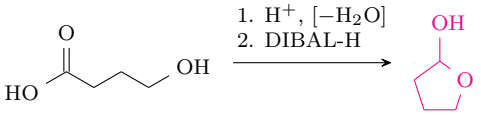
   - Notice that this is an asymmetric anhydride, so there are multiple possible products.
   - Regioselectivity goes out the window a bit due to the high temperatures, so don't worry about major and minor products

4. 

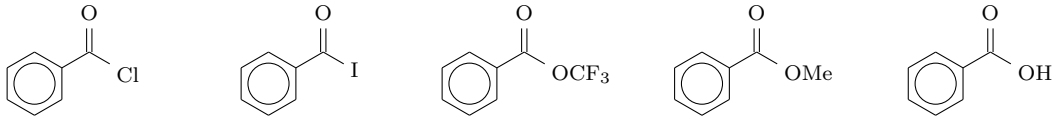
   - The products are a whole variety of coupled anhydrides.
   - We can do this selectively by transforming one of the carboxylic acids into an acid chloride with $SOCl_2$.
     - Note that we don't *have* to turn the other carboxylic acid into a carboxylate, but we can catalyze/accelerate the reaction by doing so with the addition of catalytic pyridine.

5. 

- We can also buy DIBAL-D.
- We're assuming that we're running this for only 15 mins, and thus stopping at the aldehyde. Running for longer will eventually take us down to the alcohol.
- To protonate a nitrile, we need a very strong acid (e.g., concentrated sulfuric acid).
- Goes over the mechanism, but in less depth than lecture.

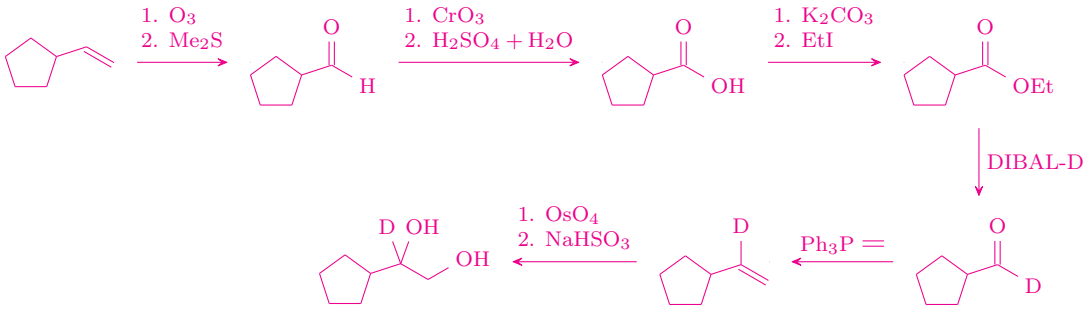
6. 

   - We first protonate the carboxylic acid oxygen, and then the alcohol at the end attacks the carbonyl.
   - Water leaves, yielding a 5-membered cyclic lactone.
     - Cyclic lactones are more stable as 5-membered rings than 6-membered rings.
   - DIBAL-H reduces the carbonyl to an alcohol.
7. Rank the following in order of rate of nucleophilic acyl substitution with an alkoxide nucleophile.



   2 | 1 | 3 | 4 | 5

   - The determining factor is the stability of the leaving group.
8. A long "propose a synthesis" question.



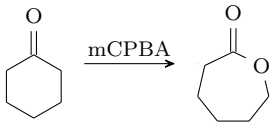
   - First thought: Dihydroxylation. But this doesn't provide a good way to incorporate deuterium. So we want our next-to-last intermediate to be like our reactant except with a deuterium in the right place.
   - Knowing that DIBAL-D is a good way to incorporate a single equivalent of deuterium, we can backtrack through a Wittig to a deuterated aldehyde.
   - If we want to follow the DIBAL-D route, we backtrack even further to an ester.
   - Then to a carboxylic acid, which we can create from the initial alkene via ozonolysis.
     - Note that we can get directly from an alkene to a carboxylic acid with 1. O_3, 2. Me_2S, H_2O_2, where the peroxide attacks either the molozonide or the ozonide.
   - This is a greater than exam strength question.

- We will not get "no reaction" questions on the exam.
- For any mechanism questions, we will get a complete acid (i.e., one with a defined conjugate base and not just H^+).

17.6 Carboxylic Acids and Derivatives 3

4/14:

- Announcements:
  - Lecture 5 has now been posted on Canvas > Panopto.
  - CHEM 23500, Fridays at 12:30 PM, Kent 107.
    - A new pilot course consisting of chem professors giving a single lecture on their research.
    - Levin goes tomorrow.
  - PSet 2 due Tuesday.
  - Midterm next Thursday.
    - Both PSet 2 and the midterm only cover through today's lecture.
    - How to study for the exam: For each reaction we've learned, we need to know the products, conditions, and mechanism.
    - The best way to master the information is to take the above information and connect it from one reaction to the next.
    - Start from a generic carbonyl compound and make a web of everywhere you can convert and what gets you where.
    - Still make a study sheet even if you don't use it because it's great preparation.
- Last time: Levin introduced a number of reactions to convert from carboxylic acid derivatives to aldehydes/ketones.
- Today: Reactions that convert from aldehydes/ketones to carboxylic acid derivatives.
  - Currently, we only know how to get a carboxylic acid, and the only way we know how to do that is using Jones reagent.
  - What we want to develop are insertion reactions, i.e., reactions that can stick a heteroatom into a C–H or C–R′ bond.
  - This is Levin's favorite lecture of the course because it's very similar to what he works on; the reactions we talk about are what inspired his research.
- Four insertion reactions.
  1. Baeyer-Villiger oxidation.
  2. Schmidt reaction.
  3. Curtius rearrangement.
  4. Beckmann rearrangement.
- The Baeyer-Villiger oxidation.
- General form.



  - Transforms a ketone into an ester; the general form above transforms a ketone into a **lactone**.
  - This is one of the most intuitive reactions to reverse engineer in a synthesis problem.
  - Important acidity properties of mCPBA.
    - The pK_a of benzoic acid is -4; benzyl alcohol is 15; mCPBA is 8. mCPBA is of intermediate acidity because there's no conjugation but the ketone is a strong EWG.
    - It's acidity means we don't need to add an external acid catalyst.

- Other reasons to use mCPBA.
  - In layman's terms, the active part of the molecule is the peracid functional group, but we use a chlorinated benzene ring to make the molecule both more reactive and less explosive.
  - More specifically, peracids are explosive. However, chlorine burns endothermically, by which we mean that making HCl from water requires heat. Thus, if the peracid were to begin combusting, a lot of the energy would go toward making HCl and not toward the explosive chain reaction. Additionally, chlorine is electron withdrawing from the meta position, meaning that the initial deprotonation is favored by having a more stable conjugate base.
  - Note that adding chlorine atoms to compounds is actually an oft-used trick to reduce their explosivity.
- In sum, other peracids can work, but mCPBA is the most practical.

- **Lactone**: A cyclic ester.
- Mechanism.

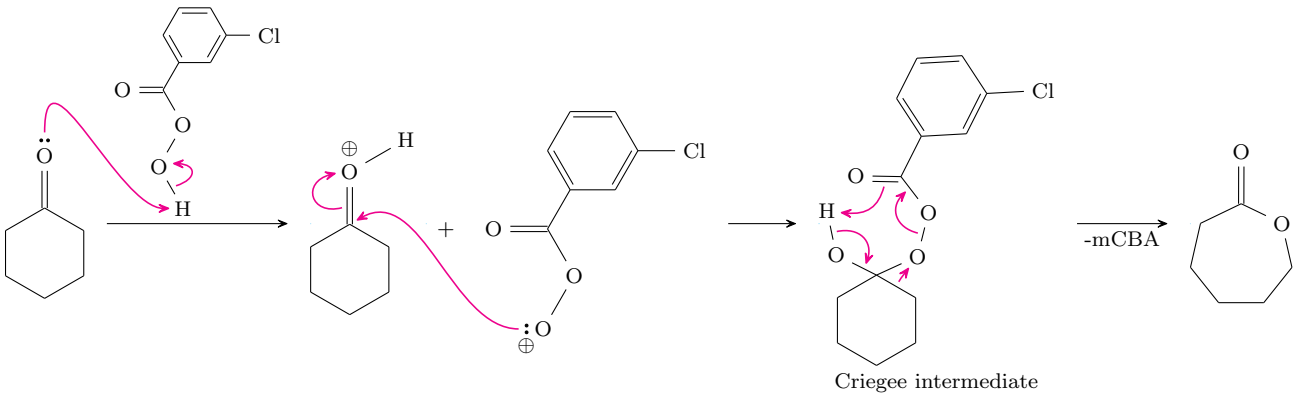
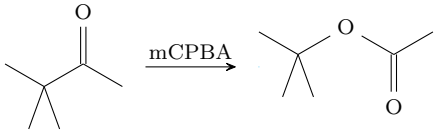


Figure 17.21: Baeyer-Villiger mechanism.

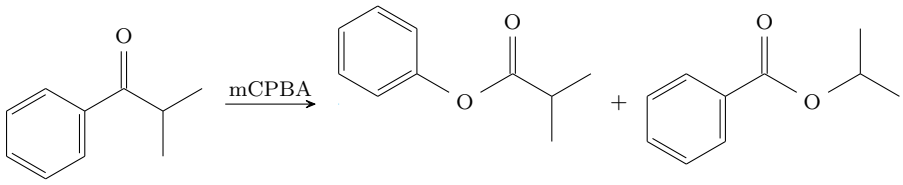
- Criegee made his fame for studying this reaction. He was the one who actually first proposed the existence of the intermediate that now bears his name.
- In the Criegee intermediate, one of the neighboring C–C bonds can slide over in a **migration**.
  - Think about the parallel to hydroboration/oxidation (Figure 16.6) and the formation of the enol boronate.
- Additionally, the O–O bond is pretty weak and can be displaced.
  - However, because this is mCPBA (with its electron withdrawing carbonyl), the O–O electrons can swing around and facilitate the attack of the carbonyl electrons on the substrate's acidic proton.
- Last step arrow pushing chronology: The O–H electrons swinging down. Reforming the carbonyl provides the oomph that breaks the C–C bond. The C–C electrons migrate. This makes everything else just swing around.
  - Note that this chronology is not technically accurate; curved arrows are a human invention we assert overtop a concerted step. However, this is a good trick to think of for memorization purposes.

- **Migratory aptitude**: How likely a group is to shift, or migrate.
  - Discussing the migratory aptitude of different R groups we might see on either side of the ketone (in a Baeyer-Villiger, for instance) allows us to predict the products of the reaction in ambiguous cases, such as with asymmetric ketones.

- Asymmetric ketones in the Baeyer-Villiger.



(a) A selective case.



(b) An unselective case.

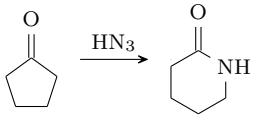
Figure 17.22: Asymmetric ketones in the Baeyer-Villiger.

  - How likely a C–C bond is to move depends on what's attached to the α-carbon.
  - Selectivity for this reaction (not the same for all reactions):

$$3^\circ \text{ alkyls} > 2^\circ \text{ alkyls} \approx \text{aromatics} > 1^\circ \text{ alkyls} > \text{methyl}$$

    where the α-carbon being 3° promotes the reaction the most and it being a methyl group promotes it the least.
    - This does work with aldehydes; hydrogen will migrate faster than anything else (i.e., forming carboxylic acids).
    - Jones is a cheat to do the same thing, though.
  - Because of differing migratory aptitudes, the Baeyer-Villiger is not always useful synthetically.
  - Always think about a precursor being asymmetric when doing a retrosynthetic analysis!

- Note that epoxidation is usually faster than the Baeyer-Villiger. Thus, compounds with both an alkene and a ketone that react with mCPBA will form epoxides and the carbonyls will be untouched.
- Schmidt reaction.
- General form.



  - You can use catalytic acid, but you don't need it.

- **Hydrazoic acid**: A toxic, volatile, and explosive substance. *Structure* $HN{=}N^{+}{=}N^{-}$
  - This is useful industrially, but less useful in the lab (because of all the associated hazards).
- Mechanism.
  - Getting rid of nitrogen is a massive thermodynamic sink/driving force.
  - One of the molecules of hydrazoic acid is being incorporated, and the other is a catalyst (which we can supplement with external acid catalyst). It will go faster with an acid catalyst if the acid used is stronger than hydrazoic acid, but the acid is not necessary.

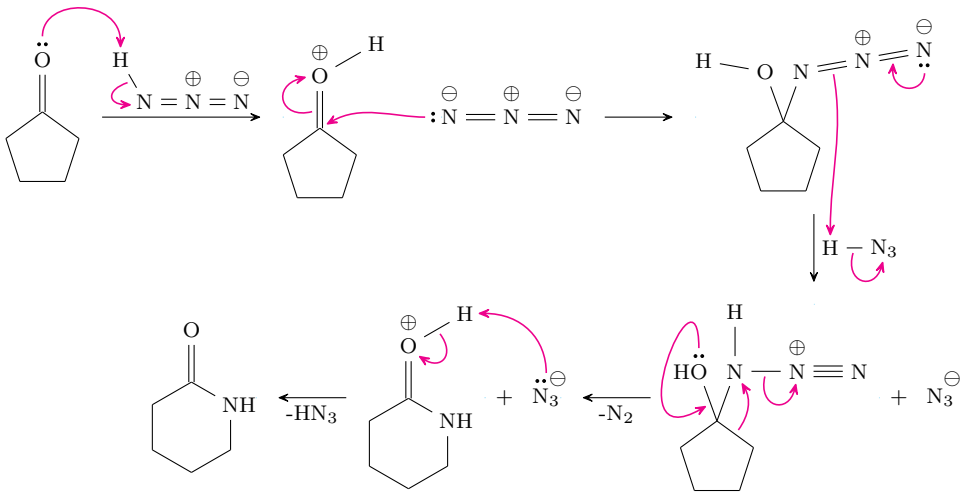


Figure 17.23: Schmidt reaction mechanism.

  - Again, the arrow pushing chronology starts at the alcohol oxygen for the final step.

- Migratory aptitude is the same for Schmidt as for the Baeyer-Villiger.
- The Schmidt does work with aldehydes; hydrogen will migrate faster than anything else.
  - You would form an amide in this case.
  - It's rare to see this in the literature, though.
- Using an alkyl group in place of the hydrogen on the hydrazoic acid *requires* catalytic acid (the new acid isn't strong enough to catalyze its own chemistry). The alkyl group just gets added to the nitrogen in the product.
- The Schmidt reaction also works intramolecularly.

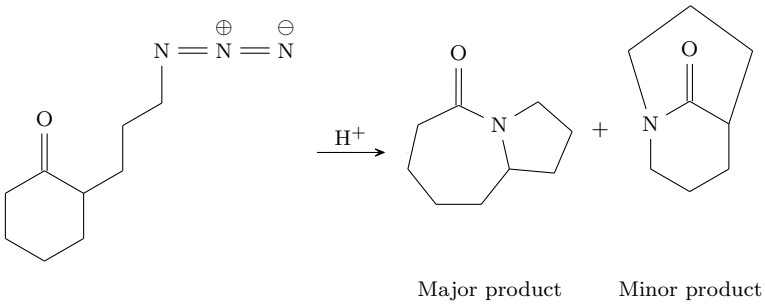


Figure 17.24: Intramolecular Schmidt reaction.

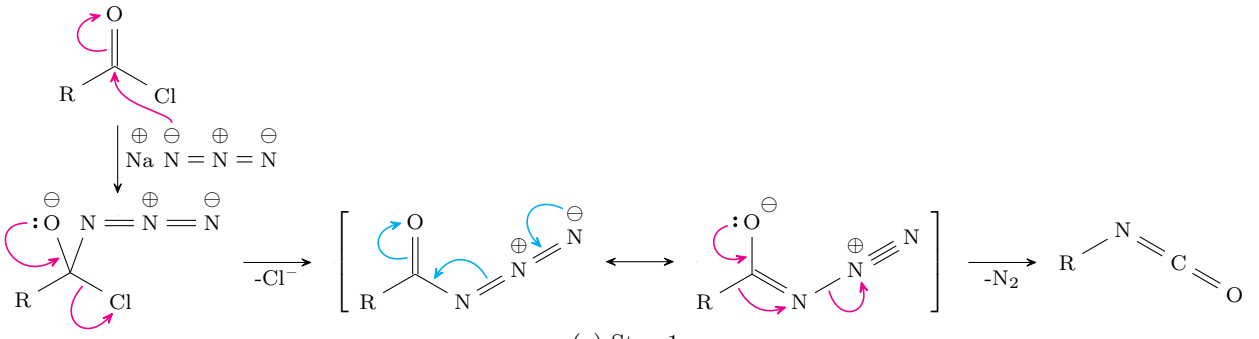
  - The intramolecular Schmidt builds complexity really quickly.
  - When you're building natural molecules, it allows you to get up from simple cheap starting materials to complex polycycles quite quickly, which you want.

- The Curtius rearrangement.
- General form.

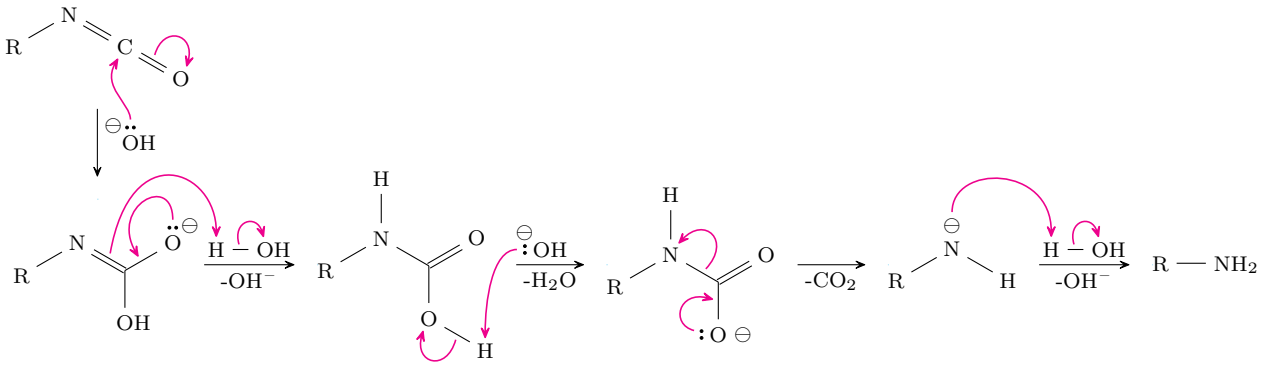
$$\text{RCOCl} \xrightarrow[\Delta]{\text{NaN}_3} \text{RNCO} \xrightarrow[\text{H}_2\text{O}]{\text{NaOH}} \text{RNH}_2$$

  - The product of the first step is an **isocyanate**.

- Mechanism.



(a) Step 1.



(b) Step 2.

Figure 17.25: Curtius rearrangement mechanism.

  - Acyl azides are sometimes isolable. Heating one up will always cause it to convert, though.

- Isocyanates can also be trapped to form carbamates.

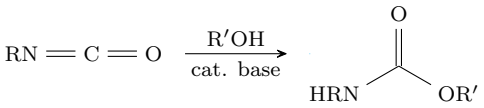
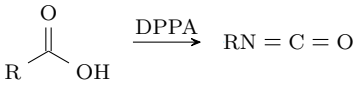


Figure 17.26: Carbamate formation.

  - Use an alcohol and catalytic base.

- This is the reaction behind guys on YouTube spraying insulation/fire retardant foam and it expanding on the wall behind them.
  - You have one diisocyanate and add ethylene glycol at the last second; the foaming up is the polymerization resulting in polyurethane.
  - We will not be asked about the foam thing specifically, but we may be asked to draw the product of a compound with two isocyanates at each end.
  - Levin disses Snyder lol – "not gonna ask you what color tie I'm wearing either."

- Converting from a carboxylic acid to an isocyanate without going through an acid chloride intermediate.



- **DPPA**: Diphenylphosphoryl azide. *Structure*

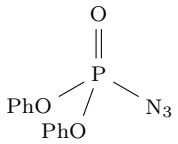
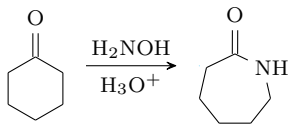


Figure 17.27: Diphenylphosphoryl azide (DPPA).

  - Just like $SOCl_2$ and $POCl_3$ work as dehydrating agents (with chloride), DPPA works as a dehydrating agent (with azide).

- Beckmann rearrangement.
- General form.



  - You can do this all in one go, or you can isolate the oximes from the first reagent and removing water, and then add in acid to finish it off.
  - Quite similar to the Schmidt, but hydroxyl amine is not as toxic, volatile, or explosive, so this is the preferred one.

- Mechanism.

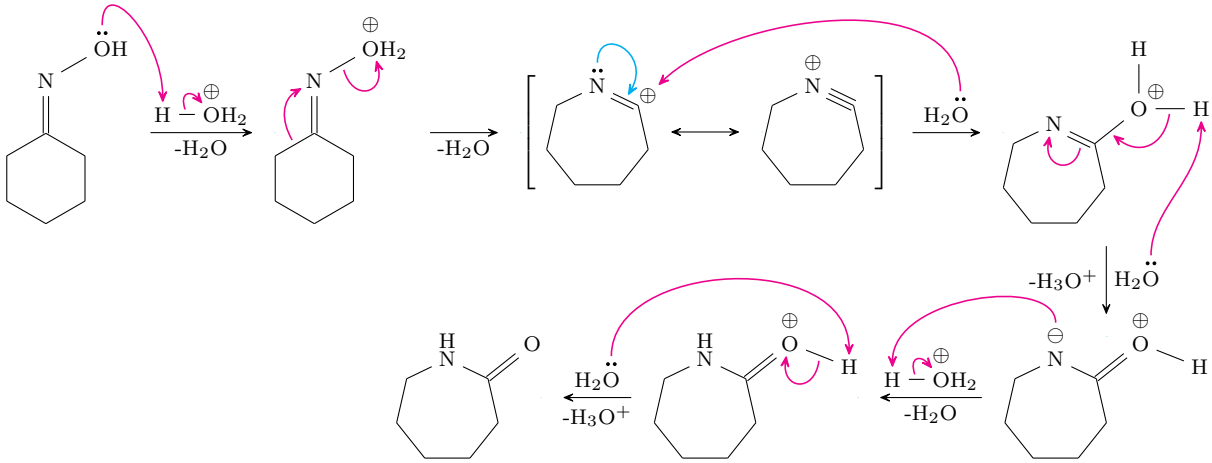


Figure 17.28: Beckmann rearrangement mechanism.

  - The first part of the mechanism proceeds just like oxime formation (see Aldehydes and Ketones 1). This is why we show the mechanism beginning from an oxime.
  - There is debate over the mechanism. We are only responsible for the one above, though.
  - The triple-bonded nitrogen resonance form is quite strained, and thus the carbocation species is the major contributor.

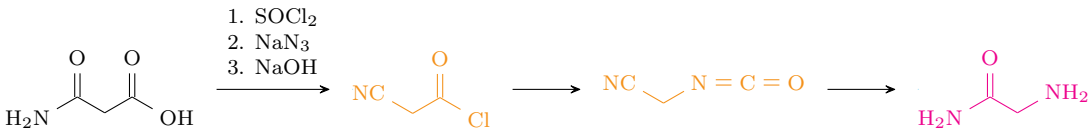
- Caperlactam (the end product in Figure 17.28) is made from cyclohexanone in quantites of millions of tons per year because it is a precursor to nylon, which is just caperlactam following a ring opening.

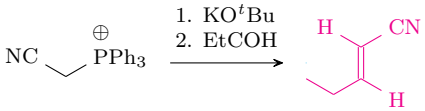
- Migratory aptitude (same as for Baeyer-Villiger and Schmidt).
- An orbital explanation of the migratory aptitude in this case.
  - The step 2 migration is an S_N2 process.
  - As such, we want to see donation into the antibonding σ orbital of the N–O bond to make this proceed. This is why the carbon "behind" the oxime selectively migrates.
  - However, in acidic solution, oximes exist in equilibrium with their *cis*/*trans* counterpart.
  - As such, since sterics disfavor the OH being on the same side as a bulky group, we will more commonly observe the oxime in solution where the OH points away from the bulky group, thus forming more of this product.
- The Beckmann rearrangement also helps create azithromycin, the active ingredient in the common Z-pak antibiotics.
  - Erythromycin is produced by some bacteria to defend against other bacteria.
  - You need a big dose of it because it's half-life in your body is 1.5 hours. It also is really tough on your body because it kills all your gut bacteria.
  - A couple of chemical steps including the Beckmann rearrangement takes it to azithromycin, which has a half-life of 68 hours.

17.7 Problem Session

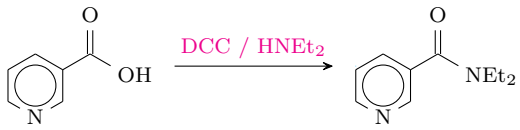
4/19:

- Practice problems.

1. 

2. 

   - This reaction involves a stabilized ylide, hence the formation of the *trans* product.

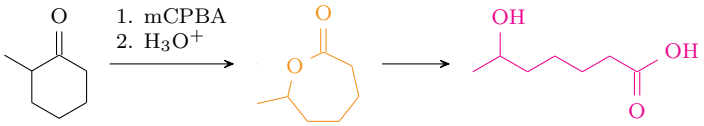
3. 

   - You could add catalytic amounts of pyridine, DMAP, or any other nonnucleophilic source of nitrogen to speed up this reaction.

4. 

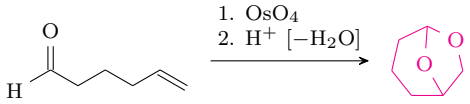
   - In an exam setting, we won't be charged with knowing that we need heat.

5.

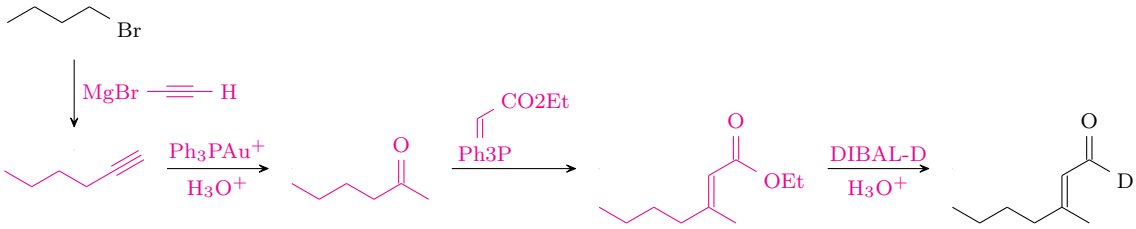


- The second step proceeds as a consequence of the acid $H-OH_2$ to a carboxylic acid derivative, as per Figure 17.3a.

6.

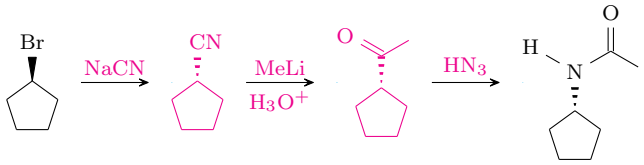


7. Mechanism: Goes over the Curtius rearrangement.
8. Retrosynthesis.

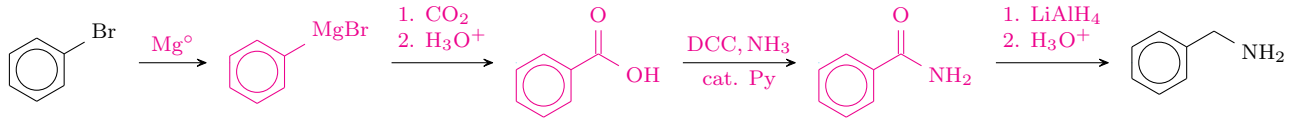


- That deuterated aldehyde should indicate DIBAL-D.
- COOEt is an EWG, and we will get the desired trans product in a Wittig with it.

9. Retrosynthesis.



10. Retrosynthesis.



- We will get credit if our synthesis is right even if it is not the most efficient.

- For mechanism questions, if we're struggling, think back to the sentence trick from the very beginning of the course.
- For synthesis questions, just throw as many reactions out there as we can think of.

Chapter 18

Carbonyl Compounds' α-Carbons

18.1 Reactions at the α-Carbon of Carbonyl Compounds 1

4/19:

- Comparing Units 1-3.
  - Units 1 and 2 were about nucleophiles adding to electrophilic carbonyls.
  - Unit 3 talks about carbonyls as nucleophiles (when they've been deprotonated at the α-position).
- **Enolate**: The class of molecules that resonate between a carbonyl with a carbanion at the α-position and a deprotonated, negatively charged enol. *Structure*

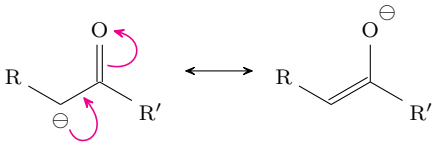


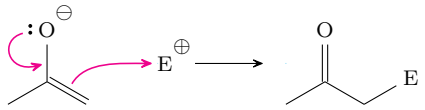
Figure 18.1: Enolate.

  - We care about enolates as a way to form C–C bonds.
- Our current list of C–C bond forming reactions includes...
  1. Wittig.
     - Combines an ylide and a carbonyl electrophile.
  2. Friedel-Crafts.
     - Combines an arene and a carbonyl electrophile.
  3. Cyanide nucleophile.
     - Combines HCN or a CN^- source and a carbonyl electrophile.
  4. Organometallics: Grignards, lithiates, and alkylyl anions.
     - Combine carbanions and a carbonyl electrophile.
  5. Diels-Alder.
  6. **Simmons Smith cyclopropanation**.
- Simmons Smith cyclopropanation.
- General form.

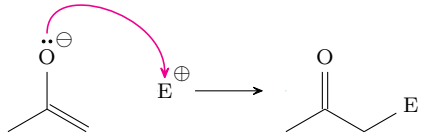
$$C_2H_4 \xrightarrow[CH_2I_2]{Zn/Cu} C_3H_6$$

  - This reaction is commonly taught in CHEM 22000 or CHEM 22100; the fact that it was not our year does not now make it our responsibility on tests.

- The takeaway from this refresher of C–C bond forming reactions is that of the six ways we know to make C–C bonds, four involve carbonyls (and in all of these, the carbonyl role plays as an electrophile).
  - As mentioned above, Unit 3 is about flipping this paradigm, i.e., making carbonyls into nucleophiles.
- pK_a's.
  - Deprotonating an O–H bond: Recall that acetic acid (p$K_a \approx 15$) is 10^{10} times more acidic than ethanol (p$K_a \approx 5$) due to resonance stabilization of the conjugate base in the former.
  - Deprotonating a C–H bond: A hydrogen on the 1-carbon of propane (p$K_a \approx 50$) is 10^{25}-10^{30} times more acidic than a hydrogen on acetone (p$K_a \approx$ 20-25) once again due to resonance stabilization (note that deprotonated acetone constitutes an enolate).
- Enolates have two main modes of reactivity.



(a) Adding an electrophile at the carbon.



(b) Adding an electrophile at the oxygen.

Figure 18.2: Reactions of enolates and electrophiles.

  - We will focus on the mode in Figure 18.2a because we're most interested in making new bonds to carbon.
- If $E^+ = H^+$, then we can either generate a ketone (via Figure 18.2a) or an **enol** (via Figure 18.2b).
- **Enol**: The class of molecules containing adjacent alkene and alcohol functional groups. *Structure*

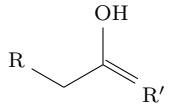
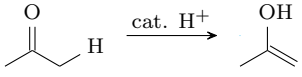


Figure 18.3: Enol.

- **Tautomers**: Two constitutional isomers that rapidly interconvert. *Etymology* from Greek **taut** "same" and **mer** "part."
  - Example: Enols and ketones are tautomers.
- Enol formation (acid-catalyzed).
- General form.



- Mechanism.

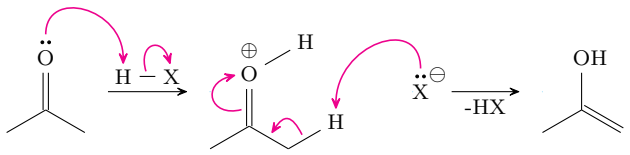
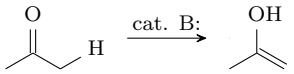


Figure 18.4: Acid-catalyzed enol formation mechanism.

- Enol formation (base-catalyzed).
- General form.



- Mechanism.

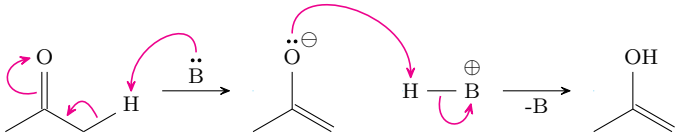
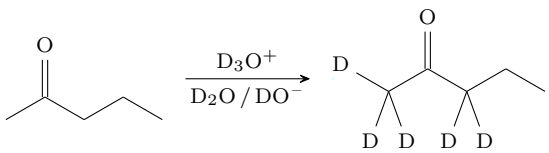
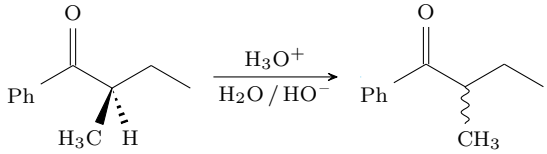


Figure 18.5: Base-catalyzed enol formation mechanism.

  - If the base has a pK_a greater than that of the carbonyl, then the compound gets stuck at the enolate.
    - In other words, the enol will only form when the base is weak enough to do the initial deprotonation but not the reverse deprotonation, i.e., it can set up a keto-enol equilibrium but not stoichiometrically deprotonate the ketone.
  - All of next lecture is on really strong bases and enolates.
- Levin also draws the reverse mechanism for both of these as per the principle of microscopic reversibility.
  - It follows that there is an equilibrium between a ketone and its enol.
- The position of the equilibrium depends largely on the resonance stability of both tautomers.
  - The equilibrium between 1-phenylpropan-1-one and (Z)-1-phenylprop-1-en-1-ol lies heavily on the side of the ketone.
    - Resonance between the carbonyl and the benzene ring favors the ketone.
  - The equilibrium between pentane-2,4-dione and (Z)-4-hydroxypent-3-en-2-one lies mostly on the side of the ketone.
    - An extra resonance form stabilizes the enol.
  - The equilibrium between cyclohexa-2,4-dien-1-one and phenol lies heavily on the side of the enol.
    - Aromaticity stabilizes the enol.
- Evidence for the existence of enols (which are usually present in such a small portion as to not be isolable).



(a) Deuteration.

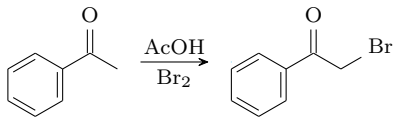


(b) Racemization.

Figure 18.6: Evidence for the existence of enols.

1. Deuteration of carbonyl compounds (Figure 18.6a).
   - Proves the existence of a process that is "washing in" the deuterium, but only at the α-positions.
   - Note that D_2O / DO^- denotes basic deuterated water, and that only acidic or basic deuterated water is used at one time.
2. Racemization of compounds that are enantiopure at the α-position (Figure 18.6b).
   - Thus, we're removing the hydrogen, forming an achiral intermediate, and then putting that hydrogen back but randomly this time.

- Halogenation of enols (acid-catalyzed).
- General form.



- Mechanism.

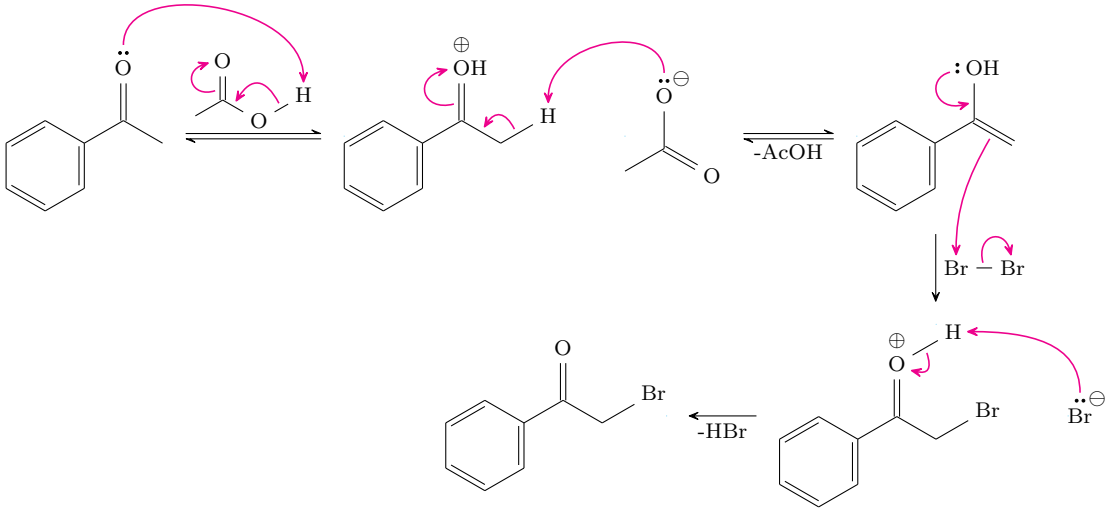
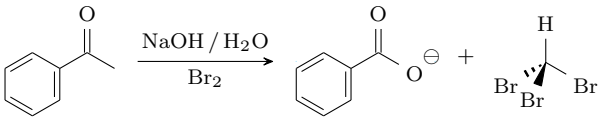


Figure 18.7: Acid-catalyzed halogenation of enols mechanism.

   - Remember that only a tiny percentage of the enol will be formed in the equilibrium constituting the first two steps, but these few molecules formed will be piped through the rest of the reaction over time and will pull more through via Le Châtelier's principle.

- Haloform reaction.
- General form.



   - This reaction essentially constitutes the base-catalyzed halogentation of enols.
   - We can run this reaction with any halogen (not just bromine), hence the name "*halo*form reaction."
   - This is how chloroform is made!

- **Bromoform**: The right product of the haloform general reaction above. *Also known as* **tribromomethane**.
  - More generally, any trihalomethane has an old-school, common -form name. For example, we alo have **chloroform** (trichloromethane) and **iodoform** (triiodomethane).
- Mechanism.

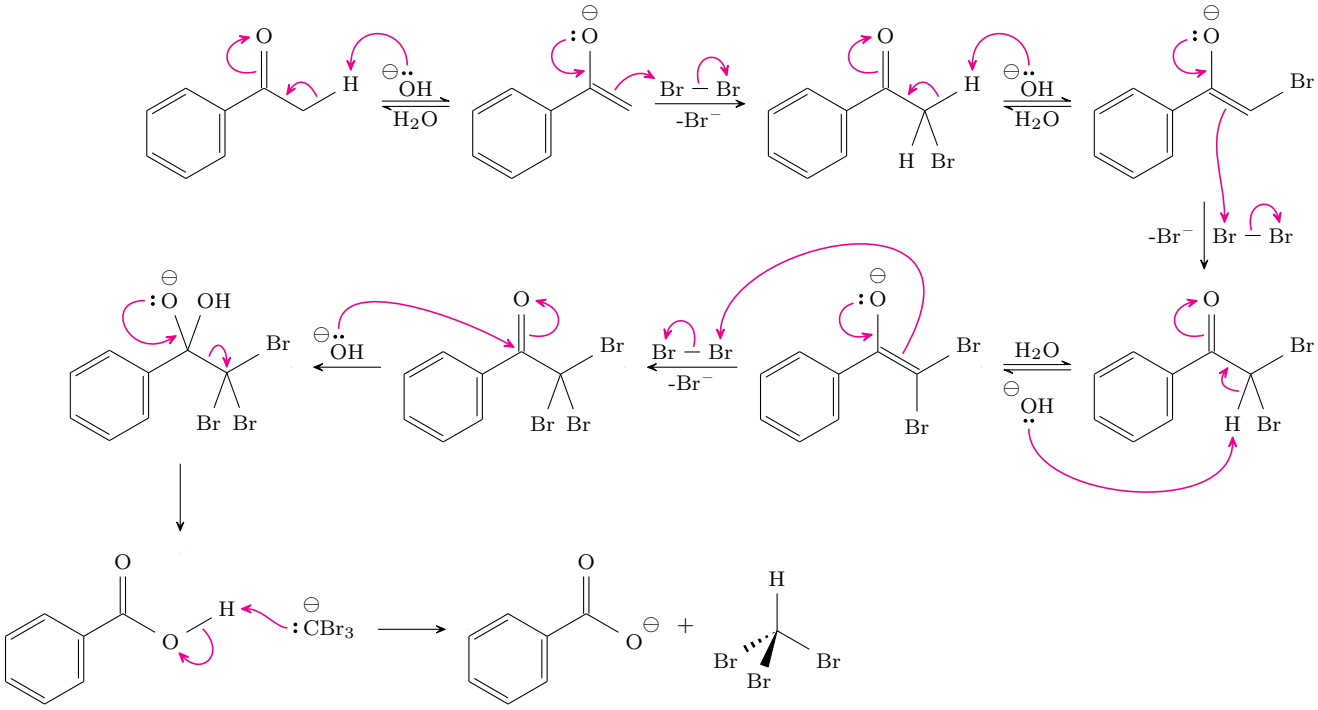


Figure 18.8: Haloform reaction mechanism.

  - As with the acid-catalyzed version, only a little bit of the enol will be present at each stage, but Le Châtelier's principle is our friend here.
  - Carbons are not usually good leaving groups, but with three strongly electron-withdrawing halogens, it will leave when the hydroxide is out of options in a last-ditch nucleophilic acyl substitution.
- Explaining the difference in the acid- vs. base-catalyzed halogenation of enols.
  - Consider the molecule which doubles as the product in the acidic mechanism and the second intermediate in the basic mechanism.
  - If we are to react this molecule further in the acidic mechanism...
    - The first step is protonation of the carbonyl.
    - The bromine (an EWG) *destabilizes* the positive oxygen.
    - Thus, the SM (which lacks the EWG bromine) reacts faster under acidic conditions. Therefore, all of it will react before any of the product reacts.
  - If we are to react this molecule further in the basic mechanism...
    - The first step is deprotonation at the α-carbon, resulting in an alkoxide anion.
    - The bromine (an EWG) *stabilizes* the negative oxygen.
    - Thus, the monobrominated species reacts faster under basic conditions. This favoritism is exacerbated by the addition of further bromines. Therefore, one molecule of the monobrominated species will react to completion before any more of the SM reacts.

  - As further evidence, if we do the basic version with only 1 equivalent of bromine, we observe 1/3 carboxylate, a corresponding amount of bromoform, and 2/3 SM in the products.

- The haloform reaction doesn't always work.

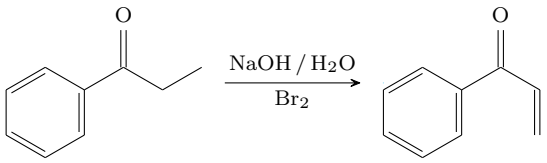


Figure 18.9: β-hydrogens in the haloform reaction.

  - When there are β-hydrogens, we generate an α,β-unsaturated ketone.
  - This is because we'll brominate once (the α-hydrogens still have a far lower pK_a than the β-hydrogens, so they attract the base) and then do an E2.

- Synthetically, the haloform reaction has uses most similar to the Baeyer-Villiger.

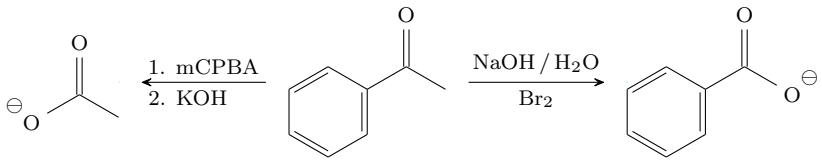


Figure 18.10: Synthetic uses of the haloform reaction.

  - Suppose we have a ketone and want to create a carboxylate.
  - The haloform reaction selectively cleaves methyl groups, installing an oxygen anion.
  - The Baeyer-Villiger selectively inserts an ether into the bond to larger groups.
    - We can then cleave the larger group via the saponification mechanism.
  - Note also that this reaction is useful as a C–C bond *cleaving* reaction.
    - We have even less of these than we do C–C bond forming reactions.
    - The only ones we have are periodate cleavage, ozonolysis, and the two techniques just described here.

- Midterm questions and review.
- Origin of selectivity for the Beckmann?
  - Discusses the transition state.
  - Goes into the σ^* orbital explanation.
  - Since σ^* is higher in energy than σ is low, filling σ^* breaks the bond.
  - The external lobe is significantly bigger than the internal (along the bond) lobe.
- The more sterically hindered the ketone, the harder it will be to do stuff to it.
- $SOCl_2$ releases HCl when there's no pyridine around.
  - We're only being graded on the presence of the organic products, though.
- In the Wolff-Kirshner, we do need both hydrogens in the hydrazone.
  - Modify notes!

- If we have some steps in the beginning of a mechanism and some steps in the end with a gap in between, we will get credit for what's on both sides.
- DPPA is paired with NEt_3.
  - Modify notes!
- Ketal formation happens on ketones and aldehydes only (not carboxylic acid derivatives).
  - Modify notes!

References

Labalme, S. (2021). *CHEM 22000 (Organic Chemistry I) notes*. Retrieved March 29, 2022, from https://github.com/shadypuck/CHEM22000Notes/blob/master/Notes/notes.pdf

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