CHEM 22200 (Organic Chemistry III) Notes

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Chapter 16

Aldehydes and Ketones

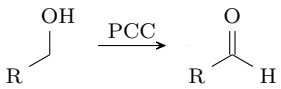
16.1 Electron Pushing

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.

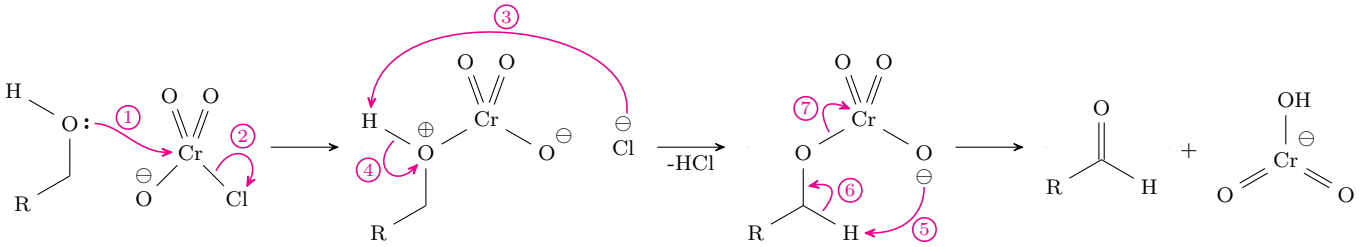
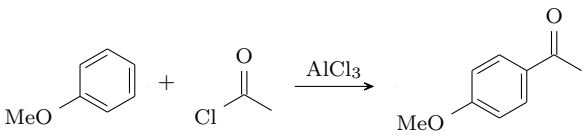


Figure 16.1: Oxidation of alcohols mechanism.

  - 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.

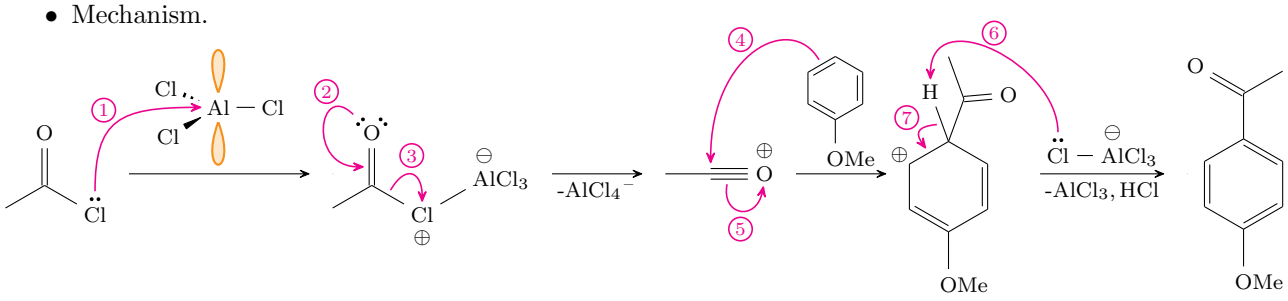
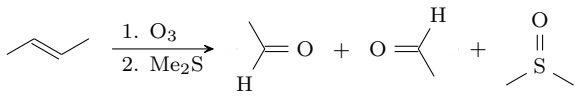


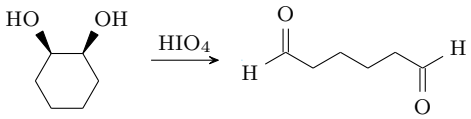
Figure 16.2: Friedel-Crafts acylation mechanism.

  - 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.

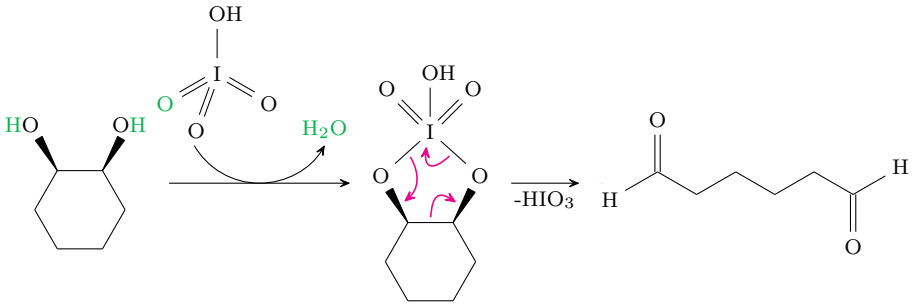
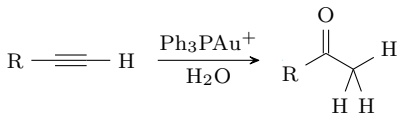


Figure 16.3: Diol cleavage mechanism.

- 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.

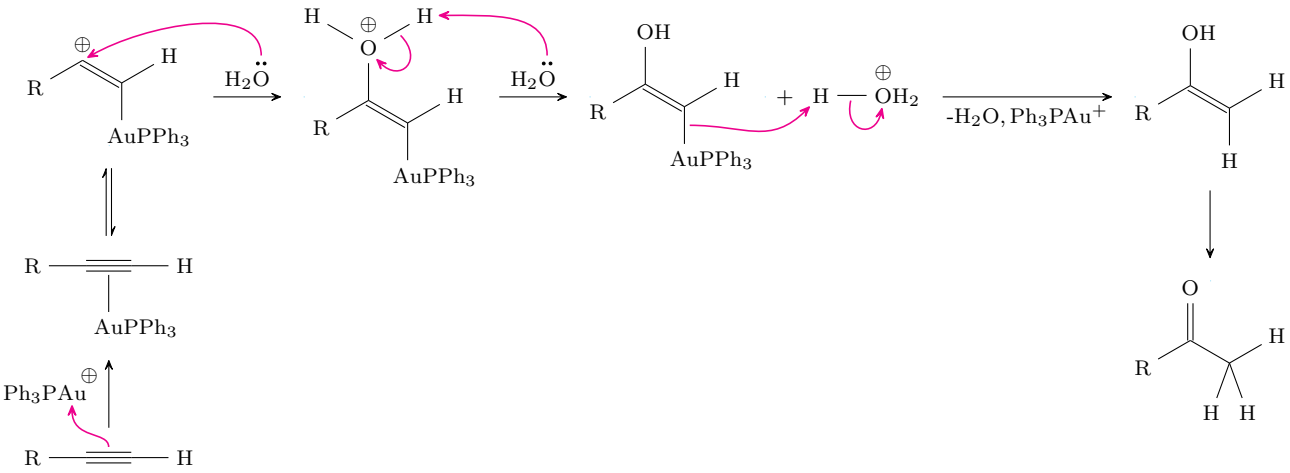
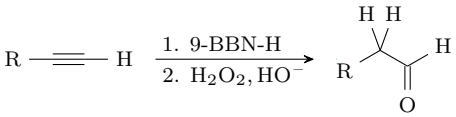


Figure 16.4: Alkyne hydrogenation mechanism.

  - 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

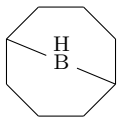


Figure 16.5: 9-Borabicyclo[3.3.1]nonane (9-BBN-H).

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

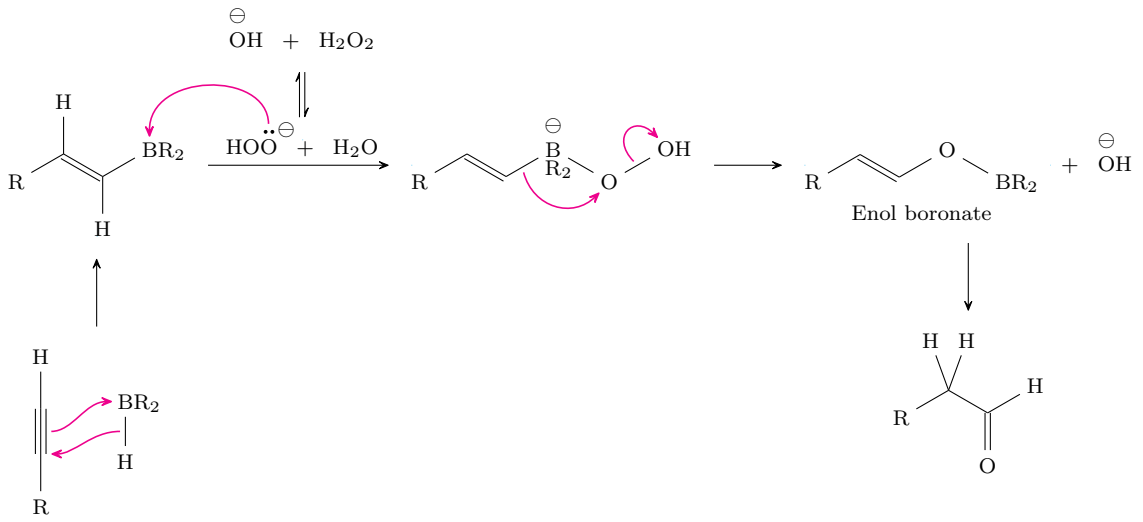


Figure 16.6: Alkyne hydroboration mechanism.

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

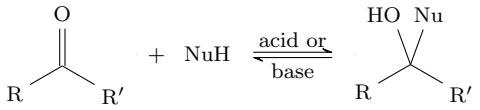
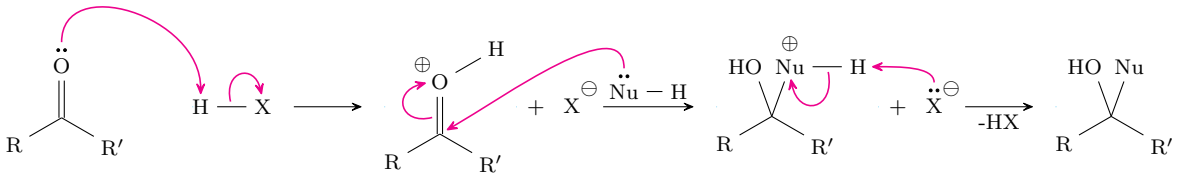
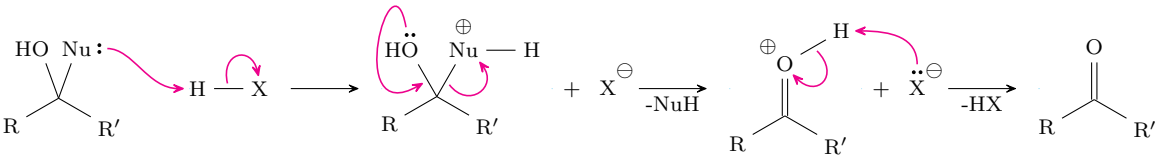


Figure 16.7: The key mechanism in CHEM 22200.

- Acidic mechanism.



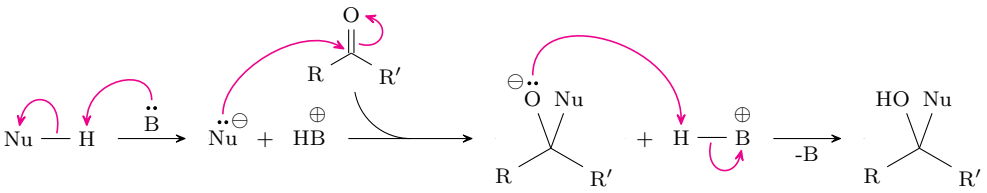
(a) Forward direction.



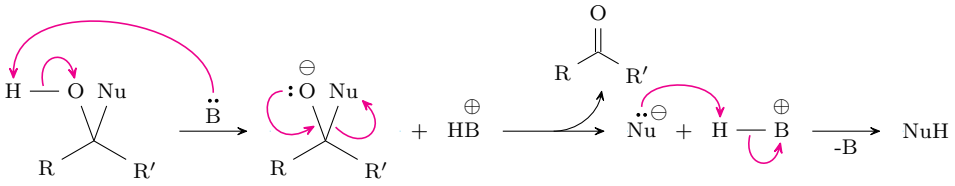
(b) Reverse direction.

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*

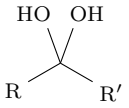
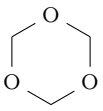
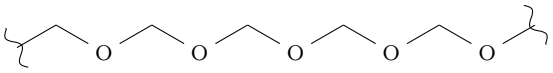


Figure 16.10: Carbonyl hydrate ($R' = H, C$).

- 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*

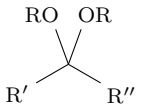


Figure 16.12: Ketal.

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

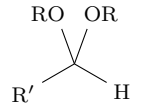
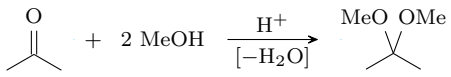


Figure 16.13: Acetal.

- 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.

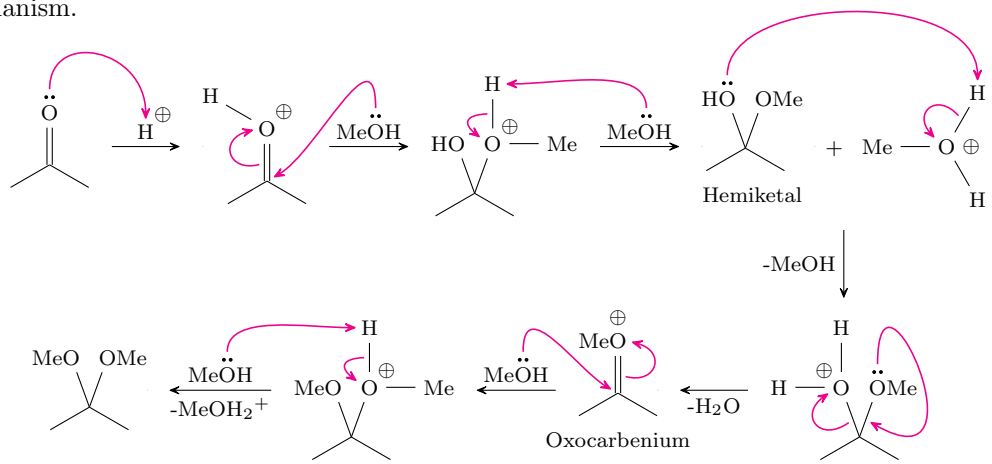


Figure 16.14: Ketal formation mechanism.

  - 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.

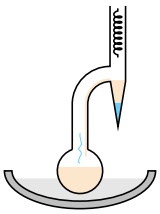
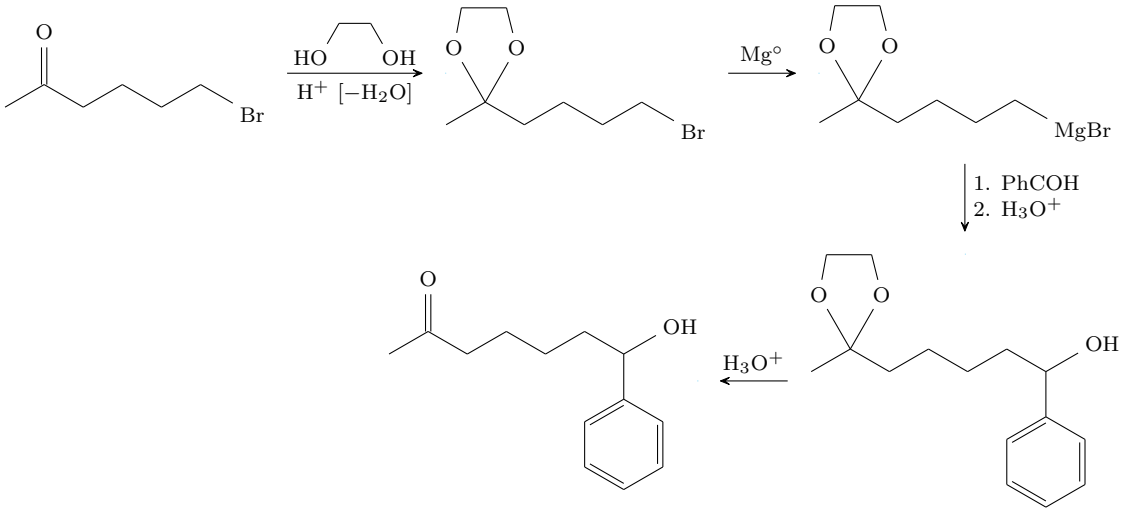


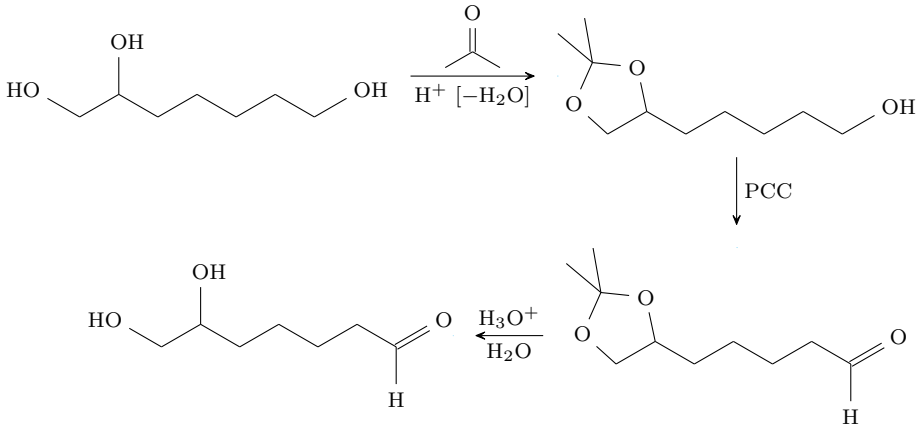
Figure 16.15: Dean-Stark apparatus.

  - 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 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*

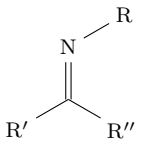
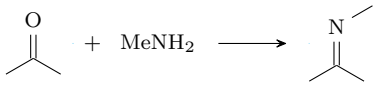


Figure 16.17: Imine.

  - 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*

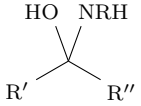


Figure 16.18: Hemiaminal.

- 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*

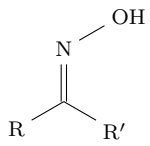
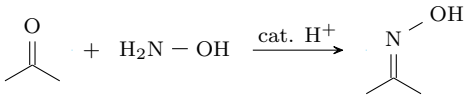


Figure 16.19: Oxime.

- 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*

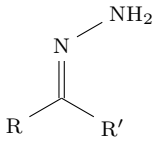
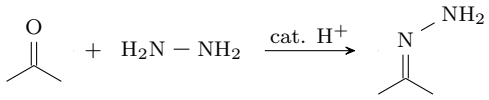
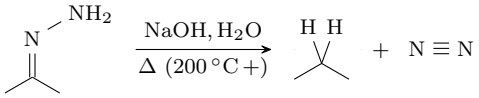


Figure 16.20: Hydrazone.

- 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.

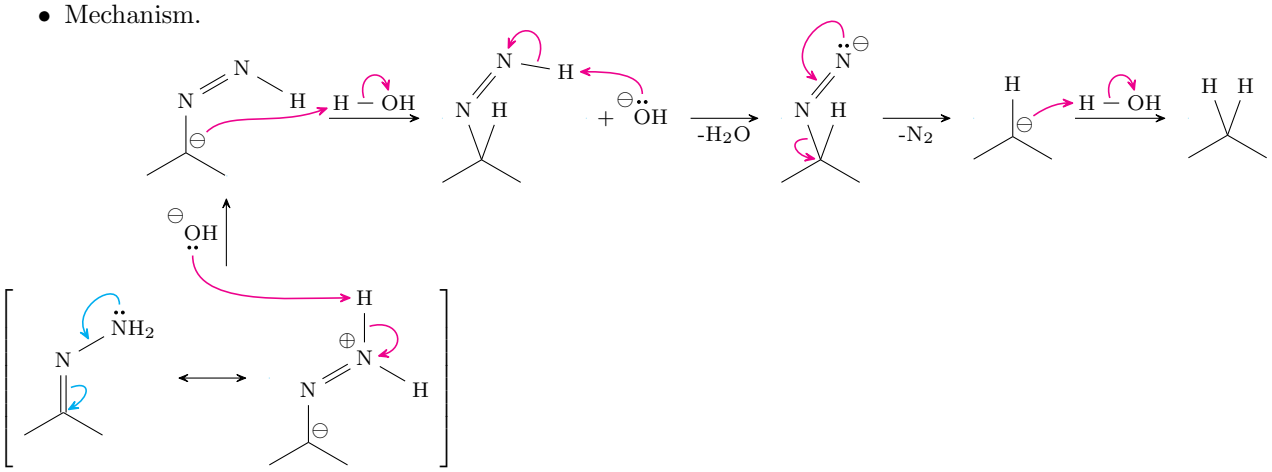


Figure 16.21: Wolff-Kirshner reduction mechanism.

  - 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*

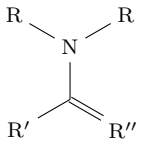
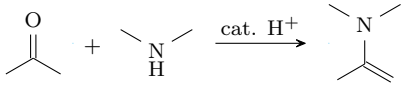


Figure 16.22: Enamine.

- General form.



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

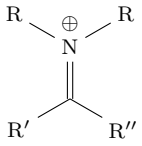


Figure 16.23: Iminium.

- 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 resultin from the nucleophilic addition of HCN to a ketone or aldehyde. *Structure*

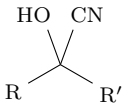
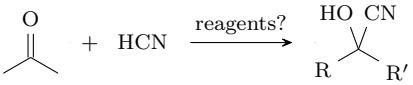


Figure 16.24: Cyanohydrin.

- 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*

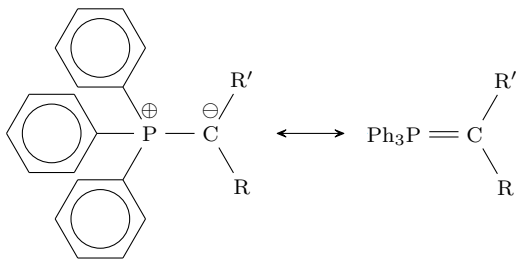


Figure 16.25: Phosphorous ylide.

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

- Synthesis of phosphorous ylides.

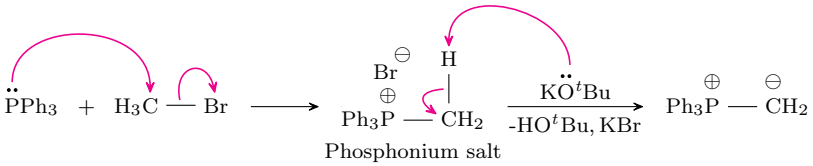


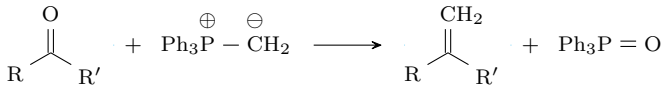
Figure 16.26: Synthesizing phosphorous ylides.

  - 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).

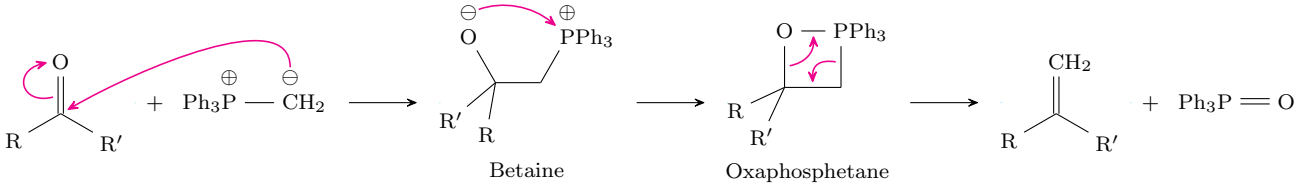


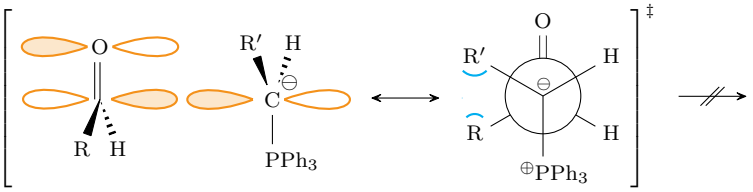
Figure 16.27: Wittig olefination mechanism (stepwise).

  - 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.

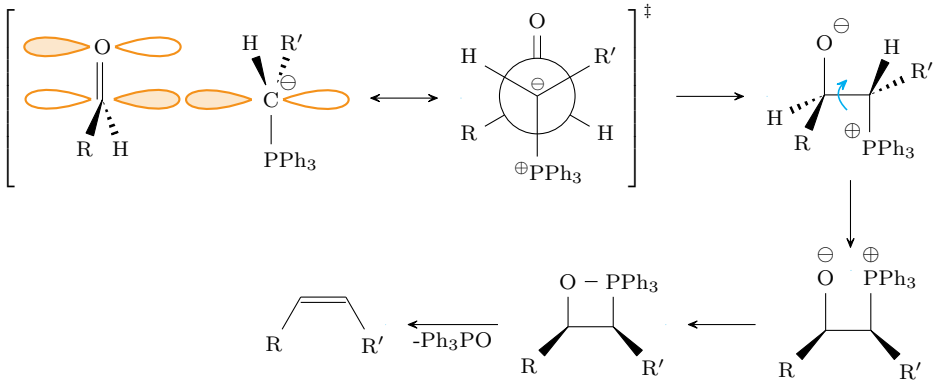
- The Wittig olefination is stereoselective for the *cis*-product.
  - This is strange since the *cis*-product is the less thermodynamically stable one.

[2] "VIT-tig"

- Three-dimensional intuition for the stereoselectivity.



(a) Unsuccessful collision.

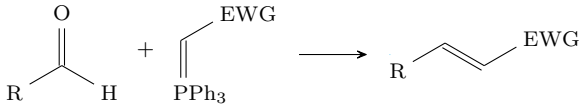


(b) Successful collision.

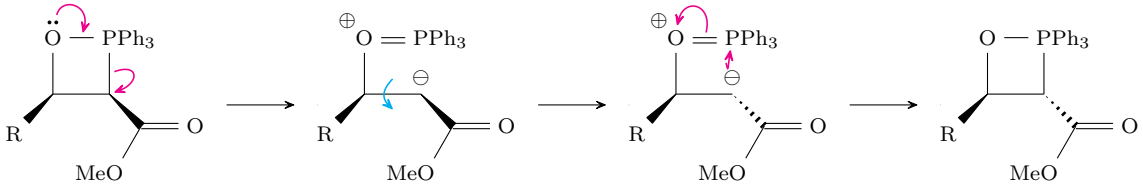
Figure 16.28: Wittig olefination stereoselectivity.

  - 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).

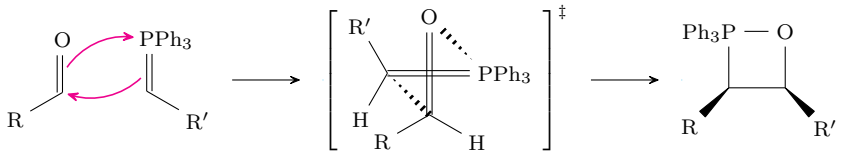


Figure 16.30: Wittig olefination mechanism (modern).

  - 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

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

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

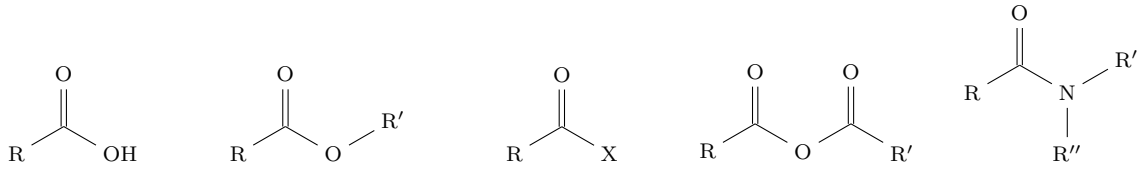
Chapter 17

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.

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

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

- Mechanism.

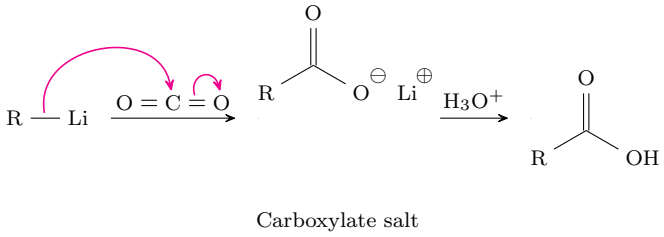
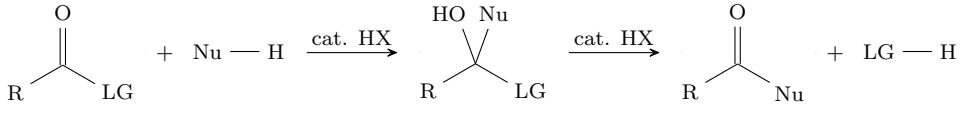
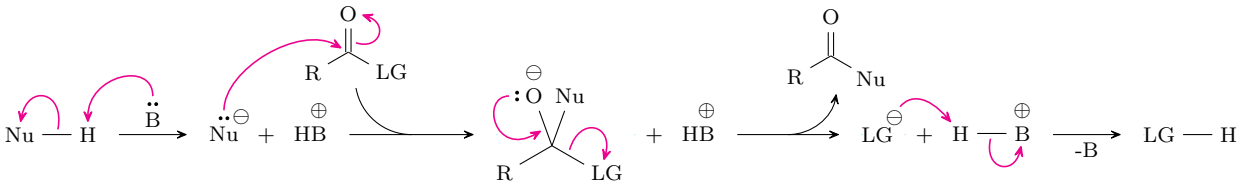


Figure 17.2: Carboxylation of lithiates mechanism.

- 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).

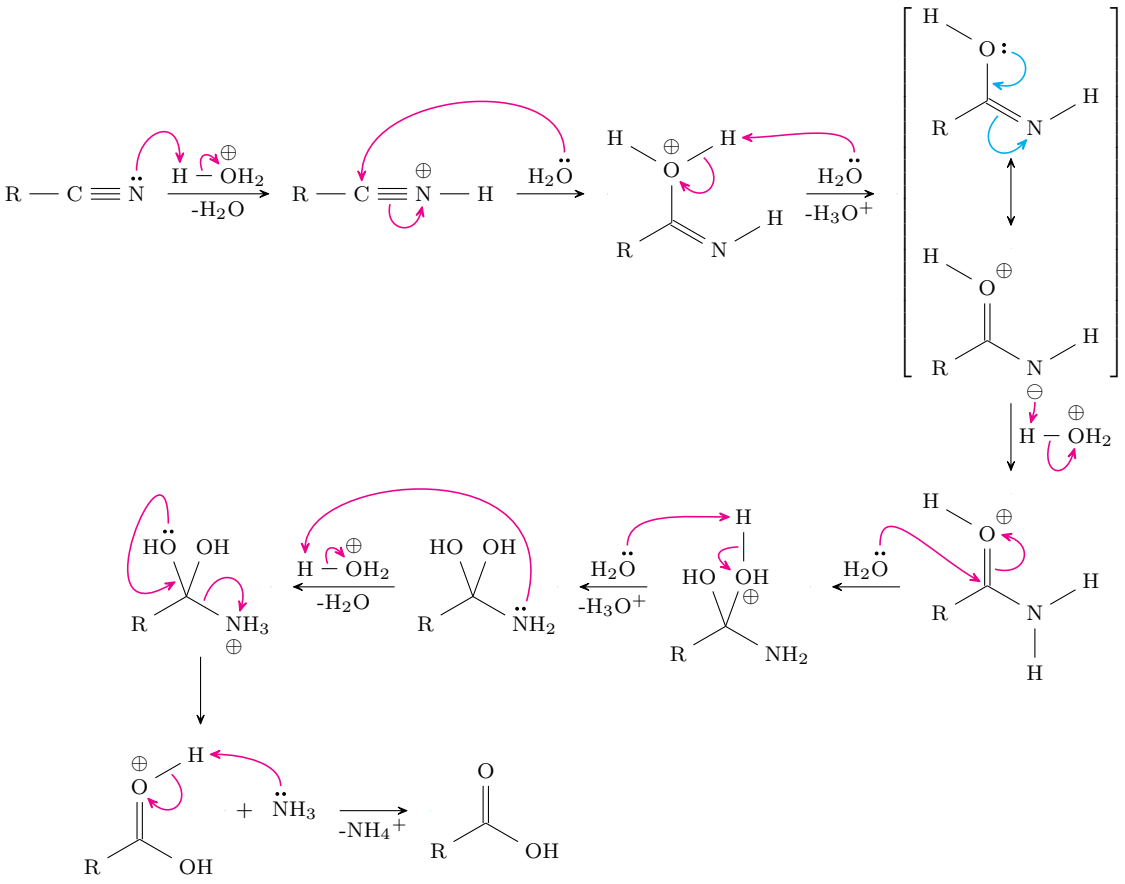


Figure 17.5: Nitrile hydrolysis mechanism.

- 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 $POCl_3$.

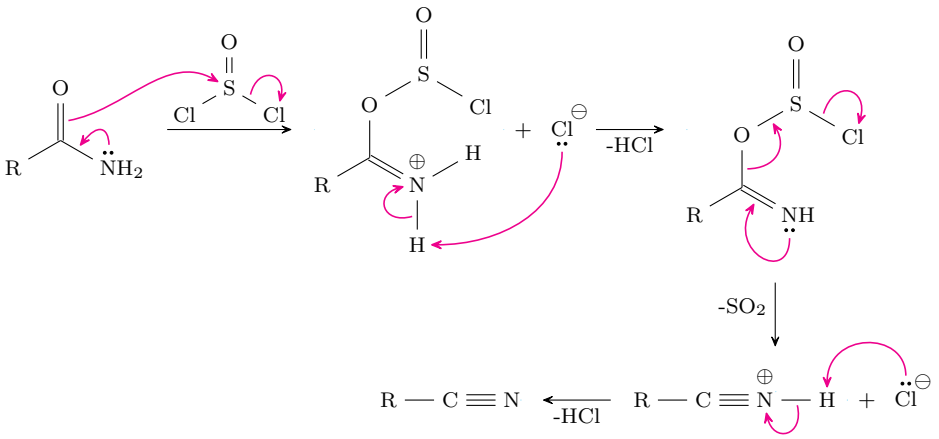


Figure 17.6: Dehydration of amides mechanism.

- Comparing methods 2 and 3 of synthesizing carboxylic acids.

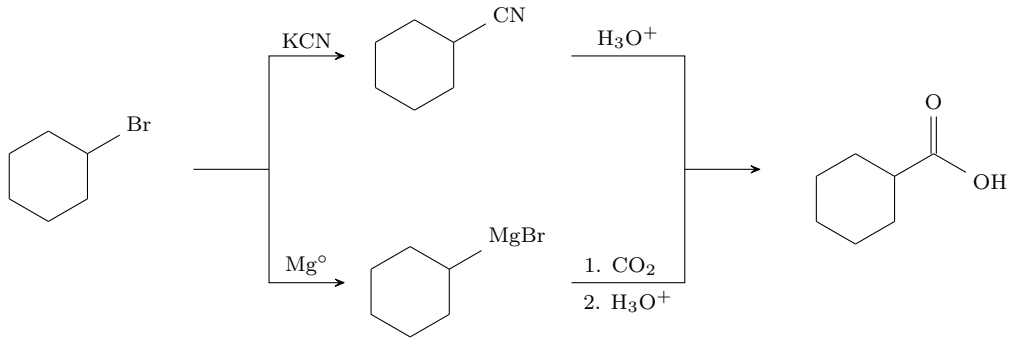


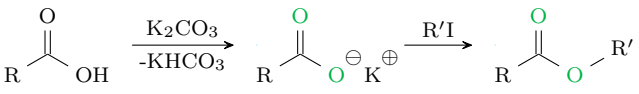
Figure 17.7: Two ways to synthesize a carboxylic acid from an alkyl halide.

  - 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.

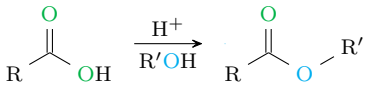
- General form.



  - 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.

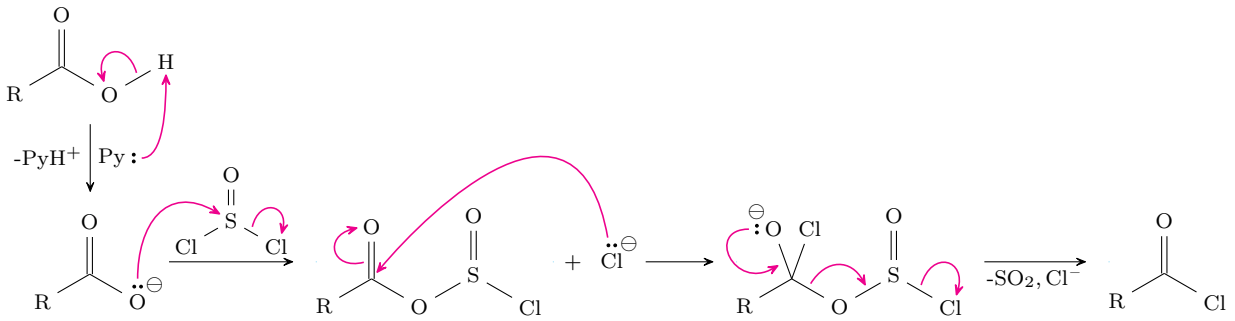


Figure 17.8: Acid chloride synthesis mechanism.

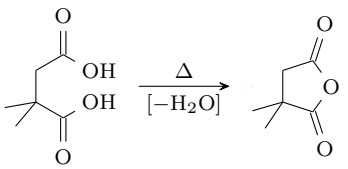
  - Since chloride is a fairly week nucleophile, it's addition in step 3 takes a while and is reversible.
    - However, this step is driven in the forward direction by releasing SO_2 gas from the resulting tetrahedral intermediate (Le Châtelier's principle).

- Anhydride synthesis.
- General form (standard).

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

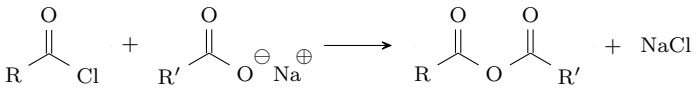
  - High heat is required.
  - If you use two different carboxylic acids, you will get a statistical mixture (no real selectivity).

- 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.

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

- Mechanism.

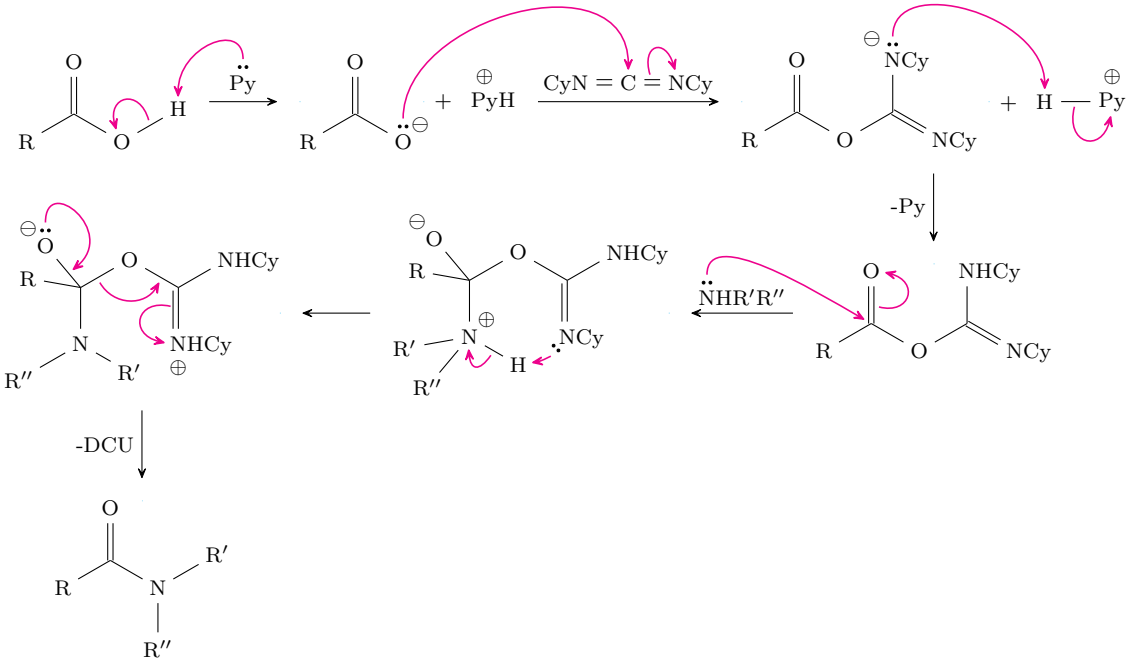


Figure 17.9: Amide synthesis mechanism.

  - 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*

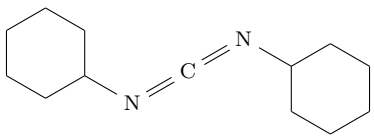
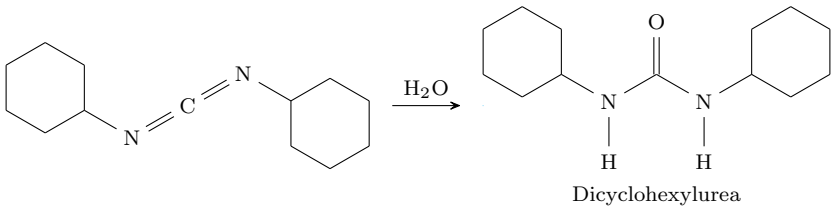


Figure 17.10: Dicyclohexylcarbodiimide (DCC).

- 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.

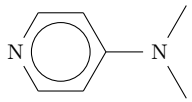


Figure 17.12: Dimethylaminopyridine (DMAP).

    - 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. The first two byproducts (HCl and RCOOH) protonate amines in solution, whereas ROH does not (as much).

References

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Labalme, S. (2022). *CHEM 22100 (Organic Chemistry II) notes*. Retrieved April 6, 2022, from https://github.com/shadypuck/CHEM22100Notes/blob/master/Notes/notes.pdf