Week 1

Carbonyl Synthesis and Heteroatom Nucleophiles

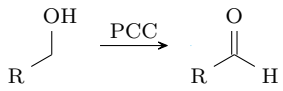
1.1 Electron Pushing

3/28:

- Levin (took the class just 13 years ago) and Weixin[1] are teaching.
- Problem sets are based on lecture content.
- Unit 1 (Chapter 16) is additions to carbonyls (there is a strong focus on carbonyls this quarter).
- 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.

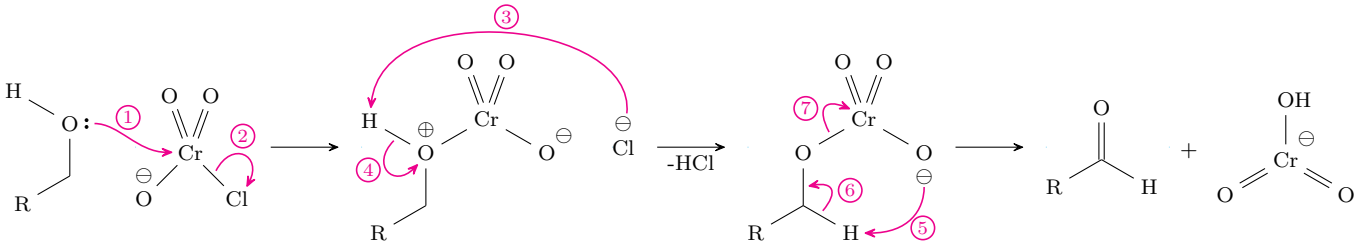
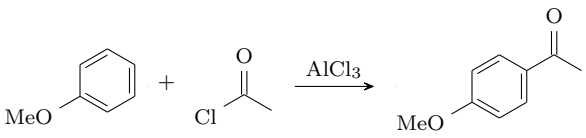


Figure 1.1: Oxidation of alcohols mechanism.

  - 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 O–H bond.
    6. C–H 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.

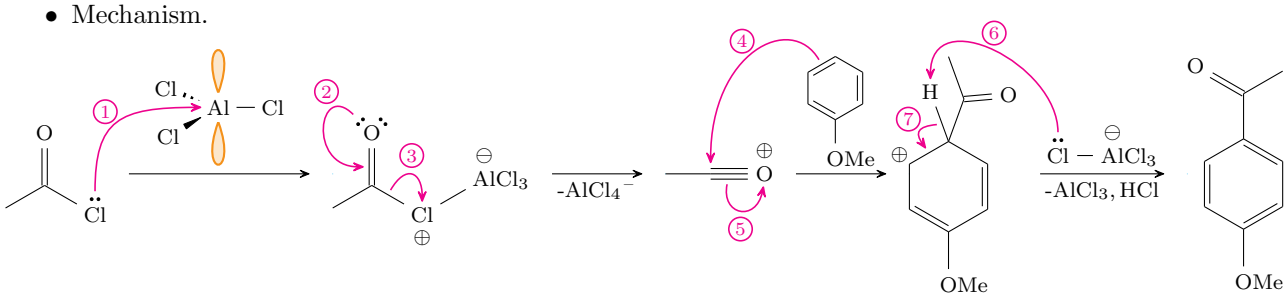
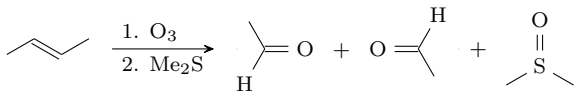


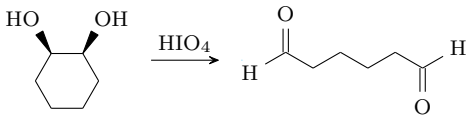
Figure 1.2: Friedel-Crafts acylation mechanism.

  - 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.

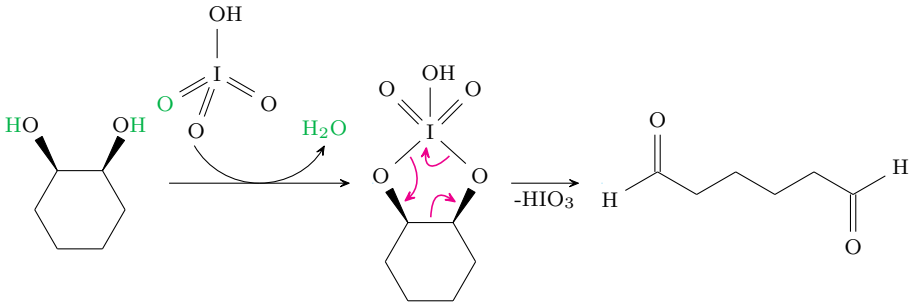
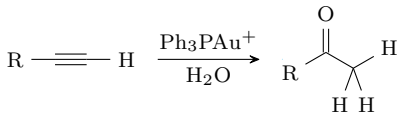


Figure 1.3: Diol cleavage mechanism.

- 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[2].

- Mechanism.

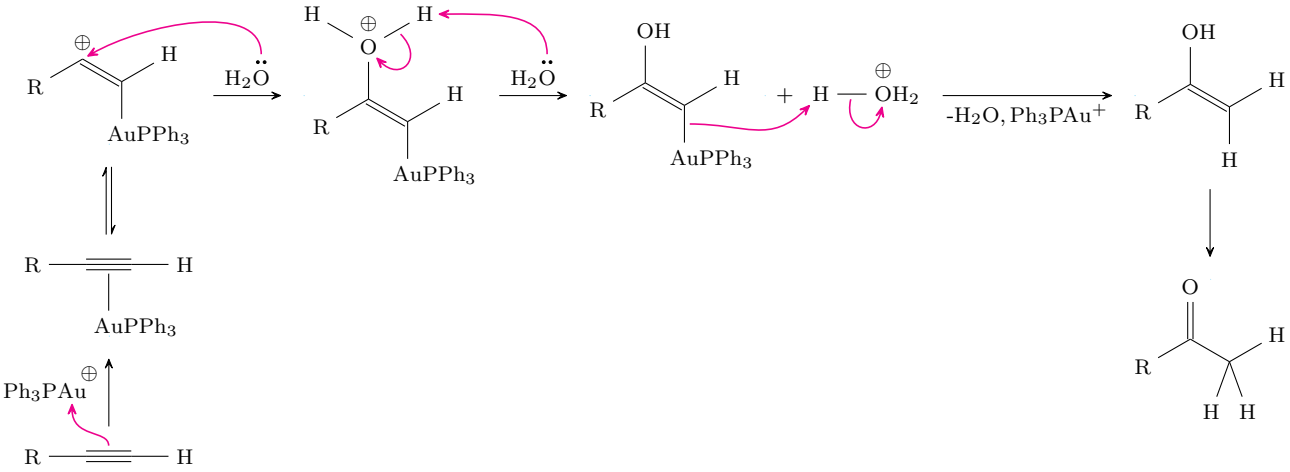
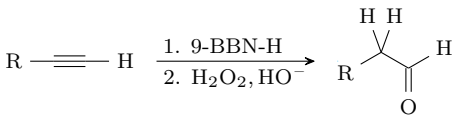


Figure 1.4: Alkyne hydrogenation mechanism.

  - We won't need to know the arrow-pushing mechanism for the final tautomerization until Unit 3.
  - Recall this enol-keto tautomerization from first quarter, specifically Figure 7.6 of Labalme (2021).
    - At the same time, we alluded to a catalytic mechanism using $HgSO_4$; this mechanism is presumably very similar to the above, since mercury is like gold as mentioned earlier.

- 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

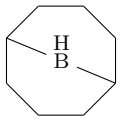


Figure 1.5: 9-Borabicyclo[3.3.1]nonane (9-BBN-H).

[2]Gold acts as a soft π-Lewis acid here! Just like in the Gold MOL project from Lin lab (Zheng et al., 2022).

- Mechanism.

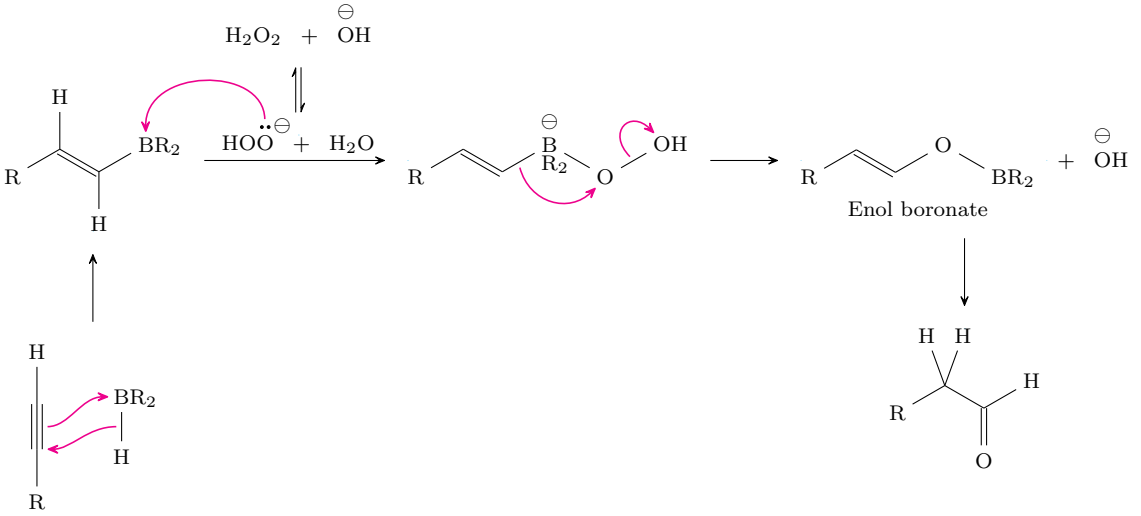


Figure 1.6: Alkyne hydroboration mechanism.

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

- The two(-ish) most important mechanisms in CHEM 222 are Figure 1.7 promoted either by acid or base.

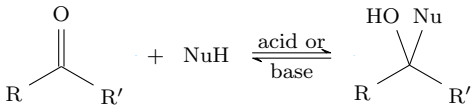
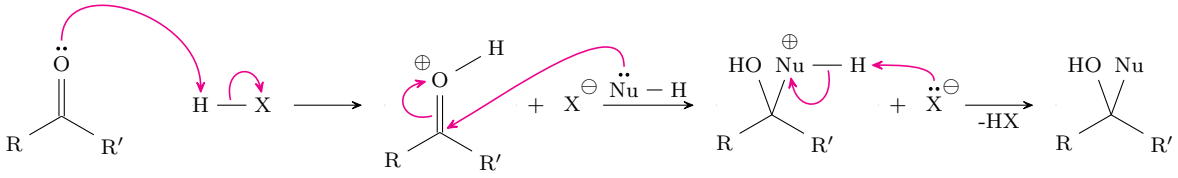
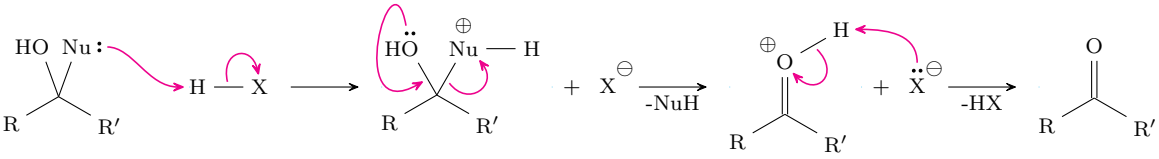


Figure 1.7: The key mechanism in CHEM 22200.

- Acidic mechanism.



(a) Forward direction.



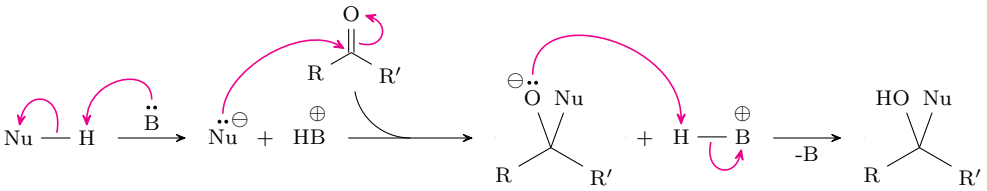
(b) Reverse direction.

Figure 1.8: Nucleophilic addition/elimination with carbonyls (acid-promoted).

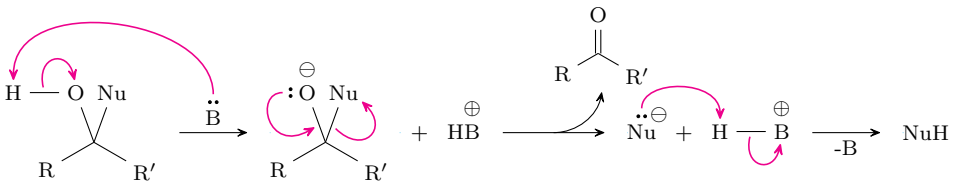
  - The forward and reverse mechanisms are the same.

- **Principle of microscopic reversibility**: The lowest energy path in the forward direction must be the lowest energy path in the reverse direction.

- Basic mechanism.



(a) Forward direction.



(b) Reverse direction.

Figure 1.9: Nucleophilic addition/elimination with carbonyls (base-promoted).

  - B: means base, not boron.

1.2 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 1.8 and 1.9).
  - Today: Specific nucleophiles and mechanisms.
- **Carbonyl hydrate**: The class of molecules resulting from the nucleophilic addition of H_2O to a carbonyl group. *Structure*

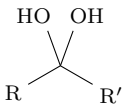
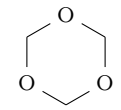


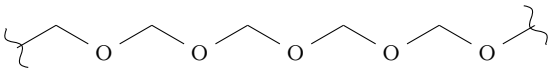
Figure 1.10: Carbonyl hydrate ($R' = H, C$).

- 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.



(a) Trioxane.



(b) Paraformaldehyde.

Figure 1.11: Anhydrous nongaseous formaldehyde forms.

  - Outside of the gas phase (and aqueous solution), formaldehyde is very unstable; it will either exist as **trioxane** or **paraformaldehyde** (see Figure 1.11).

- Hydrate formation.
  - Occurs under both acidic and basic conditions.

- Mechanism.
  - Identical to Figures 1.8a and 1.9a with Nu−H = HO−H and H−X = H−OH_2^+ or B = OH^-.
  - Note that it is not necessary to show the first step of Figure 1.9a (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; even a couple of excess positive molecules would generate a huge static field.

- **Ketal**: The product of the nucleophilic addition of an alcohol (ROH) to a ketone. *Structure*

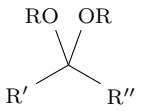


Figure 1.12: Ketal.

- **Acetal**: The product of the nucleophilic addition of an alcohol (ROH) to an aldehyde. *Structure*

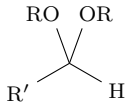
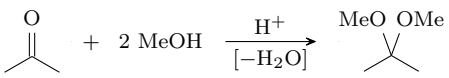


Figure 1.13: Acetal.

- 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.
  - Ketals and acetals can only form under acidic conditions.

- Mechanism.

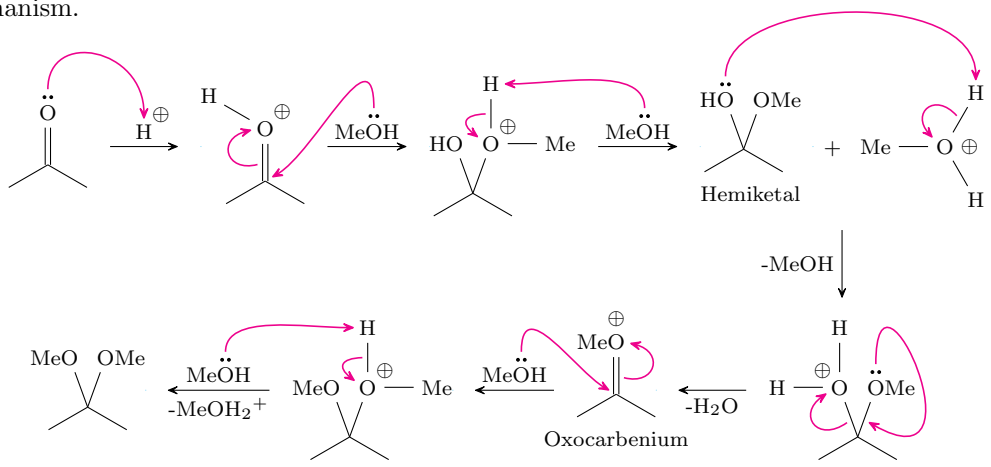


Figure 1.14: Ketal formation mechanism.

  - 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.

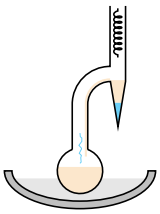
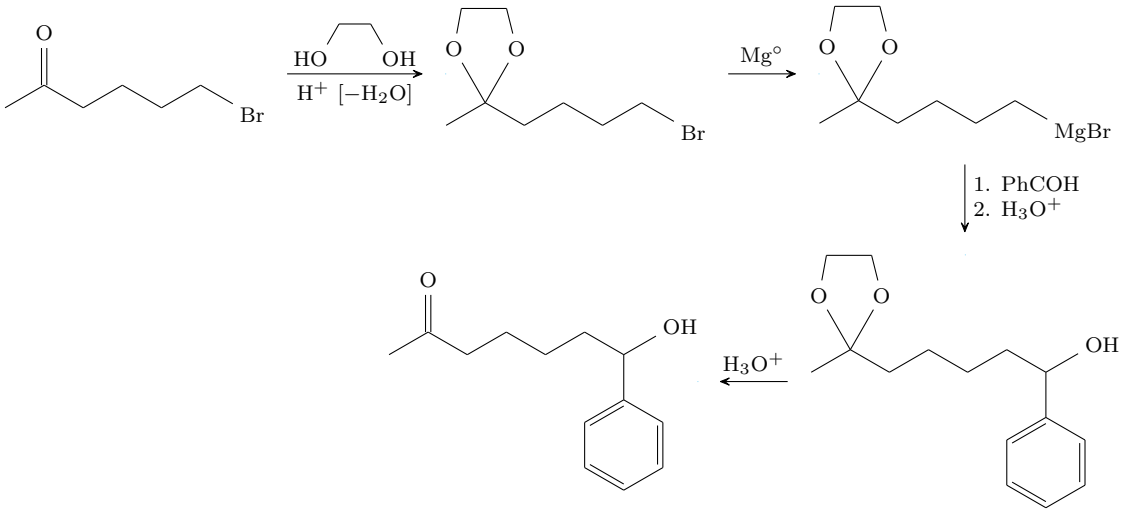


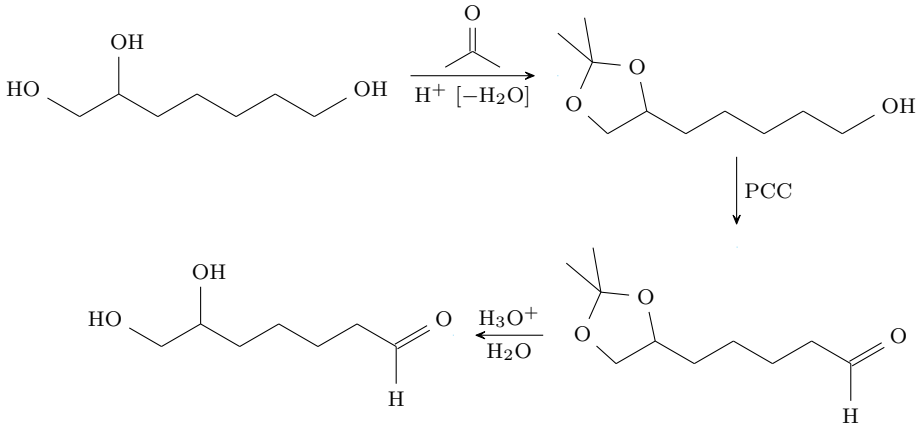
Figure 1.15: Dean-Stark apparatus.

  - The bowl at the bottom of Figure 1.15 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 1.16: Using ketals as protecting groups.

- Using a ketal to protect a carbonyl (Figure 1.16a).
  - If we convert 1-bromo-5-hexanone (the starting material in Figure 1.16a) 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 (think chelate effect).
  - 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 1.16a. 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 1.16a.
- Using a ketal to protect a 1,2-diol (Figure 1.16b).
  - 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 this class to selectively convert the other alcohols to carbonyl groups.
- Hemiacetals and hemiketals are rarely isolable.
  - Exception: Hemiacetals in ring systems.
  - For example, glucose contains a hemiacetal (we will discuss its chemistry more later).
  - Hemiketals are almost never observed.
- **Imine**: The class of molecules containing a C=N double bond. *Structure*

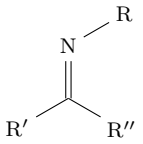
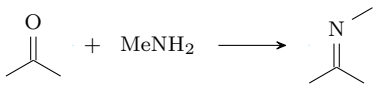


Figure 1.17: Imine.

  - 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.
  - $Me_2COH^+ + MeOH \rightleftharpoons Me_2CO + MeOH_2^+$: $K \approx 100$.
    - This equilibrium is related to ketal formation (Figure 1.14).
    - 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.
  - $Me_2COH^+ + MeNH_2 \rightleftharpoons Me_2CO + MeNH_3^+$: $K \approx 10^{16}$.
    - Thus, acid catalysis is far slower for amines than for alcohols.
- Mechanism (acidic conditions).
  - The mechanism is entirely analogous to Figure 1.14 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*

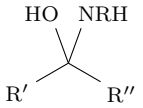


Figure 1.18: Hemiaminal.

- Regeneration of the acid catalyst in both Figure 1.14 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 product of the nucleophilic addition of hydroxylamine to a carbonyl group. *Structure*

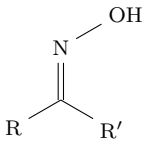
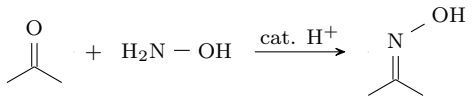


Figure 1.19: Oxime.

- General form.



- **Hydrazine**: The compound $H_2N–NH_2$.
  - Also commonly written N_2H_4.
  - Hydrazine is used as rocket fuel: It is highly explosive as a reduced (and thus less stable) form of dinitrogen (a very stable molecule) that can, in addition, release hydrogen gas.
- **Hydrazone**: The product of the nucleophilic addition of hydrazine to a carbonyl group. *Structure*

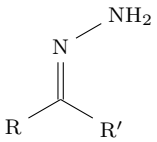
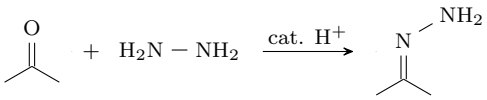
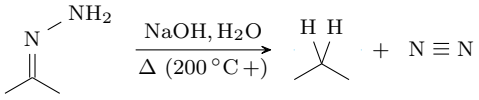


Figure 1.20: Hydrazone.

- 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**.
    - Additionally, the increased s character in the product (N is sp^2 in an oxime, sp^3 in hydroxylamine) means that the lone pair on nitrogen is held tighter in the product and hence experiences a diminished α-effect there.
  - 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-Kishner 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 move forward in chemistry.
- General form.



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

- Mechanism.

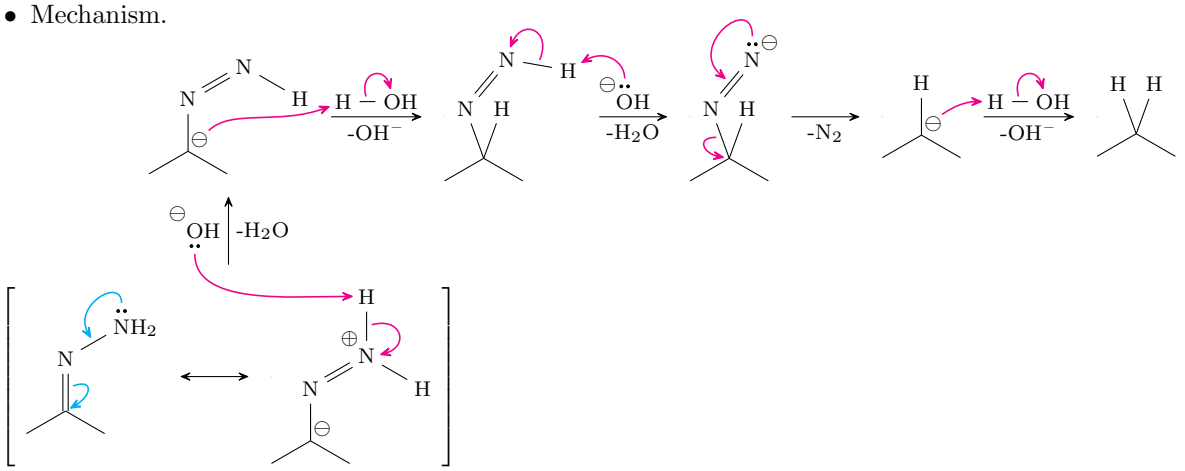


Figure 1.21: Wolff-Kishner reduction mechanism.

  - Important consequence: This allows us to remove a carbonyl in two steps (carbonyl → hydrazone → Wolff-Kishner).

- **Enamine**: The product of the nucleophilic addition of a dialkyl amine (R_2NH) to a carbonyl group. *Structure*

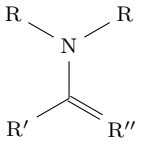
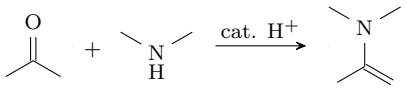


Figure 1.22: Enamine.

- General form.



- **Iminium**: An ion containing a $C{=}N^+$ double bond. *Structure*

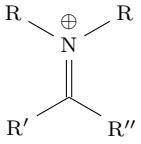


Figure 1.23: Iminium.

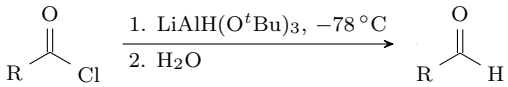
- Mechanism.
  - As with the formation of imines, we get to an iminium intermediate.
  - After that, however, we deprotonate at the α-carbon and rearrange into our final enamine.
- Summary of today: Acetone can combine with...
  1. Water to form a hydrate;
  2. Alcohols to form a ketal;
  3. Primary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

1.3 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 (more on this later in the course) and lithium tri-*tert*-butoxy-aluminum 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).