CHEM 22200 (Organic Chemistry III) Notes

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May 31, 2022

Weeks

List of Figures

Week 1

Carbonyl Synthesis and Heteroatom Nucleophiles

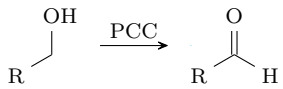
1.1 Electron Pushing

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.

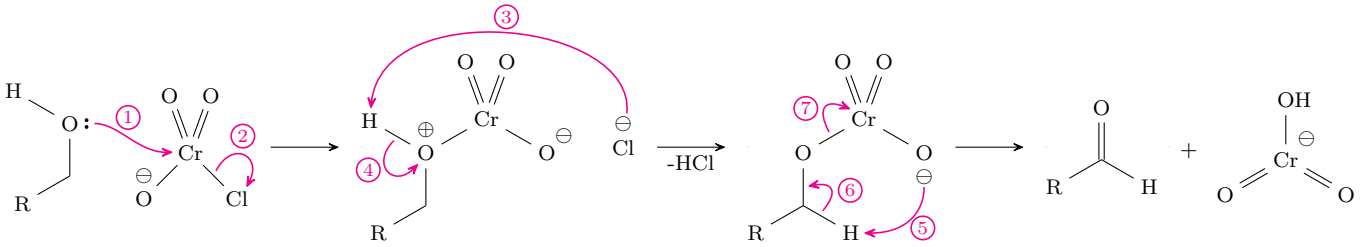
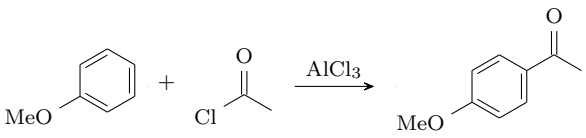


Figure 1.1: Oxidation of alcohols mechanism.

  - 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 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.

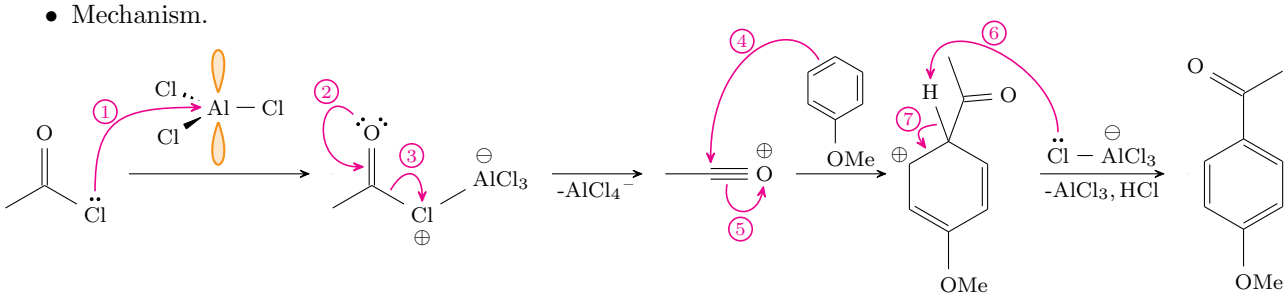
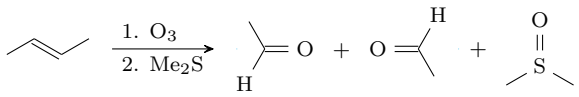


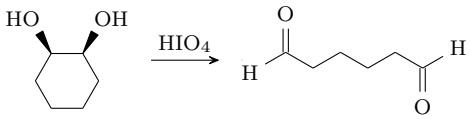
Figure 1.2: Friedel-Crafts acylation mechanism.

  - 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.

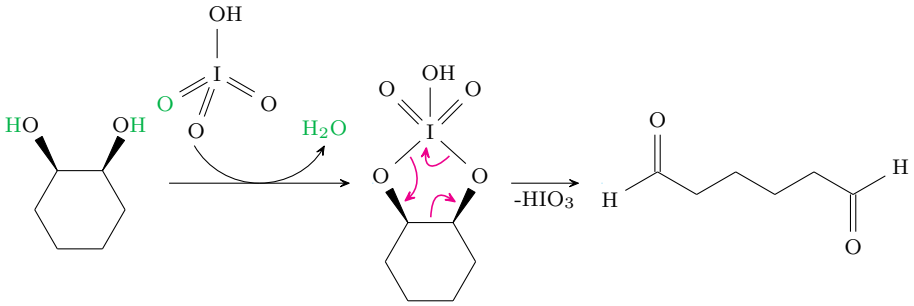
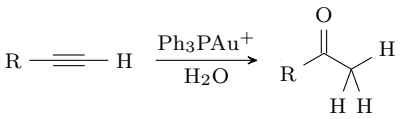


Figure 1.3: Diol cleavage mechanism.

- 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.

- Mechanism.

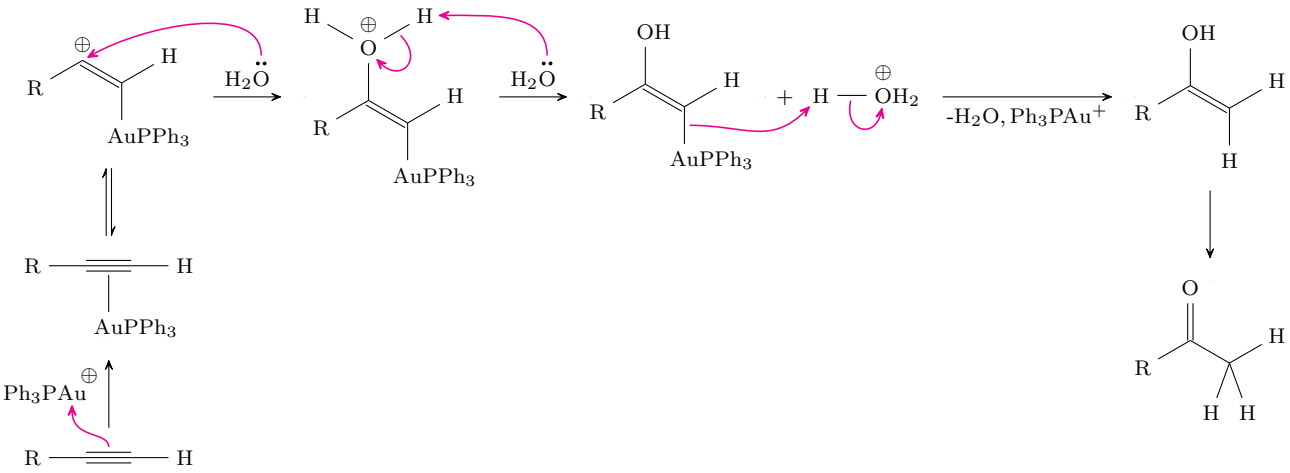
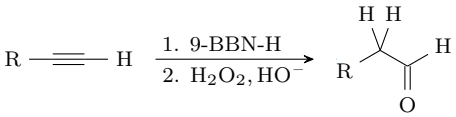


Figure 1.4: Alkyne hydrogenation mechanism.

  - 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

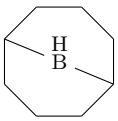


Figure 1.5: 9-Borabicyclo[3.3.1]nonane (9-BBN-H).

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

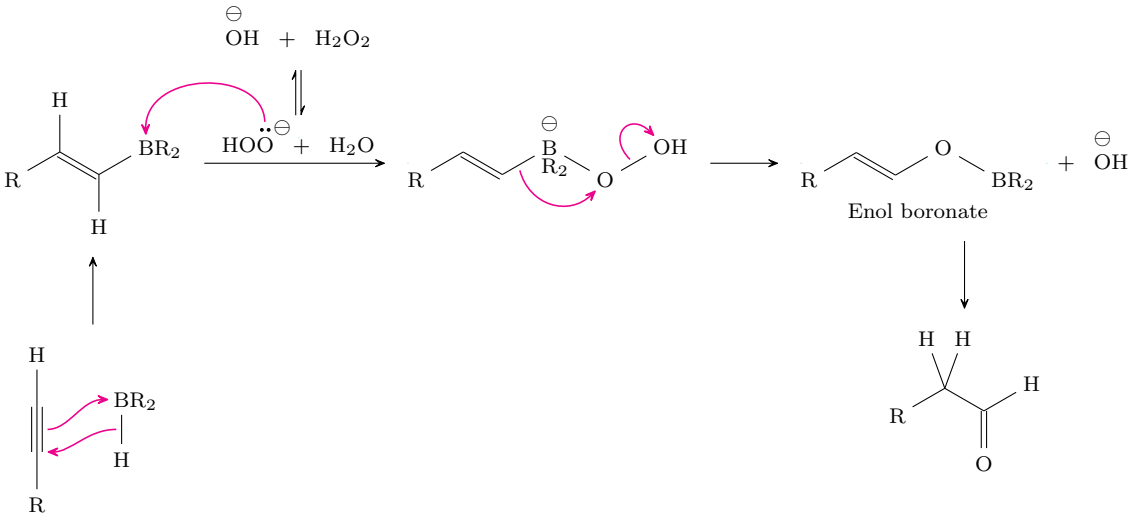


Figure 1.6: Alkyne hydroboration mechanism.

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

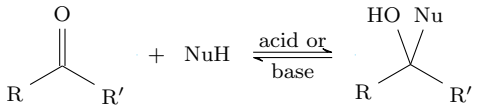
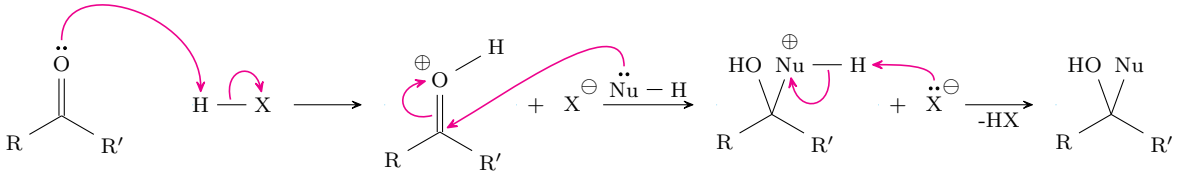
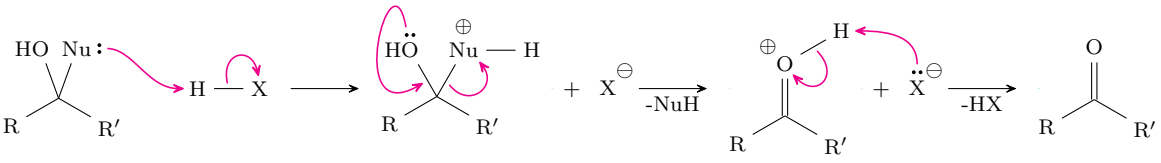


Figure 1.7: The key mechanism in CHEM 22200.

- Acidic mechanism.



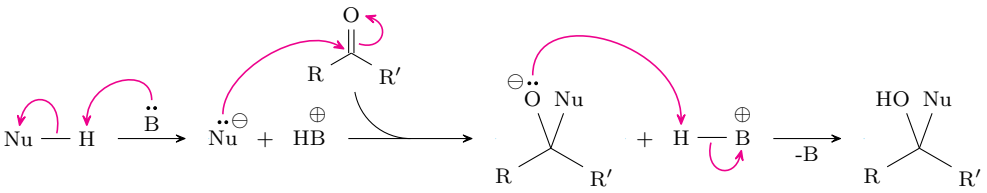
(a) Forward direction.



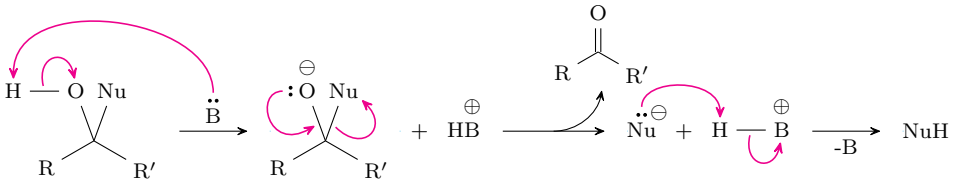
(b) Reverse direction.

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.
  - B: means base, not boron.



(a) Forward direction.



(b) Reverse direction.

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

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*

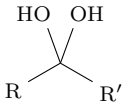
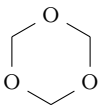
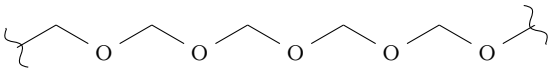


Figure 1.10: Carbonyl hydrate ($R' = H, C$).

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



(a) Trioxane.



(b) Paraformaldehyde.

Figure 1.11: Anhydrous nongaseous formaldehyde forms.

- Hydrate formation.
  - Occurs under both acidic and basic conditions.
- Mechanism.
  - The mechanisms are identical to Figures 1.8a and 1.9a 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 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; 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*

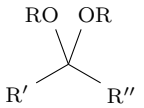


Figure 1.12: Ketal.

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

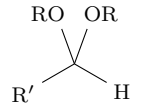
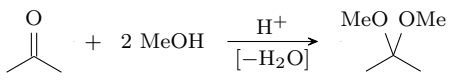


Figure 1.13: Acetal.

- 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.
  - The formation of ketals and acetals incorporates two molecules of ROH.
  - Ketals and acetals can only form under acidic conditions.

- Mechanism.

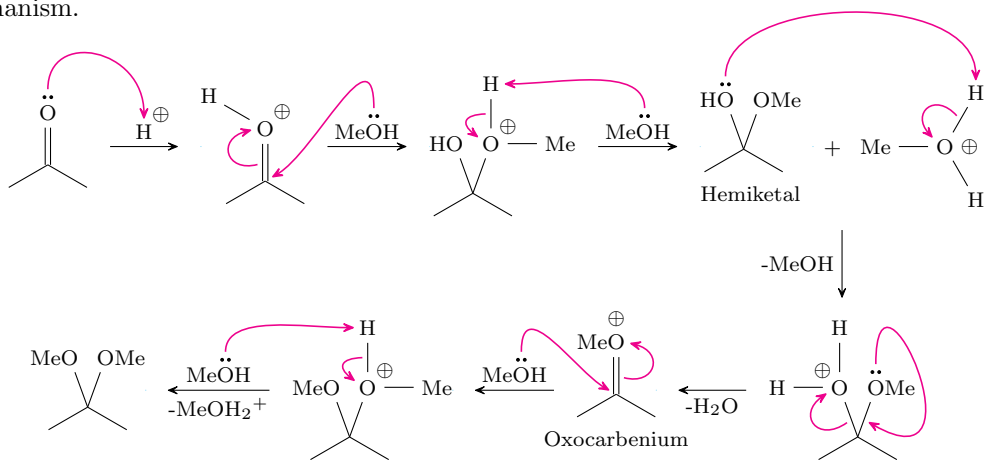


Figure 1.14: Ketal formation mechanism.

  - 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.

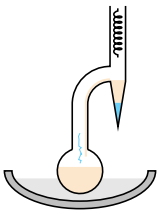
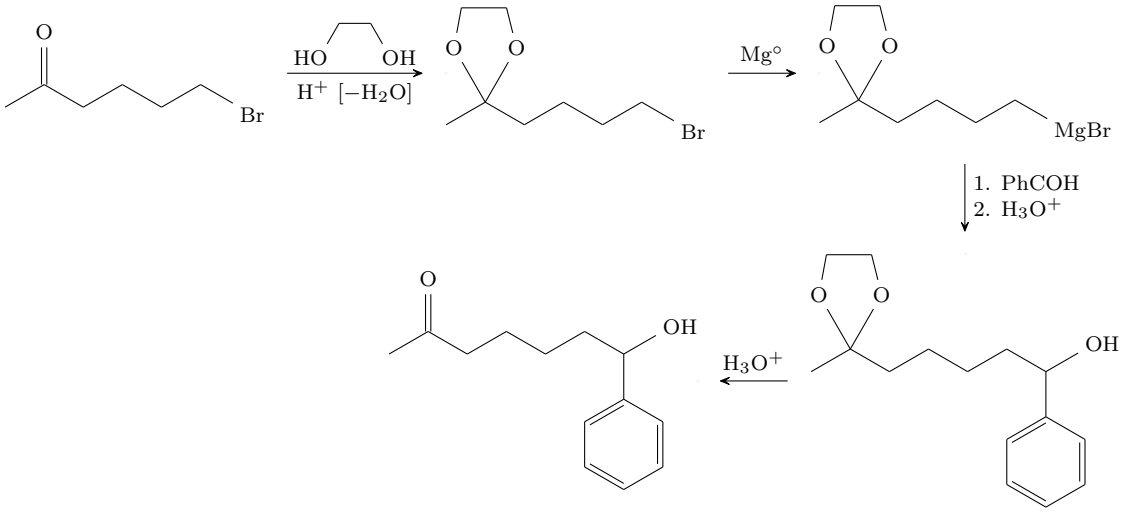


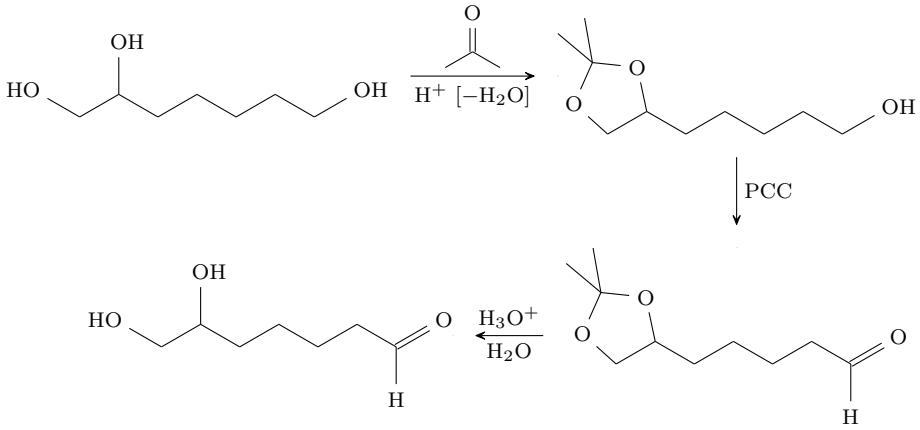
Figure 1.15: Dean-Stark apparatus.

  - 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.
  - 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 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*

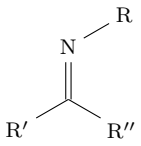
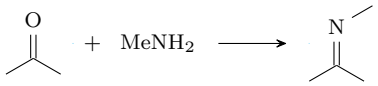


Figure 1.17: Imine.

  - 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.
  - $CMe_2(OH)^+ + MeOH \rightleftharpoons COMe_2 + MeOH_2$: $K \approx 100$.
    - 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.
  - $CMe_2(OH)^+ + MeNH_2 \rightleftharpoons COMe_2 + MeNH_3^+$: $K \approx 10^{16}$.
    - Thus, acid catalysis is far slower for amines than for alcohols.

- Mechanism (acidic conditions).
  - The mechanism is entirely analogous to Figure 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*

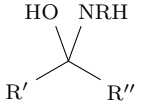


Figure 1.18: Hemiaminal.

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

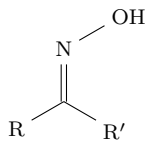
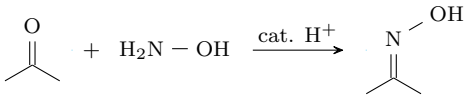


Figure 1.19: Oxime.

- 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*

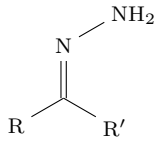
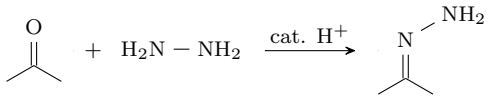
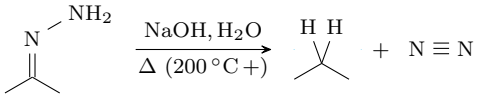


Figure 1.20: Hydrazone.

- 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**.
    - 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-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 more forward in chemistry.
- General form.



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

- Mechanism.

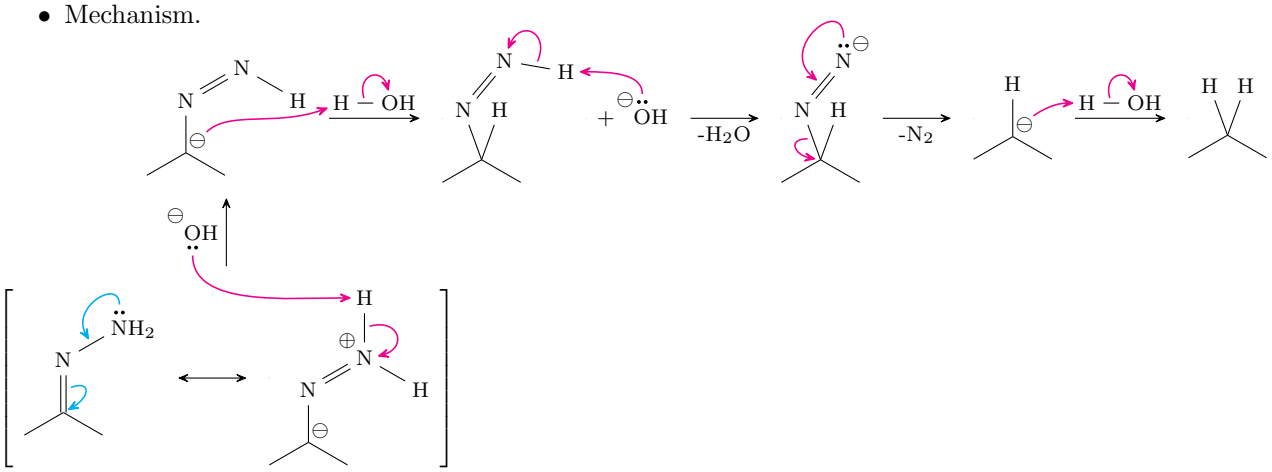


Figure 1.21: Wolff-Kishner reduction mechanism.

  - 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*

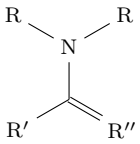
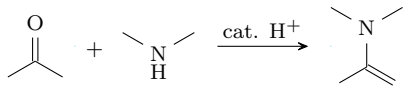


Figure 1.22: Enamine.

- General form.



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

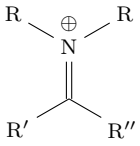


Figure 1.23: Iminium.

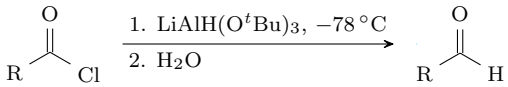
- Mechanism.
  - As with the formation of imines, we get to an iminium intermediate.
  - After that, however, we deprotonate at the α-carbon and rearrange into our final enamine.
- Summary of today: Acetone can combine with...
  1. Water to form a hydrate;
  2. Alcohols to form a ketal;
  3. Primary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

Week 2

More Nucleophiles and Carboxylic Acid Derivative Synthesis

2.1 Aldehydes and Ketones 2

4/5:

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

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

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

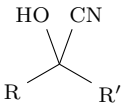
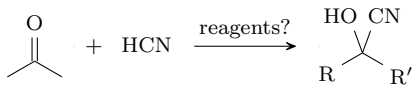


Figure 2.1: Cyanohydrin.

- General form.



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

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

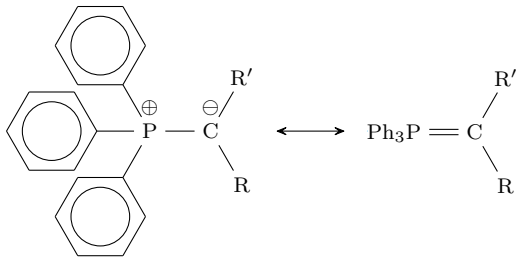


Figure 2.2: Phosphorous ylide.

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

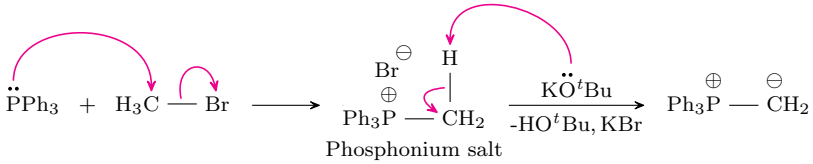
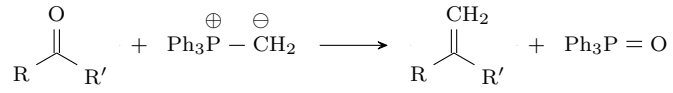


Figure 2.3: Synthesizing phosphorous ylides.

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



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

[1] "VIT-tig"

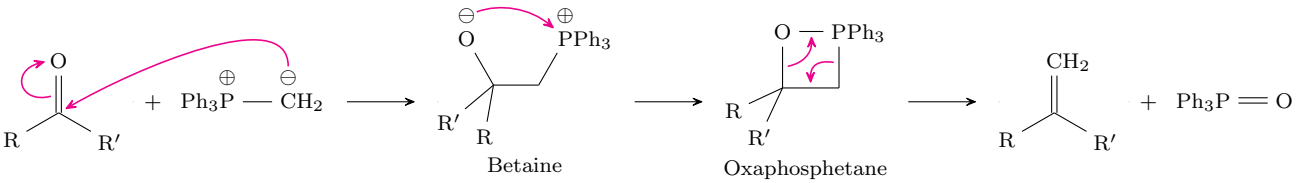
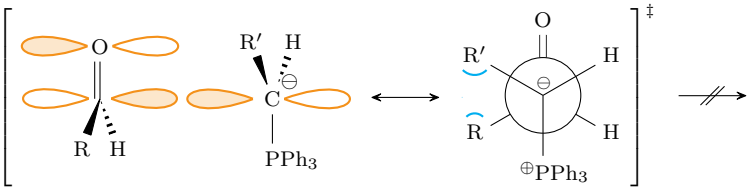


Figure 2.4: Wittig olefination mechanism (stepwise).

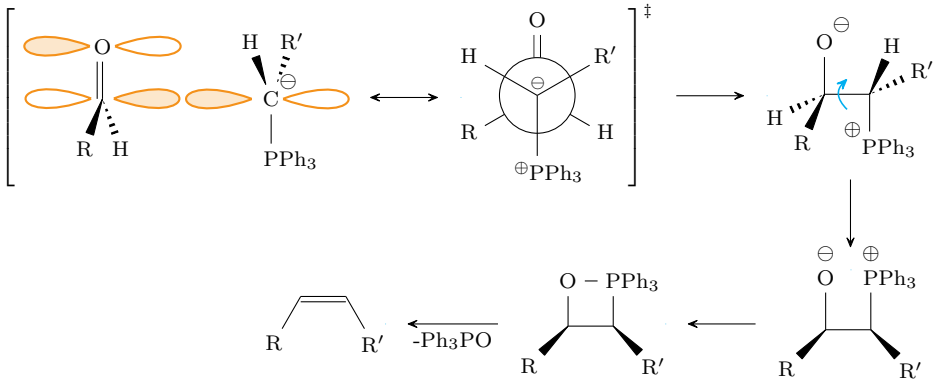
  - The Newtonian mechanics of OChem; we can get the right answer by using the wrong model.
  - The modern understanding is that the betaine never forms.
- This is a **retro-pericyclic mechanism**.
- The last step is a **retro-[2 + 2]**.
  - Note that the arrows may be drawn either of the two ways between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

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

- Three-dimensional intuition for the stereoselectivity.



(a) Unsuccessful collision.

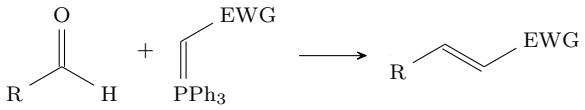


(b) Successful collision.

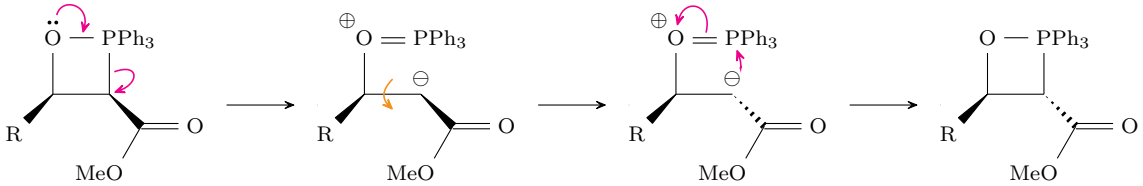
Figure 2.5: Wittig olefination stereoselectivity.

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

- Stabilized ylides.



(a) General form.



(b) Intermediate rearrangement.

Figure 2.6: Stabilized ylides.

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

- Mechanism (correct).

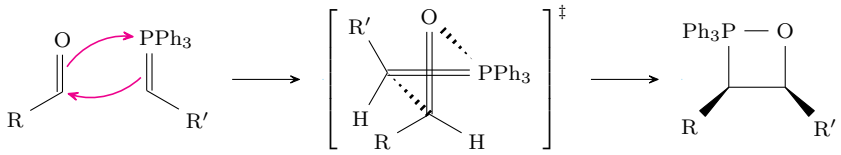


Figure 2.7: Wittig olefination mechanism (modern).

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

- Ketone Wittigs.
  - Slower but still proceed.
  - The biggest groups always end up cis.

- **α, β unsaturated carbonyl**: A carbonyl conjugated with an alkene spanning the α to β positions.
- The two possible nucleophilic additions to α, β unsaturated carbonyls are **1,2-additions** and **1,4-additions**.
- **1,2-addition**: A nucleophilic addition to the 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 (2022b). 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 (2022b). However, Levin shows a single nucleophilic attack that can't proceed to a second until reductant is added into solution, but this inactivates the $LiAlH_4$.
- The pure 1,2-addition product is the major product for both $NaBH_4$ and $LiAlH_4$, but you get a mix of products?
- Organolithiums are highly selective for the 1,2-addition product, however.
  - Lithium is small and hard and favors bonding with the oxygen.
- Grignards still give a mixture.
  - Magnesium is happy to coordinate both the oxygen and the alkene (it's of intermediate hardness/softness).
- Hard-hard interactions are preferred because of Coulombic attraction; soft-soft interactions are preferred because of van der Waals forces.
- **Cuprate**: A compound containing an anionic copper complex.
  - The cuprates relevant to us are dialkyl cuprates, which have the form $LiCuMe_2$.
  - These are formed via the reaction

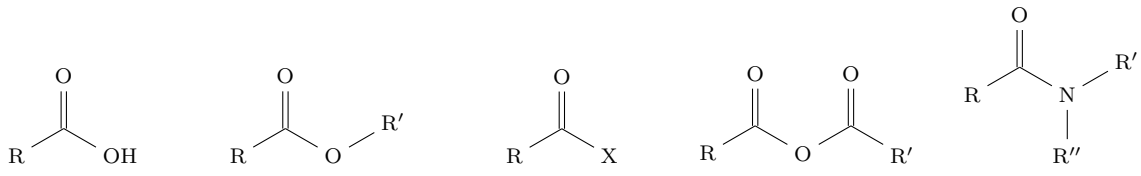
$$2\,\mathrm{MeLi} \xrightarrow[-\mathrm{LiI}]{\mathrm{CuI}} \mathrm{LiCuMe_2}$$

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

2.2 Carboxylic Acids and Derivatives 1

4/7:

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



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

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

Figure 2.8: Carboxylic acid derivatives.

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

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

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

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

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

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

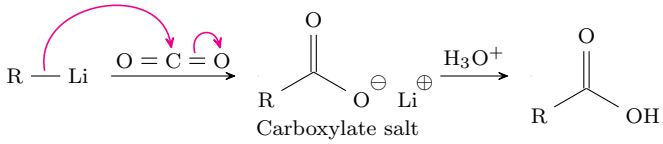
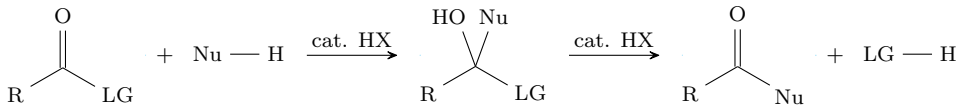
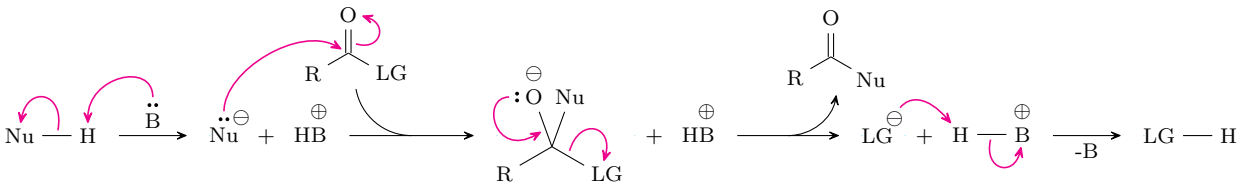


Figure 2.9: Carboxylation of lithiates mechanism.

- Mechanistic interlude: Nucleophilic acyl substitution.



(a) Acid-catalyzed reactivity.

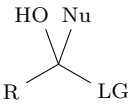


(b) Base-catalyzed reactivity.

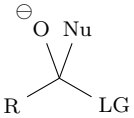
Figure 2.10: The typical reactivity of carboxylic acid derivatives.

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

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



(a) Acidic intermediate.



(b) Basic intermediate.

Figure 2.11: The tetrahedral intermediates.

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

- Nitrile hydrolysis.
- General form.

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

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

- Mechanism.

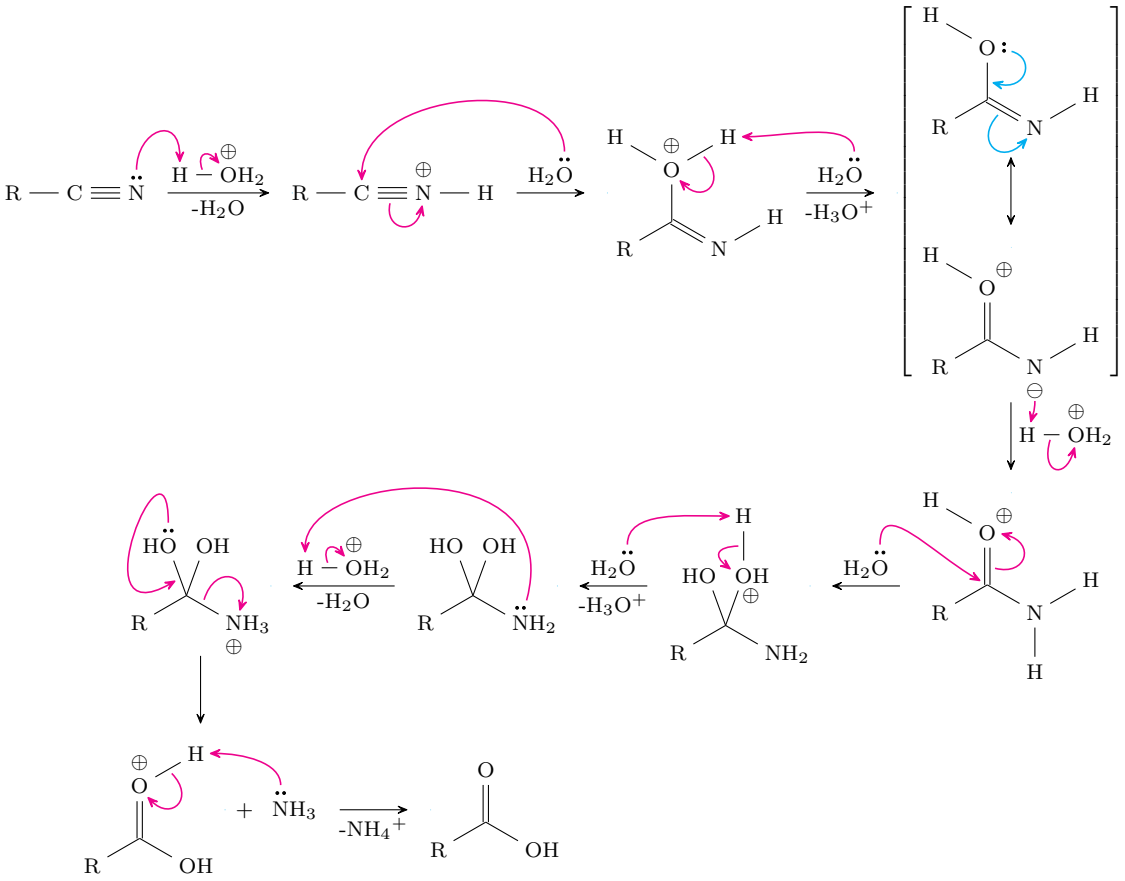


Figure 2.12: Nitrile hydrolysis mechanism.

  - Note that the fourth intermediate is one deprotonation away from being an amide.
    - However, the reaction conditions 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).

- Dehydration of amides.
- General form.

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

  - This is the reverse reaction to nitrile hydrolysis.
  - Reagents is either $\mathrm{SOCl_2}$ or $\mathrm{POCl_3}$.
  - $\mathrm{SOCl_2}$ and $\mathrm{POCl_3}$ 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 2.13.
- Mechanism.

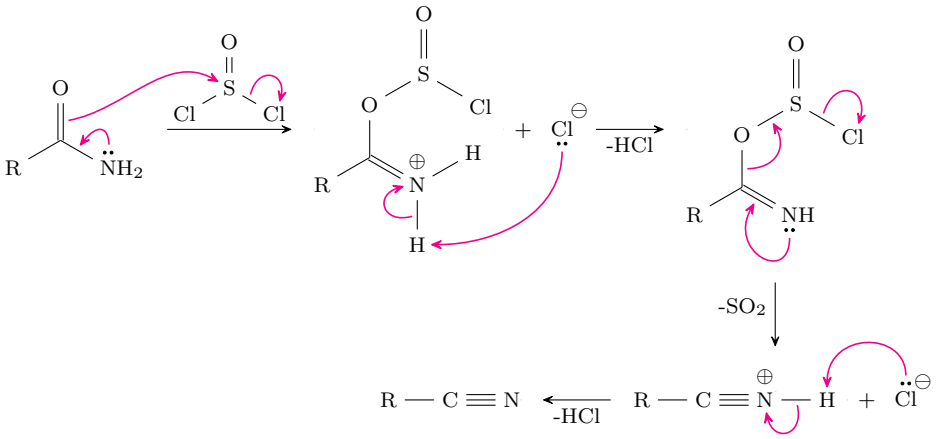


Figure 2.13: Dehydration of amides mechanism.

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

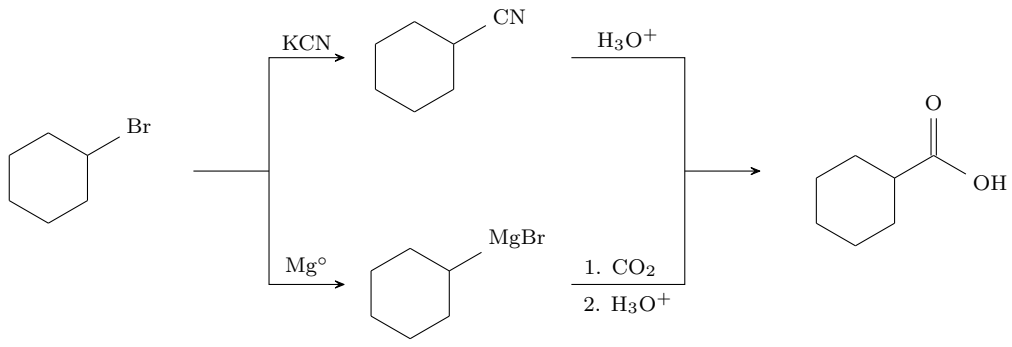
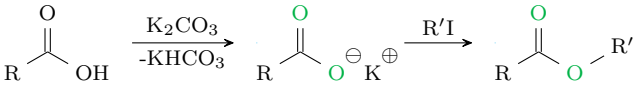


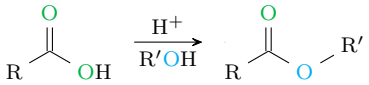
Figure 2.14: Two ways to synthesize a carboxylic acid from an alkyl halide.

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

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



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



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

- General form.

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

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

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

- Acid chloride synthesis.

- General form.

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

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

- Mechanism.

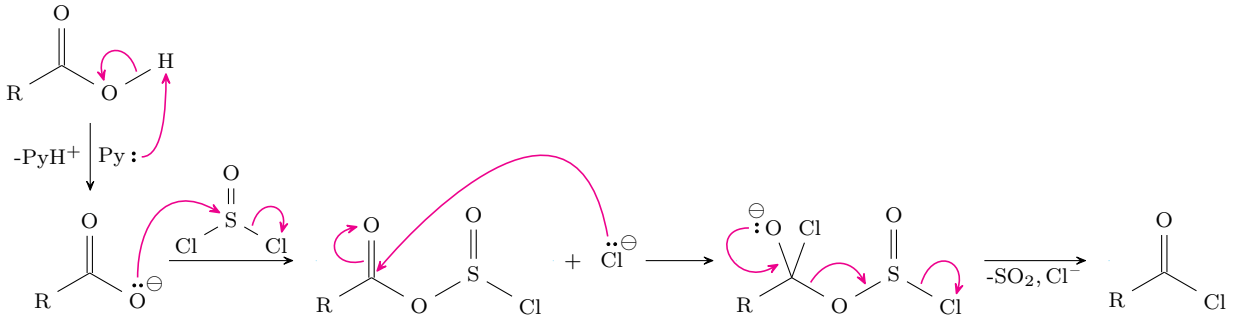


Figure 2.15: Acid chloride synthesis mechanism.

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

- Anhydride synthesis.

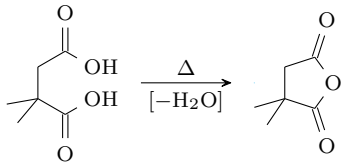
- General form (standard).

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

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

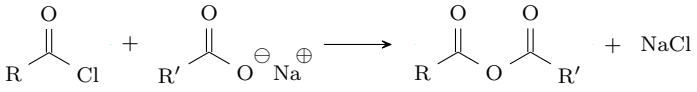
- You can selectively create 5-6 membered rings containing anhydrides because this reaction proceeds intramolecularly as well as intramolecularly.

- General form (intramolecular).



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

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



  - This reaction proceeds via nucleophilic substitution.

- Amide synthesis.
- General form.

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

- Mechanism.

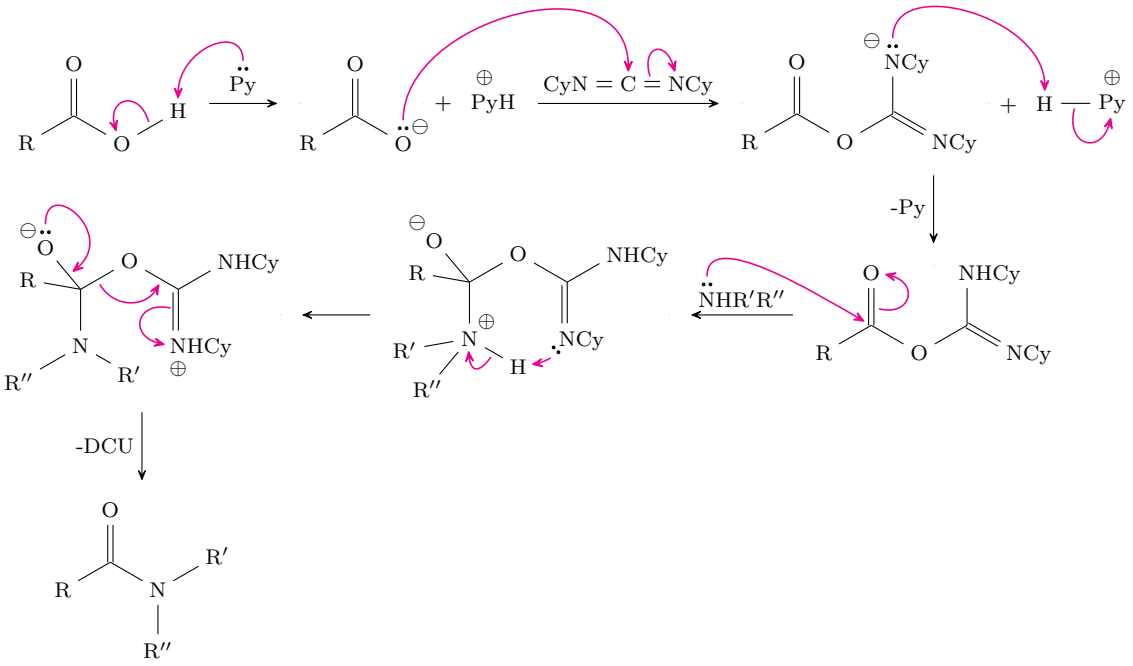


Figure 2.16: Amide synthesis mechanism.

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

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

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

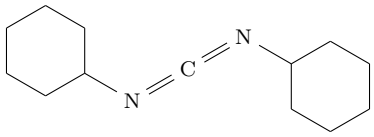


Figure 2.17: Dicyclohexylcarbodiimide (DCC).

- DCC reacts with water as follows.

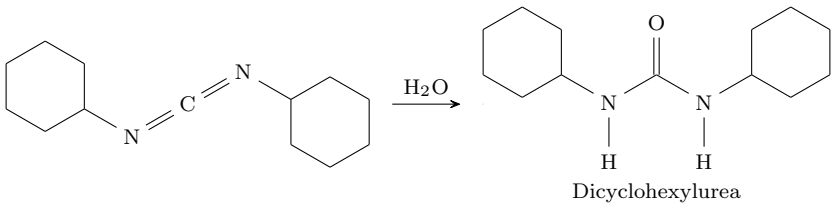


Figure 2.18: DCC and water.

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

  acid chloride > anhydride > ester > amide > carboxylate

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

- MCAT comments.
- Trialkyl amines and pyridines.

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

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

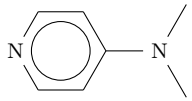


Figure 2.19: Dimethylaminopyridine (DMAP).

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

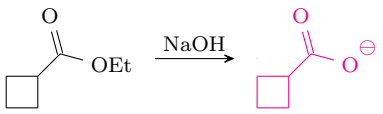
- Acid chlorides, anhydrides, and esters all create the same product (an amide) when reacting with an amine.
  - But, you need only one equivalent of the amine for esters while you need two equivalents for the first two.
  - This is because of the pK_a's.
    - In order of increasing pK_a, we have HCl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

2.3 Discussion Section

4/8:

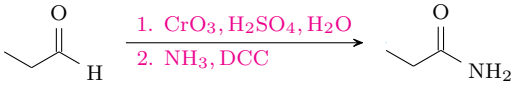
- We will be working with hot sand baths in the next lab, so just leave them to cool and do not dispose of the contents unless you're sure they're cool.
- Practice problems.

1.

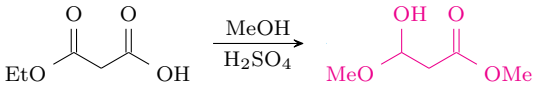


  - We form a COO^- ion instead of the carboxylic acid because we are in basic solution.
  - The mechanism is a nucleophilic attack on the carbonyl, the oxygen electrons swinging back down and kicking out EtO^-, and then deprotonation of the acid.

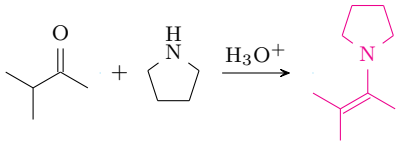
2.



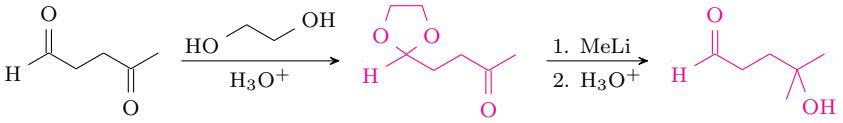
- The intermediate after step 1 is the carboxylic acid, as we have used aqueous Jones reagent.

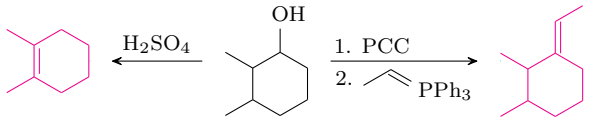
3. 

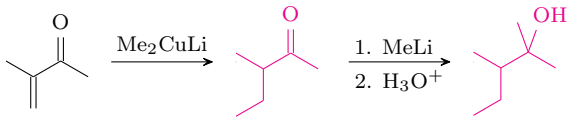
   - The reaction of the ester (left) is called **transesterification**; the reaction of the carboxylic acid (right) is called ether formation.
   - It's important to know that you can get ester formation in both of these cases.
   - This is a common problematic side reaction in synthetic chemistry.
  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

4. 

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

5. 

6. 

7. 

2.4 Chapter 17: Carboxylic Acids and Their Derivatives

From Solomons et al. (2016).

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

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

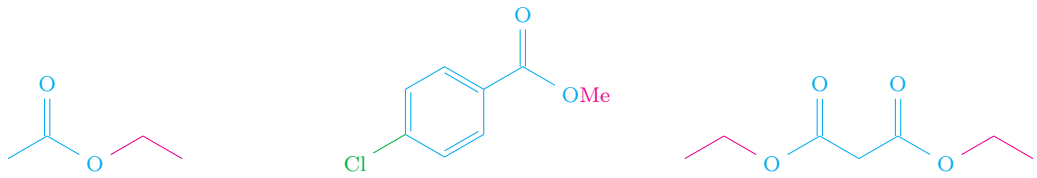


Figure 2.20: Ester nomenclature.

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

- Naming anhydrides.

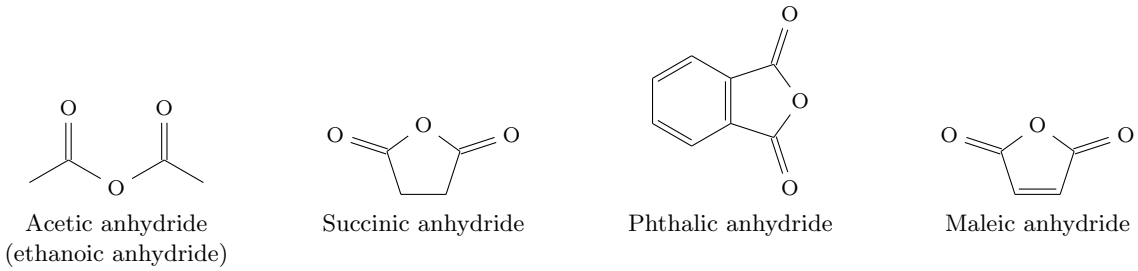


Figure 2.21: Special anhydrides.

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

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

- Naming amides.

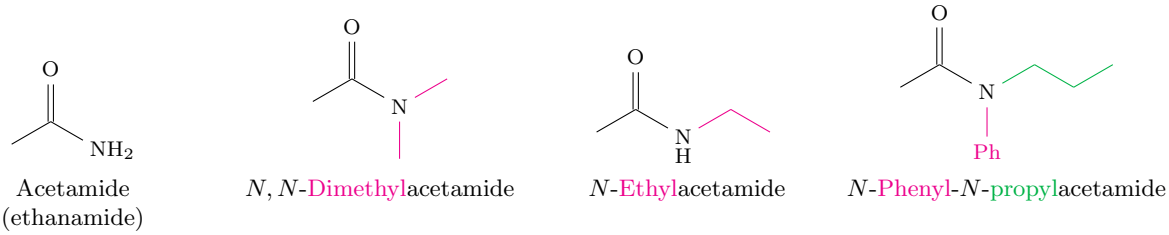
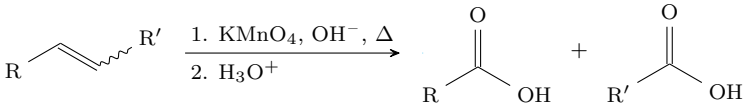


Figure 2.22: Amide nomenclature.

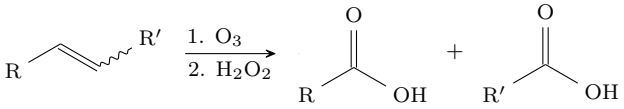
  - Drop -ic acid from the name of the acid and then add -amide.
  - "Alkyl groups on the nitrogen atom of amides are named as substituents, and the named substituent is prefaced by N- or N,N-" (Solomons et al., 2016, p. 767).

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

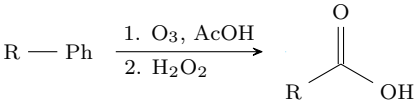
- Nitrile nomenclature.
  - Add the suffix -nitrile to the name of the corresponding hydrocarbon.
    - Examples include ethanenitrile (acetonitrile [abbrev. ACN]) and propenenitrile (acrylonitrile).
- New methods of carboxylic acid synthesis.



(a) Oxidation of alkenes 1.



(b) Oxidation of alkenes 2.



(c) Oxidation of benzene.

Figure 2.23: More methods of carboxylic acid synthesis.

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

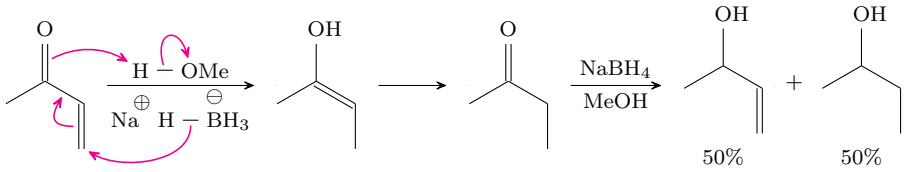
Week 3

Reactions of Carboxylic Acid Derivatives

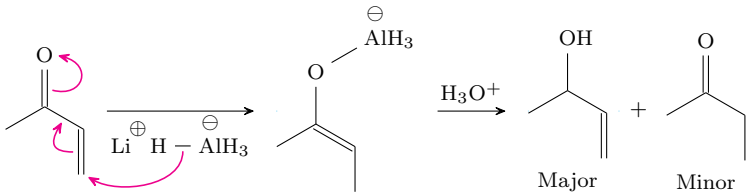
3.1 Office Hours (Levin)

4/11:

- α, β-unsaturated carbonyls?



(a) $NaBH_4$.



(b) $LiAlH_4$.

Figure 3.1: Reduction of α, β unsaturated compounds.

  - Levin's predictions basically line up with those from Labalme (2022b), 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.

3.2 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 (2022b) 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 ($LiAlH_4$).

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

  - See Figure 9.2 of Labalme (2022b) 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'll continue using aluminum ($NaBH_4$ 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*

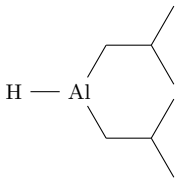


Figure 3.2: Diisobutylaluminum hydride (DIBAL-H).

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

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

- Mechanism.

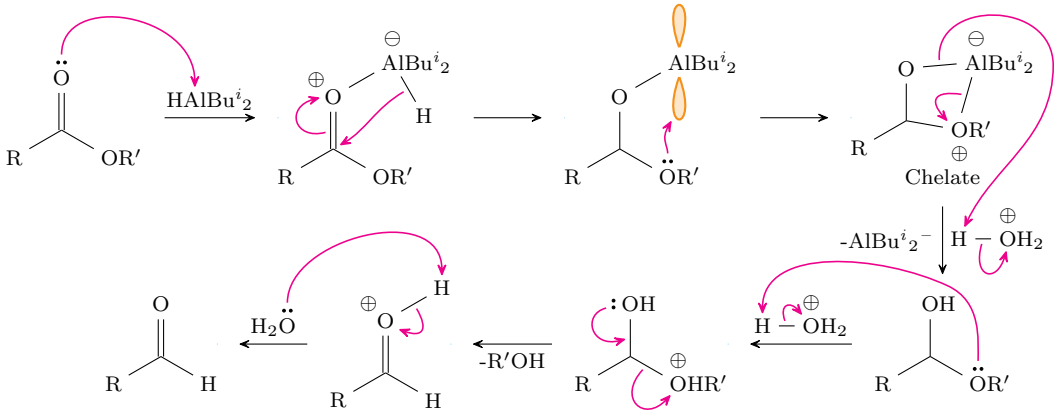


Figure 3.3: Monoreducton of esters mechanism.

  - 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.
  - 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.

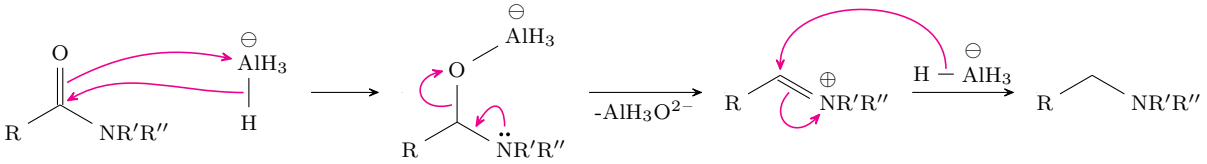


Figure 3.4: Reduction of amides mechanism.

  - 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.

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

- Mechanism.
  - Amides coordinate with DIBAL much more easily than esters.

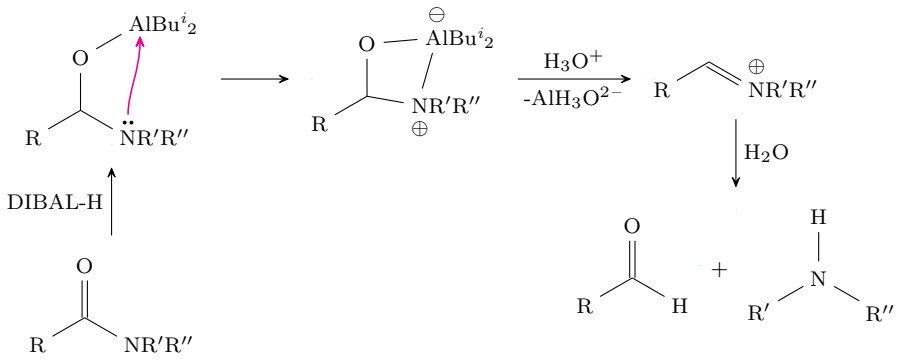


Figure 3.5: Monoreducton of amides mechanism.

- 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 2.12.

- 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.

$$\text{RCN} \xrightarrow[2.\ \text{H}_3\text{O}^+]{1.\ \text{R}'\text{Li}} \text{RCOR}'$$

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

- Mechanism.

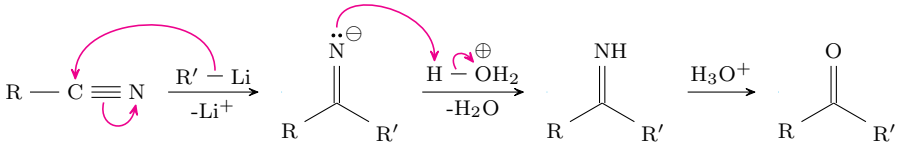


Figure 3.6: Nitrile alkylation mechanism.

  - 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.

$$\text{RCN} \xrightarrow[2.\ \text{H}_3\text{O}^+]{1.\ \text{DIBAL}-\text{H}} \text{RCOH}$$

- Mechanism.
  - As in Figure 3.3, 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 3.6, and then further to the aldehyde (also as in Figure 3.6).
- Nitriles ($LiAlH_4$).
- General form.

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

- Mechanism.

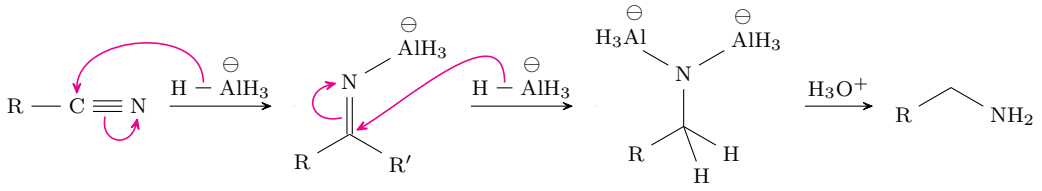


Figure 3.7: Nitrile reduction mechanism.

  - 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.

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

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

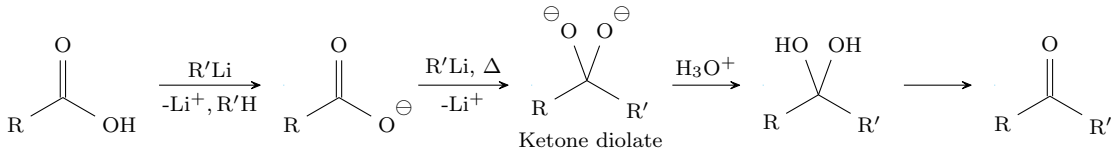
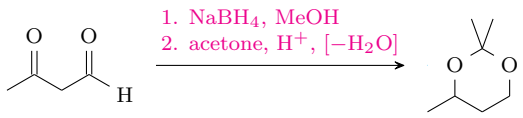


Figure 3.8: Carboxylic acid to ketone mechanism.

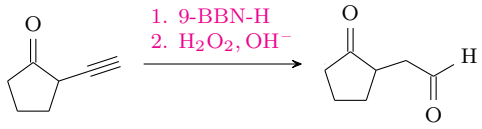
  - The excess lithiate is used to both deprotonate the carboxylic acid and alkylate the carboxylate that gets formed.
  - The heat is used to overcome the low electrophilicity of the carboxylate.

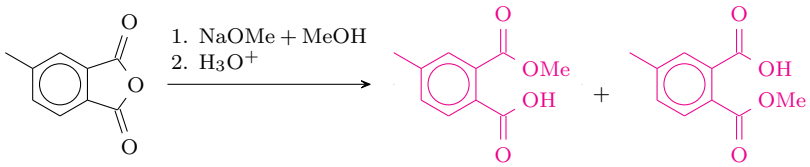
3.3 Problem Session

- Practice problems.

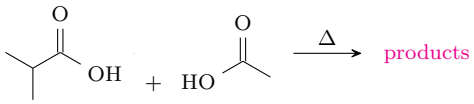
1. 

   - Sulfuric acid is a dehydrating acid.

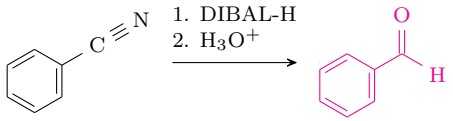
2. 

3. 

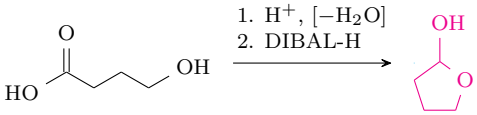
   - Notice that this is an asymmetric anhydride, so there are multiple possible products.
   - Regioselectivity goes out the window a bit due to the high temperatures, so don't worry about major and minor products

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. 

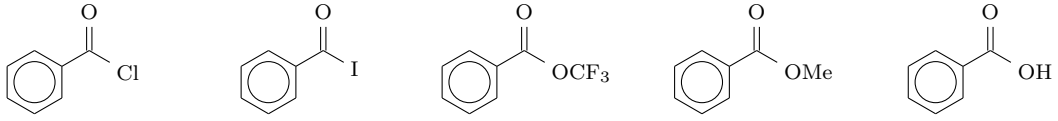
   - We can also buy DIBAL-D.
   - We're assuming that we're running this for only 15 mins, and thus stopping at the aldehyde. Running for longer will eventually take us down to the alcohol.
   - To protonate a nitrile, we need a very strong acid (e.g., concentrated sulfuric acid).
   - Goes over the mechanism,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

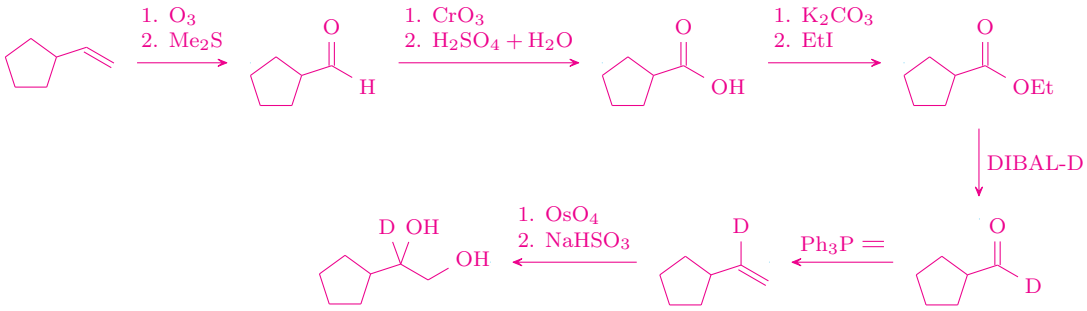
7. Rank the following in order of rate of nucleophilic acyl substitution with an alkoxide nucleophile.



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^+).

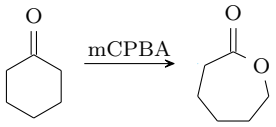
3.4 Carboxylic Acids and Derivatives 3

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.

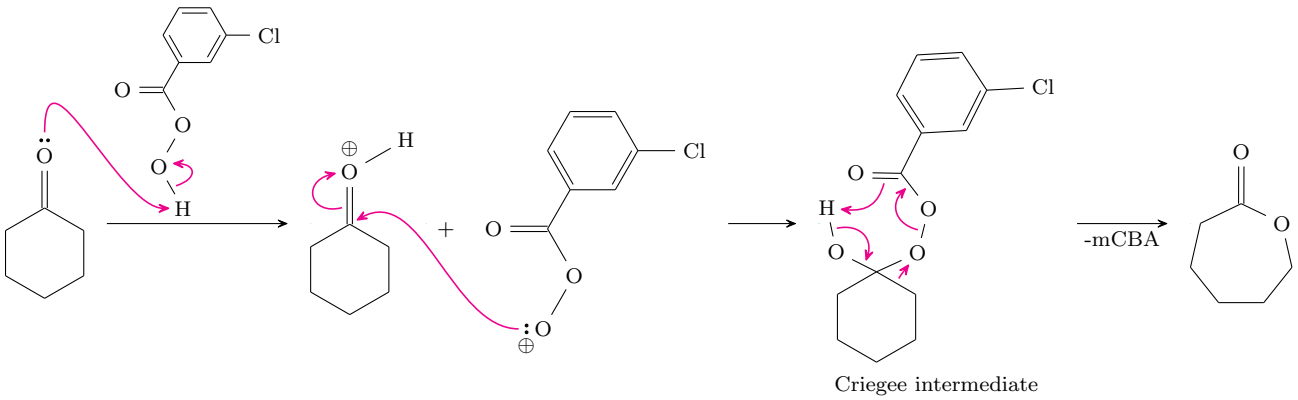
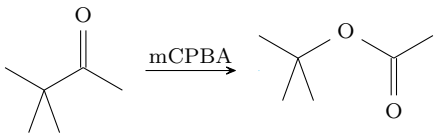


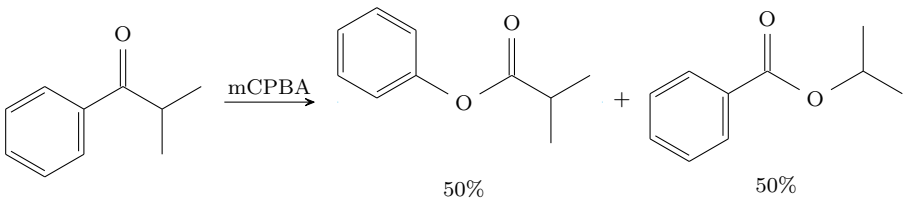
Figure 3.9: Baeyer-Villiger mechanism.

  - 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 the formation of the enol boronate in Figure 1.6.
  - Overall 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 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.

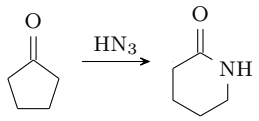
Figure 3.10: Asymmetric ketones in the Baeyer-Villiger.

  - 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 a 3° α-carbon greatly promotes the reaction a methyl α-carbon does the opposite.
    - 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.

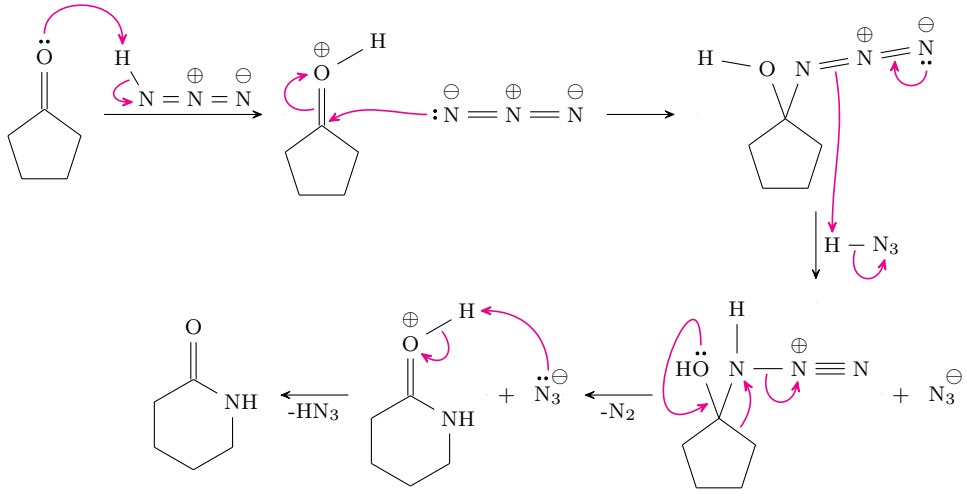


Figure 3.11: Schmidt reaction mechanism.

  - 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.
  - 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 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.

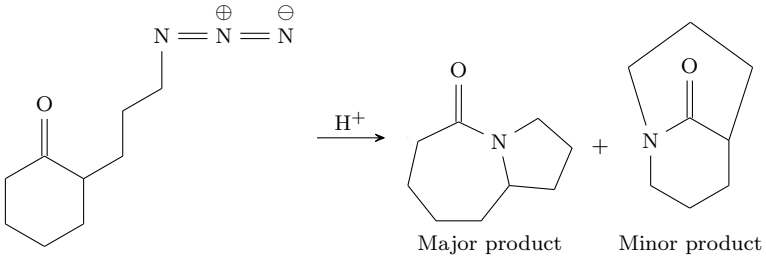
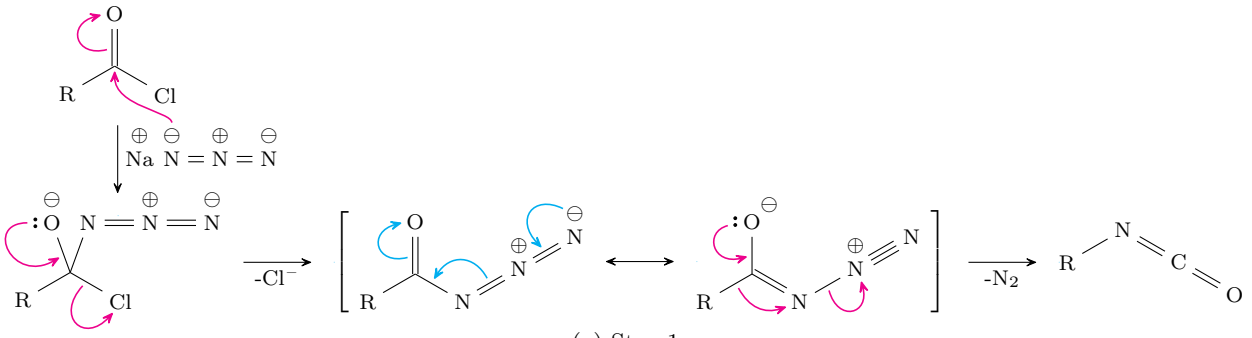


Figure 3.12: Intramolecular Schmidt reaction.

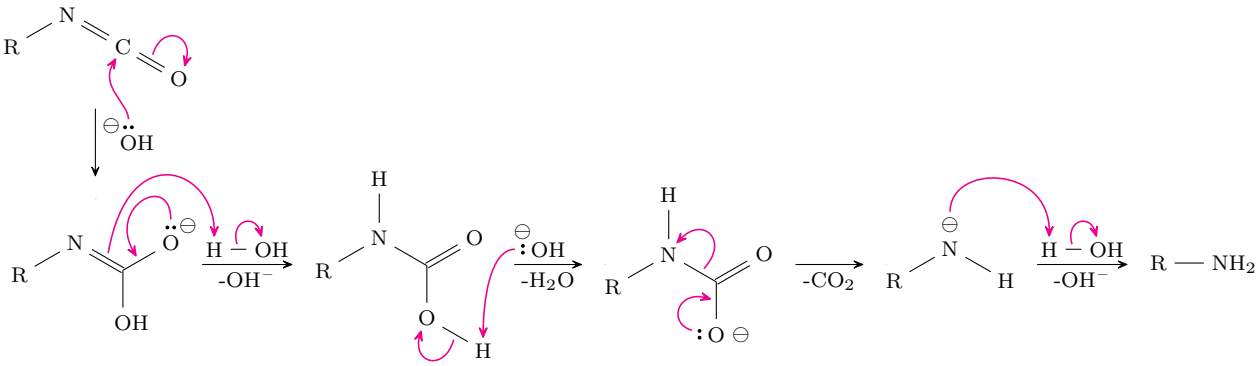
  - The intramolecular Schmidt builds complexity really quickly.
  - When you're building natural molecules, it allows you to get up from simple cheap starting materials to complex polycycles quite quickly, which you want.
- The Curtius rearrangement.
- General form.

$$\mathrm{RCOCl} \xrightarrow[\Delta]{\mathrm{NaN_3}} \mathrm{RNCO} \xrightarrow[\mathrm{H_2O}]{\mathrm{NaOH}} \mathrm{RNH_2}$$

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



(a) Step 1.



(b) Step 2.

Figure 3.13: 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.

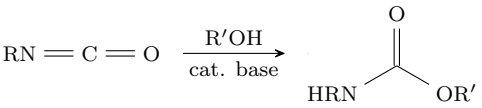
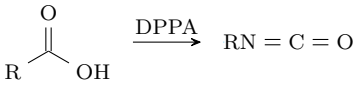


Figure 3.14: Carbamate formation.

  - 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*

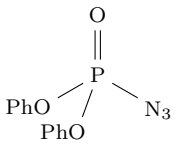
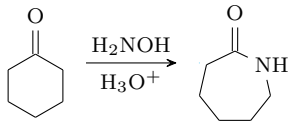


Figure 3.15: Diphenylphosphoryl azide (DPPA).

  - 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.

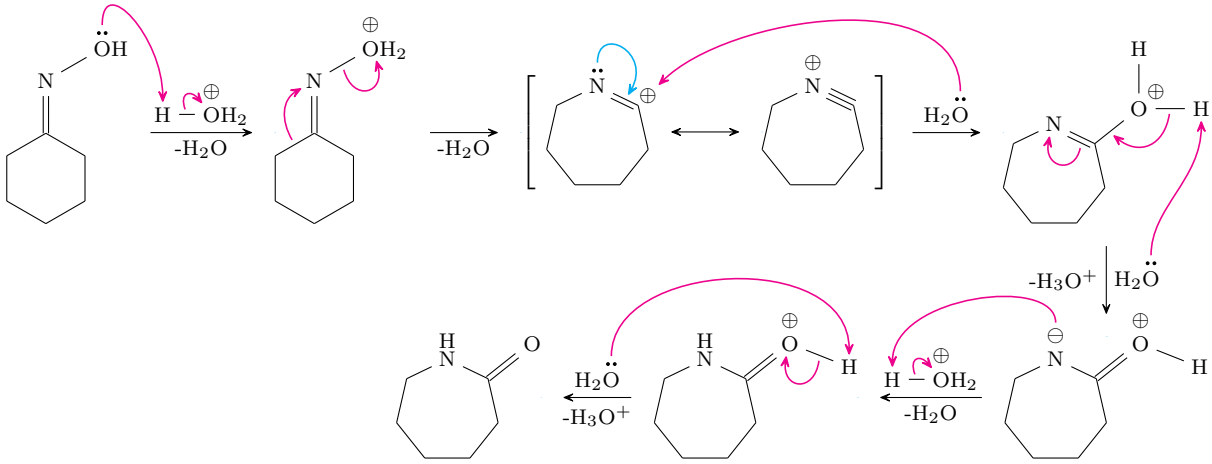


Figure 3.16: Beckmann rearrangement mechanism.

  - 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 3.16) 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.

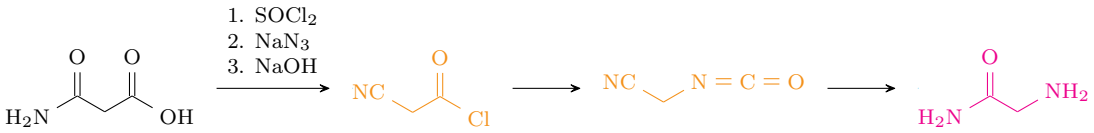
Week 4

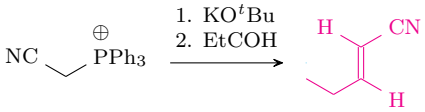
Exam and Enol(ate) Reactivity

4.1 Problem Session

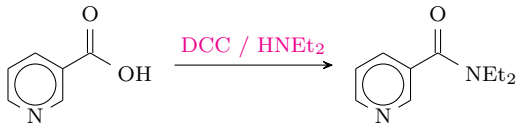
4/19:

- Practice problems.

1. 

2. 

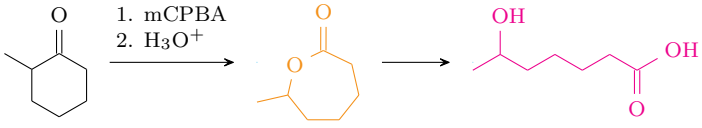
   – This reaction involves a stabilized ylide, hence the formation of the *trans* product.

3. 

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

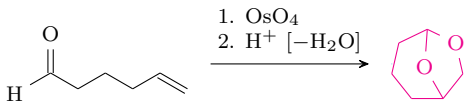
4. 

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

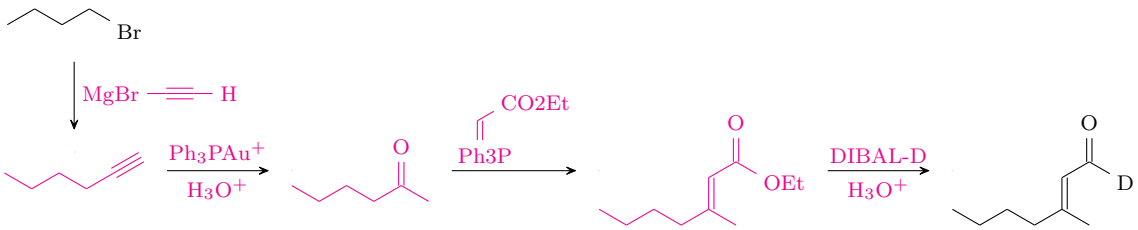
5. 

   – The second step proceeds as a consequence of the acid H–OH_2 to a carboxylic acid derivative, as per Figure 2.10a.

6.

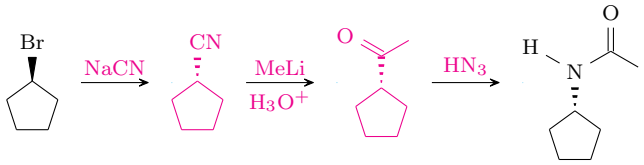


7. Mechanism: Goes over the Curtius rearrangement.
8. Retrosynthesis.

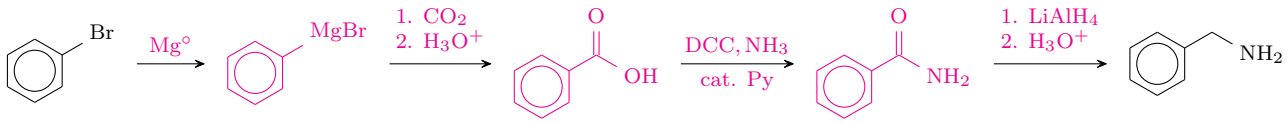


   - That deuterated aldehyde should indicate DIBAL-D.
   - COOEt is an EWG, and we will get the desired trans product in a Wittig with it.

9. Retrosynthesis.



10. Retrosynthesis.



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

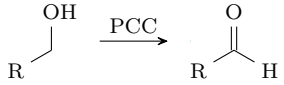
- For mechanism questions, if we're struggling, think back to the sentence trick from the very beginning of the course.
- For synthesis questions, just throw as many reactions out there as we can think of.

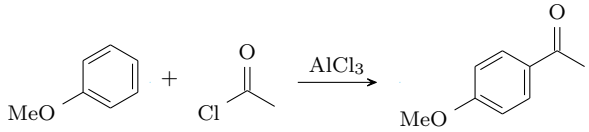
4.2 Midterm 1 Review Sheet

Reactions

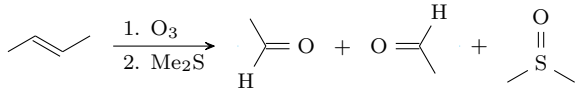
Carbonyl Synthesis

4/20:

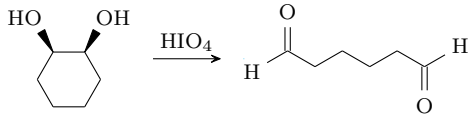
1. 

2. 

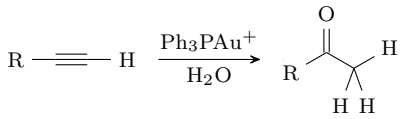
   – Recall ortho/para selectivity.

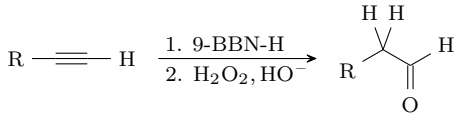
3. 

   – Not adding Me_2S traps the ozonide intermediate.

4. 

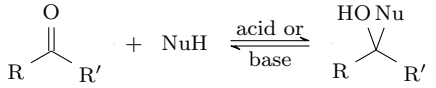
   – *cis*-diols react faster, but are not required.

5. 

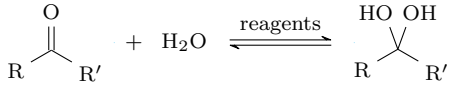
6. 

Nucleophilic Addition to Carbonyls

General

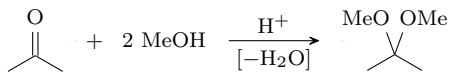
1. 

Oxygen Nucleophiles

1. 

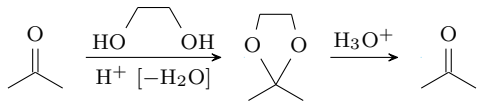
   – Reagents is either H_3O^+ or OH^-.

   – Proceeds faster for carbonyls with less bulky, more electron withdrawing substituents.

2. 

   – Remove water with a Dean-Stark apparatus (and toluene) or 3 Å aluminosilicates.

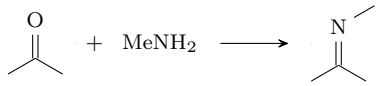
   – Will not work in basic conditions (will get stuck at the hemiketal). OH^- is not a good enough leaving group and needs an acid to protonate it.

3. 

   – We use ketals as protecting groups when we want our ketone to be able to withstand basic conditions (remember, ketals need acid to form and be unformed).

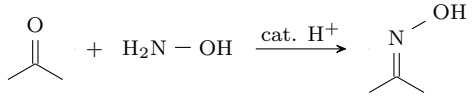
   – We can also protect 1,2- and 1,3-diols from basic conditions with acetone.

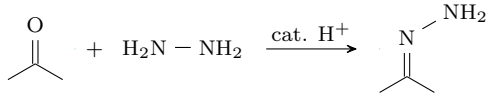
Nitrogen Nucleophiles

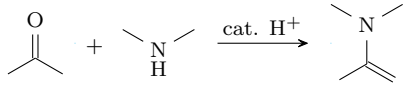
1. 

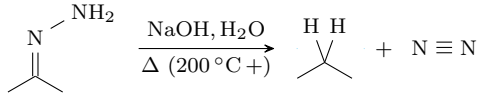
   – Acidic, basic, or neutral conditions.

   – We have only been taught the acidic mechanism, though, which is analogous to the other nucleophilic addition to carbonyl mechanisms we've been working with.

2. 

3. 

4. 

5. 

Hydride Nucleophiles

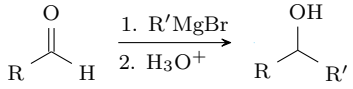
1. $NaBH_4 + MeOH$ reduces aldehydes and ketones to alcohols.

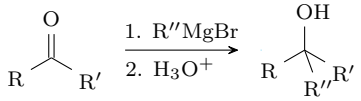
2. $LiAlH_4$ followed by H_3O^+ reduces an ester to its two component alcohols.

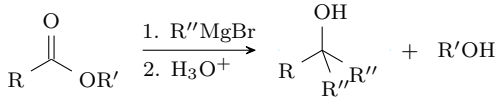
Carbide Nucleophiles

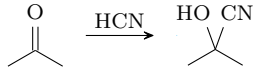
1. $RBr \xrightarrow[Et_2O]{Mg^\circ} RMgBr$

2. $RBr \xrightarrow[Et_2O]{2\,Li^\circ} RLi + LiBr$

3. 

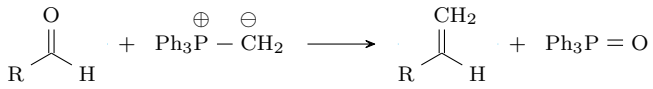
4. 

5. 

6. 

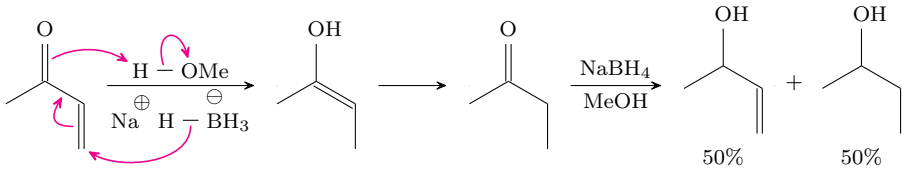
   – Can be accelerated by an acid/base catalyst, but no catalyst is necessary. Acid catalysts are more common.

Ylide Nucleophiles

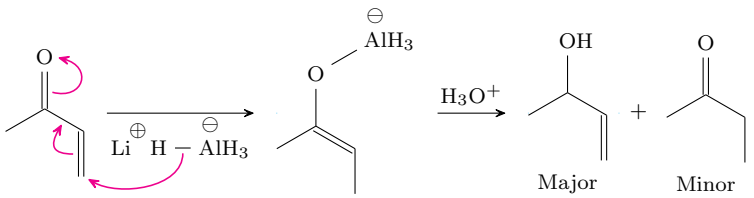
1. $Ph_3P \xrightarrow{MeBr} Ph_3BrP{-}CH_3 \xrightarrow{KO^tBu} Ph_3P{=}CH_2$
2. 

   - Presence or lack thereof of a betaine in the mechanism.
   - We need at least one hydrogen on the carbon portion of the ylide.
   - Stereoselective for the *cis* product.
     - Except if there's an EWG on the ylide; then we form the *trans* product.
   - Ketone Wittigs still proceed, but slower. Biggest groups end up *cis* (except, once again, in the case of ylide EWGs).

α,β-Unsaturated Carbonyls



$NaBH_4$.

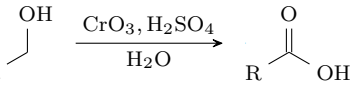
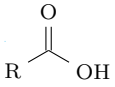
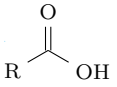


$LiAlH_4$.

Reduction of α, β unsaturated compounds.

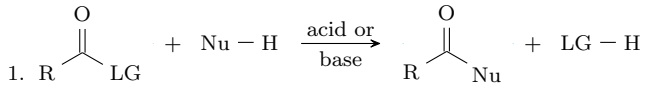
1. Organolithiums select for 1,2-addition.
2. Grignards are intermediate.
3. Cuprates select for 1,4-addition.
   - $2\,MeLi \xrightarrow{CuI} LiCuMe_2$

Carboxylic Acid Synthesis

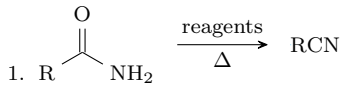
1. 
2. $RMgBr \xrightarrow[2.\ H_3O^+]{1.\ CO_2}$ 
   - Either lithiates or Grignards will suffice.
3. $RCN \xrightarrow{H_3O^+}$ 

Nucleophilic Acyl Substitution

General



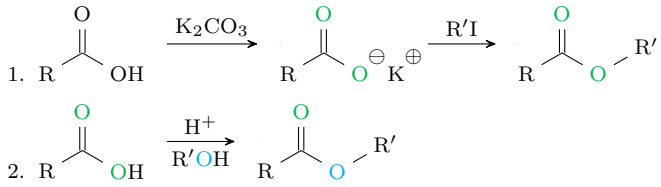
Dehydration of Amides



- Reagents are either $SOCl_2$ or $POCl_3$.
- We need an amide with two hydrogens to run this.

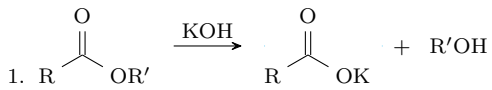
S_N2 Nitrile Formation

Ester Synthesis

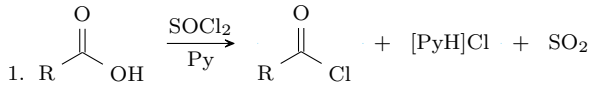


- The acid is a catalyst.
- The alcohol usually doubles as the solvent, esp. since we need it in excess.
- Removing water can drive the forward reaction; excess H_3O^+ reverses it.

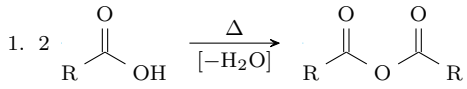
Ester Reactions



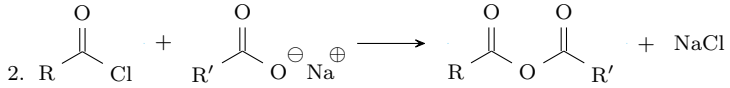
Acid Chloride Synthesis



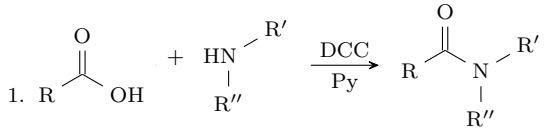
Anhydride Synthesis



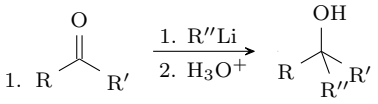
- Also works intramolecularly.
- Combining different carboxylic acids leads to a statistical mixture of products.

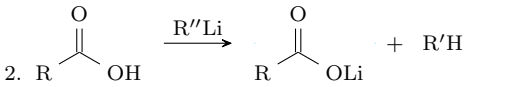


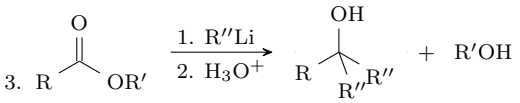
Amide Synthesis



Carbide Nucleophiles

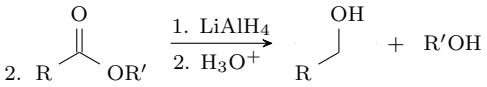
1. 

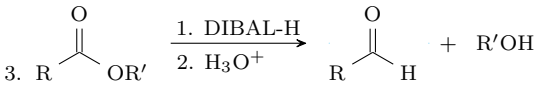
2. 

3. 

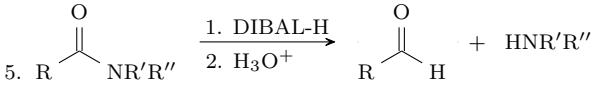
Hydride Nucleophiles

1. Esters and $NaBH_4$ do not react.

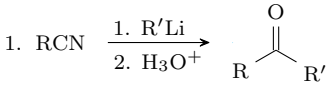
2. 

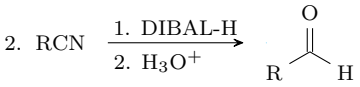
3. 

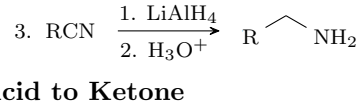
4. 

5. 

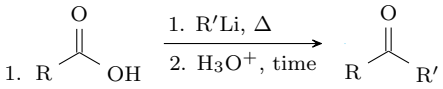
Nitrile Reactions

1. 

2. 

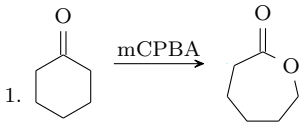
3. 

Acid to Ketone

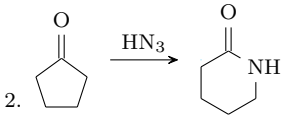
1. 

   - We need excess lithiate here.
   - Grignards won't work.

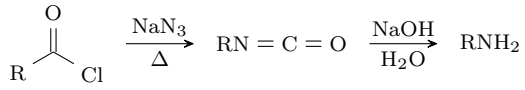
Insertion Reactions

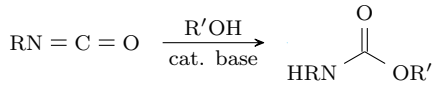
1. 

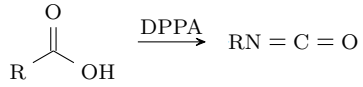
   - Migratory aptitude favors bulkier groups.

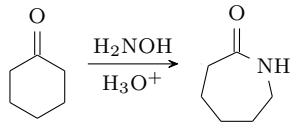
2. 

– Can be supplemented by external acid catalyst (some acid stronger than hydrazoic acid).

3. 

4. 

5. 

6. 

Reminders

- Carbonyl electrophilicity has to do with sterics (the primary factor) and electronics.
- Reactivity scale.

  acid chloride > anhydride > ester > amide > carboxylate

- DMAP is one of the best catalysts for nucleophilic acyl substitutions.

4.3 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 (i.e., 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*

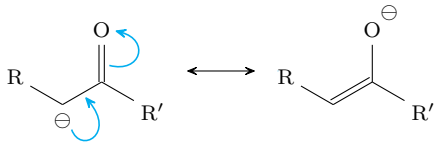


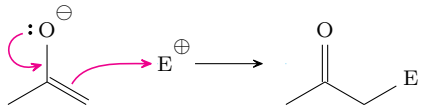
Figure 4.1: Enolate.

  - 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.

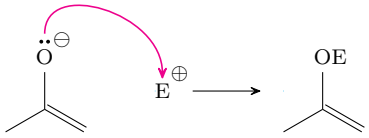
$$C_2H_4 \xrightarrow[CH_2I_2]{Zn/Cu} C_3H_6$$

  - 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$K_a \approx 5$) is 10^{10} times more acidic than ethanol (p$K_a \approx 15$) 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} to 10^{30} times less acidic than a hydrogen on acetone (p$K_a \approx 20$ to 25) once again due to resonance stabilization of the latter (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 4.2: Reactions of enolates and electrophiles.

  - We will focus on the mode in Figure 4.2a because we're most interested in making new bonds to carbon.

- If $E^+ = H^+$, then we can either generate a ketone (via Figure 4.2a) or an **enol** (via Figure 4.2b).
- **Enol**: The class of molecules containing adjacent alkene and alcohol functional groups. *Structure*

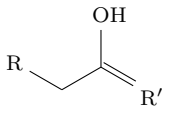
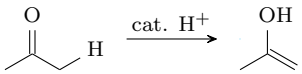


Figure 4.3: Enol.

- **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.

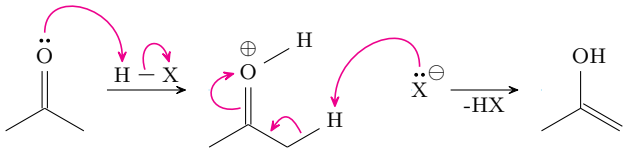
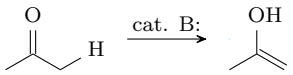


Figure 4.4: Acid-catalyzed enol formation mechanism.

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



- Mechanism.

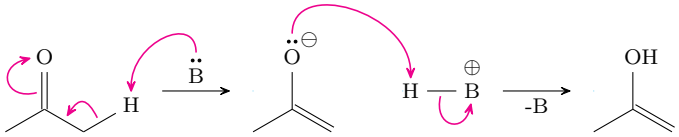


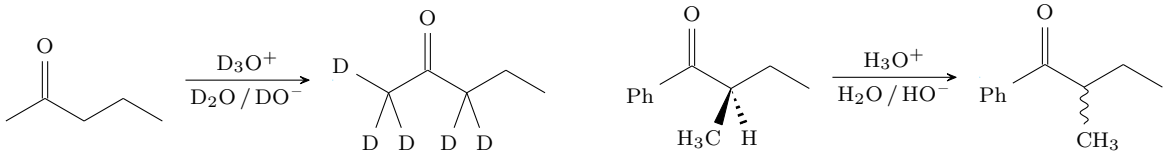
Figure 4.5: Base-catalyzed enol formation mechanism.

  - 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 reactions 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, although ketones are favored in general.
  - 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).

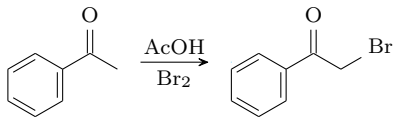


(a) Deuteration. (b) Racemization.

Figure 4.6: Evidence for the existence of enols.

1. Deuteration of carbonyl compounds (Figure 4.6a).
   - 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 one of acidic *or* basic deuterated water is used at one time.
2. Racemization of compounds that are enantiopure at the α-position (Figure 4.6b).
   - 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.

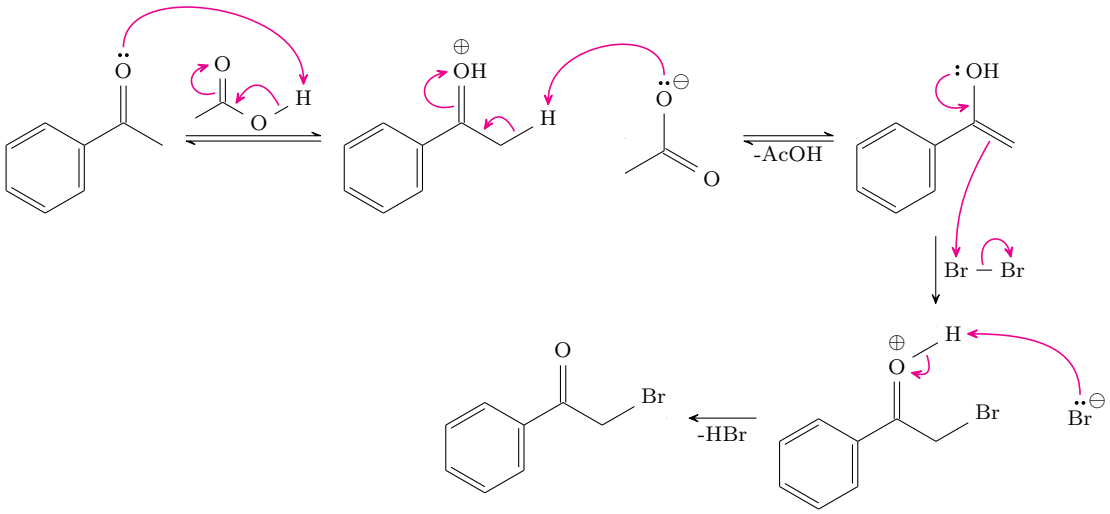
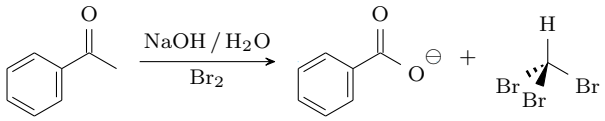


Figure 4.7: Acid-catalyzed halogenation of enols mechanism.

  - 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 also have **chloroform** (trichloromethane) and **iodoform** (triiodomethane).
- 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.

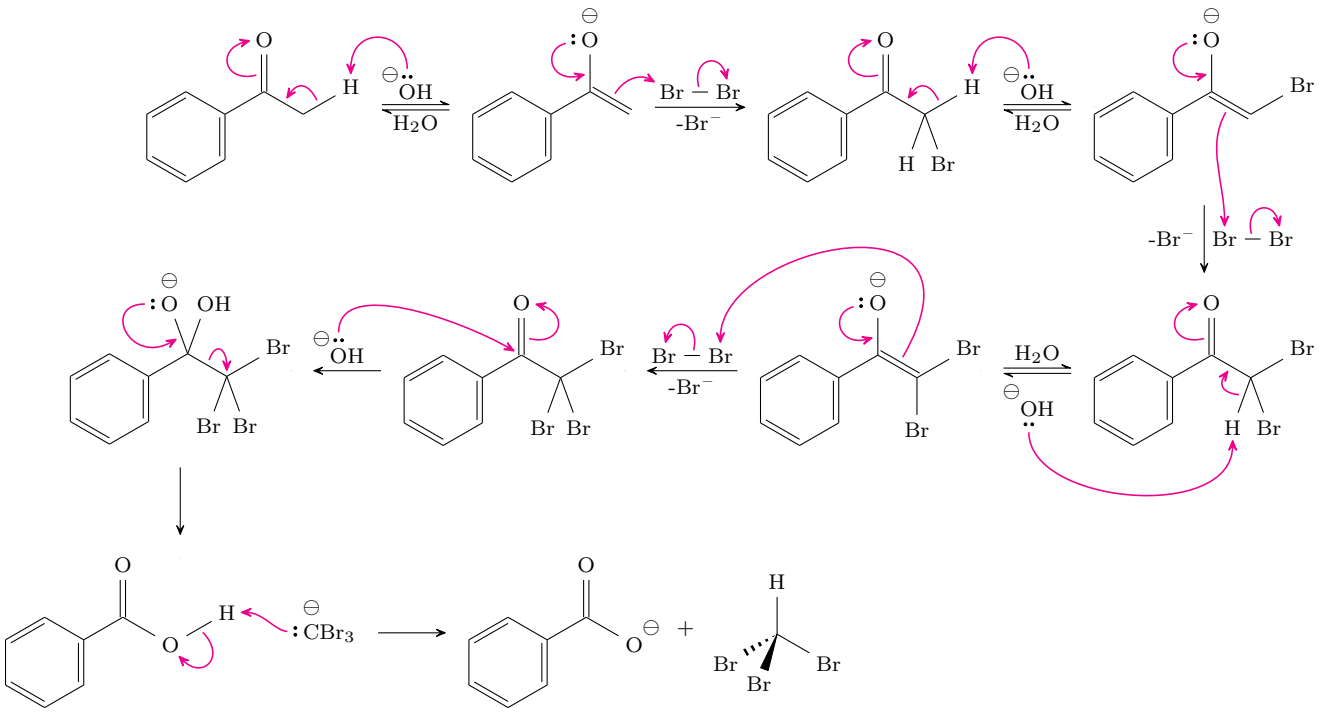


Figure 4.8: Haloform reaction mechanism.

  - 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 (see Figure 4.9).

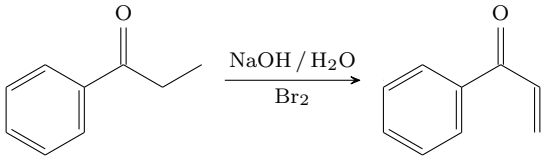


Figure 4.9: β-hydrogens in the haloform reaction.

  - 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.

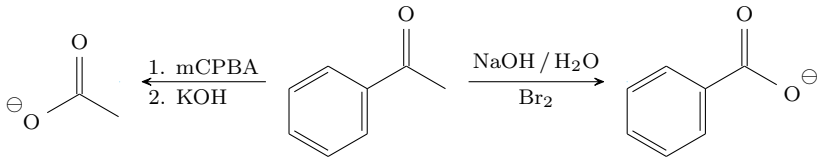


Figure 4.10: Synthetic uses of the haloform reaction.

  - 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-Kishner, 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!

Week 5

Alpha-Carbon Reactions

5.1 Reactions at the α-Carbon of Carbonyl Compounds 2

4/26:

- Announcements.
  - Professor Tang starts next Tuesday.
  - Midterm 2 will be written by Levin.
  - PSet 4-6 and the final will be written by Tang (she will release practice exams).
- Midterm 1 stats.
  - Range: 0-91.
  - Mean/st. dev: 34 ± 20 recurved to 70 ± 10.
  - Median: 33.
  - Nobody got 3a, the first mechanism.
  - Such recurving will be done for all exams.
- Midterm 1 comments.
  - This is Levin's first time teaching undergrads. As an undergrad, he had a professor for whom it was their first time and it was brutal for him, so he said he wouldn't do that but accidentally did it regardless.
  - Levin also says that for all the people who feel like they don't know what's going on, that's on him.
  - If you wanna judge how good you're doing, see how you did on the cyanohydrin formation and the amine cyclization. If those felt ok, you're doing fine; you can consider the others to have been challenge problems.
- Reversible formation of enols and enolates.
  - As discussed in the previous lecture, a ketone in the presence of a hydroxide base will equilibriate with its enolate.
  - Since $\mathrm{p}K_\mathrm{a} = 25$ for the ketone and $\mathrm{p}K_\mathrm{a} = 15$ for the enolate, 10^{10} times more of the ketone is present in solution.
  - Note that the amount of enolate present is still sufficient to do some chemistry (like that which we discussed last time). It does beg the question, however, of how stoichiometric deprotonation can be accomplished.
  - Stoichiometric deprotonation is useful (and necessary) for the reaction of enolates with relatively weaker electrophiles.

- Stoichiometric deprotonation.
- In theory, we could just use a stronger base.
  - We might assume that nBuLi[1] will deprotontate ketones to form butane and the enolate (with a lithium countercation).
  - Since butane is so basic, this would work very well ($K \approx 10^{25}$). However, nBuLi has competitive reactivity as a nucleophile attacking the carbonyl, and this is what it will do (as we discussed last unit).
  - Thus, we need an **innocent base**.
- **Innocent base**: A base that does not have reactivity competing with its ability to do deprotonations.
- **LDA**: Lithium diisopropyl amide, a sterically hindered, very strong, innocent base. *Structure*

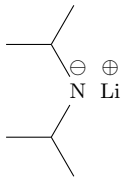


Figure 5.1: Lithium diisopropyl amide (LDA).

  - One implication of the name of this compound is that the term "amide" refers to both the carboxylic acid derivatives of nitrogen (see Figure 2.8e) and deprotonated amines (such as LDA).
  - Some chemists proclaim that there is a difference in pronunciation, i.e., that one is pronounced "AM-id" and the other "AE-mide."
- Synthesis of LDA.

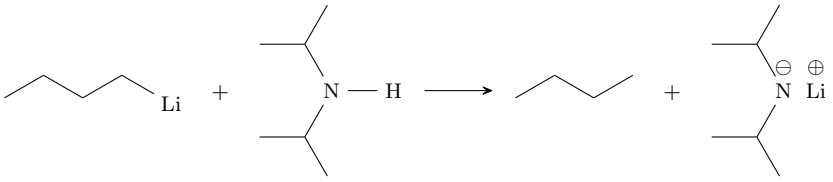


Figure 5.2: Synthesizing LDA.

  - The reactants are n-butyl lithium and diisopropyl amine.
- Consider what would happen if LDA tried to act as a nucleophile.
  - The product would be sterically disfavored.
  - Additionally, there is an easy reversible mechanism because while we an alkoxide can't kick out carbon, the amide is a good leaving group.
  - Thus, this is a reversible reaction that favors the starting material.
- Since LDA has no competitive reactivity, it will stoichiometrically deprotonate ketones.
  - Consider the reaciton of methyl phenyl ketone and LDA.
  - Since the ketone has p$K_a \approx 25$ and diisopropylamine has p$K_a \approx 36$, the equilibrium constant is approximately 10^{11}.

[1] Also pronounced "BYOO-lee".

- Orbital effects for deprotonation.

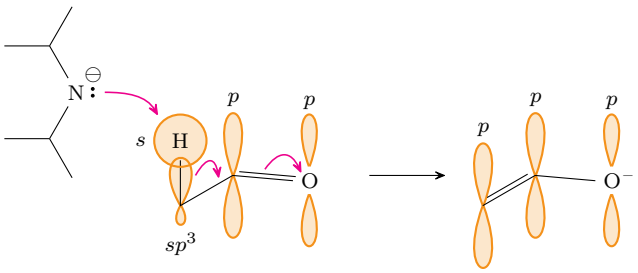
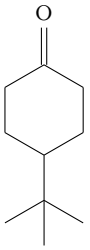


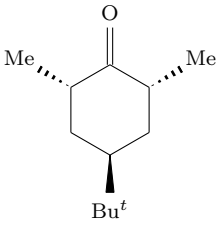
Figure 5.3: Orbital effects for LDA deprotonation.

  - In the fully formed enolate, conjugation of the oxygen anion into the π-system is stabilizing because of resonance.
  - However, for the reaction to proceed, there must be resonance stabilization from the moment the anion begins forming.
  - Thus, we need the sp^3 and the two p-orbitals to be aligned, as above. Notice how the C–H bond is parallel to the p-orbitals of the C=O π-system.
  - As we deprotonate, we continuously transform the sp^3 orbital into a third p orbital that will be in conjugation with the other two preexisting ones.

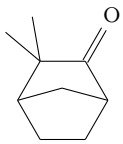
- Consequences of orbital effects.



(a) Axial vs. equatorial acidity.



(b) Blocked α-hydrogens.



(c) Locked α-hydrogen.

Figure 5.4: Molecules with deprotonation reactivity affected by orbital effects.

  - Cyclohexane conformations affect the acidity of equatorial and axial α-hydrogens.
  - Consider the molecule in Figure 5.4a.
    - Recall that *tert*-butyl groups are always equatorial.
    - It follows that the carbonyl is equatorial, too, and therefore that its π-system is axial.
    - Thus, the axial α-protons are more acidic because of their alignment with the C=O π-system.
    - Consequently, LDA selectively deprotonates these.
    - We can confirm this via selective deuteration of some cyclohexane hydrogens.
  - Now consider the molecule in Figure 5.4b.
    - Once again, conformations force the Bu^t group to be equatorial.
    - Thus, this compound cannot be deprotonated by LDA because it has no acidic protons.
  - Lastly, consider the molecule in Figure 5.4c.
    - A bicyclic hydrocarbon can be locked in the unreactive conformation.
  - Drawing the relevant chair conformations here is an important skill.

- Selectivity.
- Some compounds will not be selectively deprotonated.
  - For example, treating 1-phenylheptan-4-one with LDA will yield products that have been deprotonated at every α-hydrogen in equal amounts.
- LDA prefers to deprotonate at less substituted positions due to its sterics.
- Comparing LDA- and hydroxide-based deprotonations.
  - LDA is a lot more basic than hydroxide.
  - Thus, hydroxide deprotonations are reversible while LDA deprotonations are irreversible.
  - It follows that hydride deprotonations are under thermodynamic control (stability is important) while LDA deprotonations are under kinetic control (rate is important).
- Rate is controlled by the transition state energy.
  - Levin draws a 1D energy diagram for an exothermic reaction with a large $\Delta G^{\ddagger}$, noting that this large $\Delta G^{\ddagger}$ will make the reaction slower.
- Selectivity in terms of kinetic and thermodynamic control.

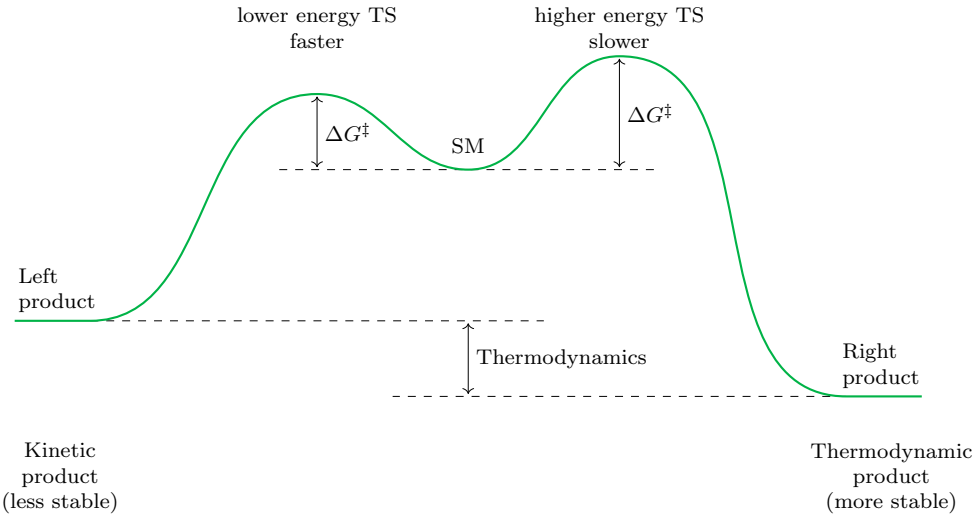
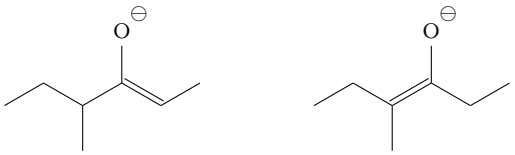


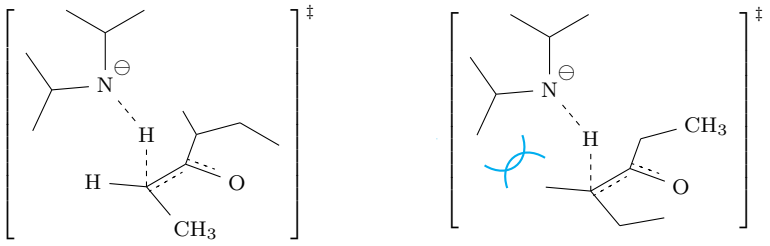
Figure 5.5: Thermodynamic vs. kinetic control.

  - A reaction that is reversible will form the thermodynamic product.
  - A reaction that is irreversible will form the kinetic product.
  - Note that there are paradigms in which one product is both the kinetic and thermodynamic one.
  - To determine the kinetic product, we compare transition states.
  - To determine the thermodynamic product, we compare the products, themselves.
- Application.



Less stable More stable

(a) Thermodynamic stability.



(b) Kinetic favorability.

Figure 5.6: Thermodynamic and kinetic stability in enolates.

  - The tetrasubstituted enolate is the more stable product by Zaitsev's rule.
  - The trisubstituted enolate has a more stable transition state.

- "An analogy may assist in understanding kinetically and thermodynamically controlled reactions. Imagine a very inebriated gentleman stumbling randomly around a pasture. Near each other in the paster are a shallow watering hole and a deep well with a high fence around it. Our drunken friend is likely to fall in the hole several times, but because it is shallow, he can climb out of it and continue staggering around the pasture. After a very long while, however, he makes it over the fence and falls into the well; once in the well, he is there to stay. If we now imagine Avogadro's number of people staggering around a (very large) pasture, we get a reasonably good picture of kinetic and thermodynamic control. Initially, a large number of people fall into the shallow hole. If we wait long enough, however, most of the will end up in the deep well. The frequent occurrence — falling in the shallow hole — is reversible, but the rare occurrence — climbing the fence and falling in the well — is irreversible" (Loudon, 1988).
  - The Avogadro's number correction is to bring an element of statistics and probability into the example.
  - In the new edition, the drunken gentleman has been changed to "disoriented steers," maybe to be PC.
- In general, we cannot guess how long it will take the thermodynamic enolate to accumulate (though it will likely be a long time), so we need an alternate method of generating them.
- Generating thermodynamic enolates.
  1. Use OH^-, which catalyzes *reversible* enolate formation.
  2. Use a sub-stoichiometric equivalent (≈ 0.95) of LDA.
- Sub-stoichiometric LDA addition.

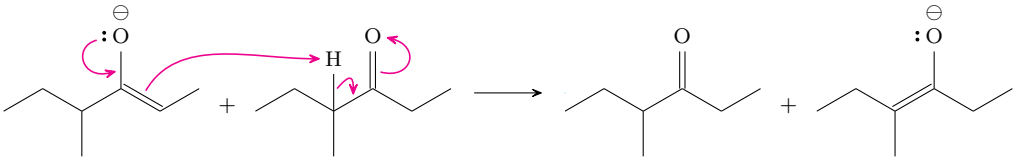


Figure 5.7: Sub-stoichiometric LDA addition.

  - Using a sub-stoichiometric amount leaves some ketone behind to react with the kinetic enolate as in the above picture, generating the thermodynamic enolate and regenerating the ketone to react again.
  - The wait time for this process to occur is usually a few hours at room temperature.

- Note that if you want to form solely the kinetic product, you will need to do it quickly and with more than one equivalent (we can just say one equivalent for the purposes of this class; we use a little excess to account for any mismeasurement/human error in real life), and you will need to keep the mixture at $-78\,^\circ\mathrm{C}$ (using a dry ice/acetone bath).
- Kinetic enolate formation.

$$\text{Ketone} \xrightarrow[-78\,^\circ\text{C}]{\text{LDA (}>1\text{ equiv)}} \text{Enolate}$$

- Thermodynamic enolate formation.

$$\text{Ketone} \xrightarrow[\text{time}]{\text{LDA (0.95 equiv)}} \text{Enolate}$$

- Uses for enolates.
  1. Halogenation.
  2. C–C bond formation.
  3. Selenium electrophile reactions.
- **N-bromosuccinimide**: A source of electrophilic bromine. *Also known as* **NBS**. *Structure*

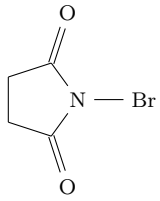
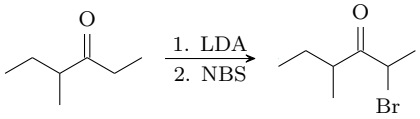
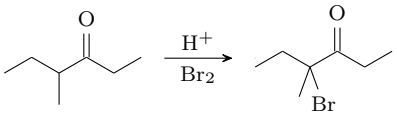


Figure 5.8: N-bromosuccinimide.

- Halogenation.
- General form.

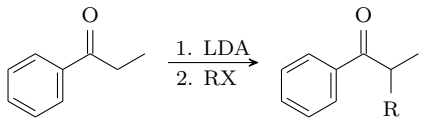


  - We get bromination of the kinetic enolate assuming we perform keep this reaction cold and perform it fast.
- Mechanism.
  - The enolate attacks the bromine of NBS, and the N–Br electrons retreat onto the nitrogen.
- Reacting the thermodynamic enolate.
  - Although we might think to use OH^- / Br_2, this would from an α,β unsaturated compound as per Figure 4.9.
  - Thus, we turn to acidic conditions.
- Acidic conditions form thermodynamic enols.



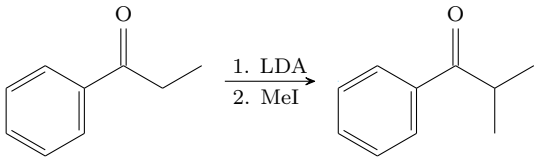
- These enols are formed reversibly (see Figure 4.7), so they have an opportunity to equilibriate and favor the thermodynamic product.
- Once the thermodynamic enol has been built up, it reacts selectively with Br_2.

- C–C bond formation with enolates.
- General form.

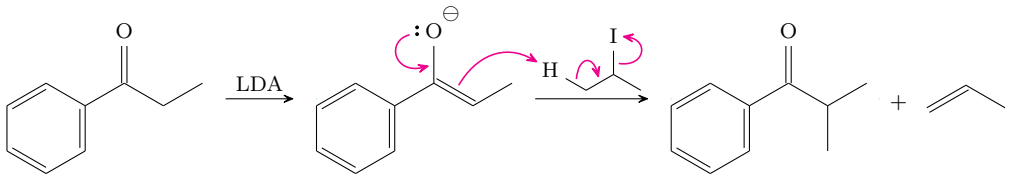


- Note that phenyl alkyl ketones have no selectivity problems because they only have α-hydrogens on one side.
- X is bromine or iodine.
- Works great if R is a methyl group.
- Works ok if R is a primary alkyl.
- E2 of the alkyl halide starts to dominate if R is secondary or tertiary.

- Examples.



(a) Methyl R group.

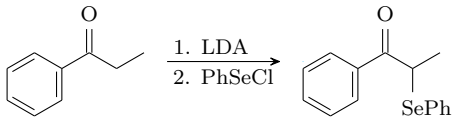


(b) Isopropyl R group.

Figure 5.9: Examples of C–C bond-forming reactions with enolates.

- We'll fix the issue that arises in Figure 5.9b next time.

- A new electrophile (selenium).
- General form.

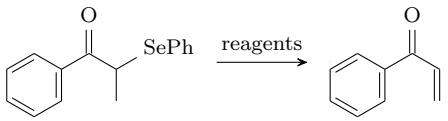


- We can use either the phenyl selenyl chloride or phenyl selenyl bromide.

- Mechanism.
  - The enolate attacks the selenium atom and kicks out chlorine in one concerted step.
- The purpose of adding selenium to compounds.

  - We put selenium in just to take it back out again.
  - We typically don't want to build molecules with it because it's quite toxic and not commonly used in biochemistry.

- Eliminating phenyl selenide.
- General form.



  - The reagents are either mCPBA or H_2O_2.
  - We use this method over hydroxide and bromine because it is compatible with LDA, which means that we can get selectivity for elimination now in addition to bromination.

- Mechanism.

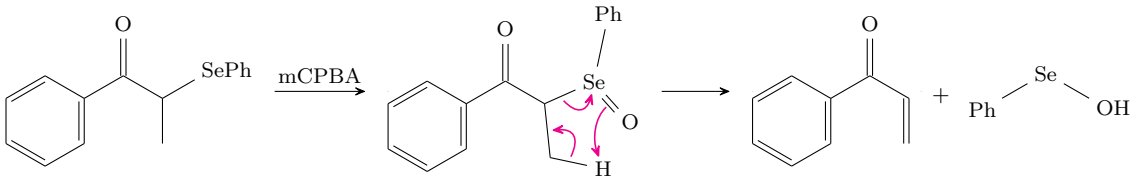


Figure 5.10: Phenyl selenide elimination mechanism.

  - The first intermediate is a **selenoxide**.

- Selectivity.

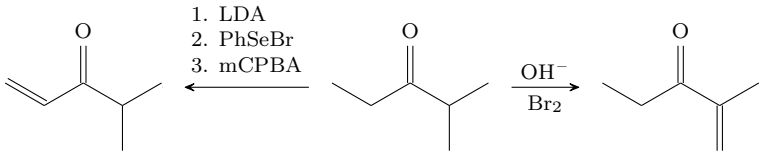
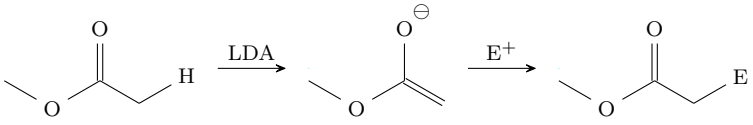


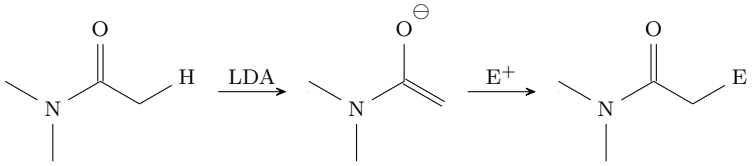
Figure 5.11: Selectivity in the formation of α, β unsaturated compounds.

  - We use the thermodynamic enolate (accessible via reversible hydroxide) for the right side and the kinetic enolate (accessible via irreversible LDA) for the left side.

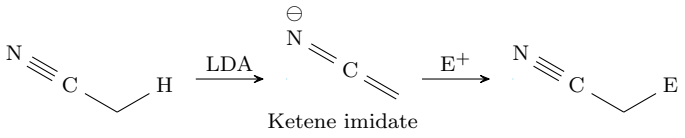
- Applications to carboxylic acid derivatives.



(a) Esters.



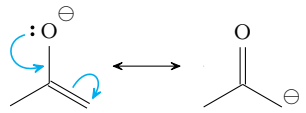
(b) Amides.



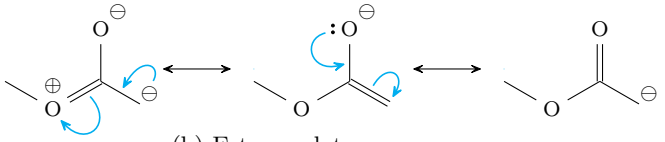
(c) Nitriles.

Figure 5.12: Carboxylic acid derivatives as enolates.

- Comparing the nucleophilicity of ketone enolates, ester enolates, and amide enolates.



(a) Ketone enolate resonance.



(b) Ester enolate resonance.

Figure 5.13: An extra resonance form for carboxylic acid derivative enolates.

  - Nucleophilicity depends on how electron-rich the π system is.
  - Oxygen and nitrogen both donate their lone pairs to the π system.
  - The additional resonance form makes the carboxylic acid derivative enolates more nucleophilic.
  - Nitrogen is the most nucleophilic (because of its lower electronegativity relative to oxygen), then oxygen, then carbon (of these three).

- We will not be asked to compare the nucleophilicity of ketene imidates to ketone, ester, or amide enolates.
- Selectivity is nice for all carboxylic acid derivatives; there's at most one set of α-hydrogens for all of them.
- Compounds whose enolates are less useful.
  - Carboxylic acids: These will become carboxylates upon the first deprotonation. The second deprotonation takes a much stronger base, forms a dianion, and doesn't work too well.
  - Amides with hydrogens: These deprotonate first as well and then run into the same dianion problem.
  - Acid chlorides: These kick out the chloride along with deprotonation, forming a **ketene**. There are things we can do with ketenes, but we won't talk about them since they aren't as useful as enolates.
  - Aldehydes: These will dimerize. In particular, one deprotonated aldehyde will engage in a nucleophilic attack on another.
    - This will form most of the rest of the class.

5.2 Reactions at the α-Carbon of Carbonyl Compounds 3

4/28:

- Last time.
  - Enolates derived from ketones that are the major species in solution.

  - Specifically, ones that are generated selectively.
  - Enolates can be used to make new C–C bonds (but in a limited number of cases).

- Today.
  - Expanding the utility of enolates in C–C bond forming reactions.
  - In particular, developing solutions to the following issues.

- Problems with enolates.
  1. Enolates are basic.
     - This means that enolates preferentially eliminate secondary and tertiary alkyls instead of adding into them via S_N2.
  2. LDA is not regioselective for similar sites.
     - Recall 1-phenylhept-4-one.
  3. Aldehyde enolates self-attack.
     - Weixin will talk at length about how to control this "problem" and actually utilize it.

- The solutions.
  - There is no unified solution; rather, we will discuss two partial solutions.
  - Both of these solutions solve problem 1. In addition, one solves problem 2, and the other solves problem 3.

- Generalizing about the problems we face.
  - The overall problem is that enolates are too reactive.
  - Solution: Use the enol — it's less reactive than the enolate because it's neutral.
  - However, enols are the minor species in solution relative to their ketone tautomers, and since these two molecules are constitutional isomers (i.e., nothing is gained or lost in the tautomerization), there is no way to push the equilibrium to one side or the other with Le Châtelier's principle.

- Solution 1 (to problems 1 and 3): Enamines.

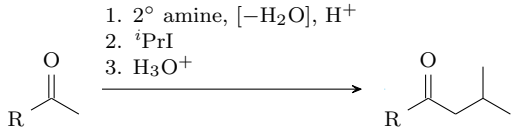
- Levin reviews enamine formation.
  - See the general form below Figure 1.22.
  - Levin notes that removing water can further drive the reaction in the forward direction.

- As one might assume from the structural homology between enols and enamines, the two compounds do indeed have similar reactivity.

- Comparing enolate, enamine, and enol reactivity.
  - Enolates are more reactive than enamines, which are more reactive than enols.
    - In layman's terms, this is due to the presence/lack thereof of formal charges and the relative electronegativities of nitrogen and oxygen, respectively.
    - More specifically, when we draw the resonance forms for all three of these compounds that put the negative charge on the α-carbon, we note two things.
    - First, enamines and enols both have a counterbalancing positive charge on their heteroatom. This makes their α-carbons significantly less basic (hence less reactive) than enolates'.
    - Second, oxygen is more electronegative than nitrogen. Thus, the positively charged oxygen withdraws electron density to an even greater extent than the positively charged nitrogen. Consequently, the enol's α-carbon is less basic than the enamine's.
  - Therefore, enamines are Goldilocks nucleophiles (with reactivity between enols and enolates).

  - Advantages of enamines over enolates.
    - Less reactive.
    - Still reactive enough.
  - Advantages of enamines over enols.
    - Enamines can be stoichiometrically generated.
    - We can use them as nucleophiles.

- Using enamines to alkylate carbonyls.
- General form.



  - This procedure permits secondary α-alkylation of carbonyl compounds, solving problem 1.
  - R = H, C.
    - Thus, this procedure α-alkylates both ketones and aldehydes, solving problem 3.
  - We can any secondary amine we like. Some examples are pyrrolidine or morpholine (the latter is used in Figure 5.14).

- Mechanism.

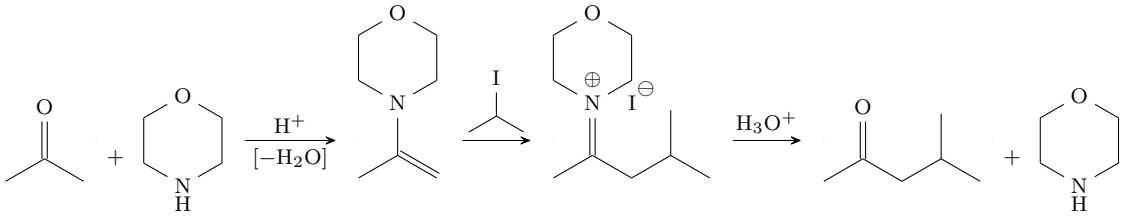


Figure 5.14: α-alkylating carbonyl compounds using enamines mechanism.

  - The α-alkylated iminium generated as the second intermediate above is stable until workup.
    - This is fairly remarkable since it is difficult (requires removing water) to generate iminiums from ketones.
    - However, since we have already isolated the enamine before the second reaction above, there is no chance of it reacting backwards. This is what leads to the stability of the iminium intermediates.
  - That being said, adding the water back in (in the form of an acid workup) readily hydrolyzes the iminium back down to a ketone.
    - Recall, wrt. the third step, that imines are prone to hydrolysis (see Lecture 2).

- Aside (will not be tested).
  - Since the amine reacts in Figure 5.14 but is regenerated at the end, it is technically a catalyst.
  - More generally, catalytic alkylations and electrofunctionalizations can be accomplished via the above mechanism. Thus, instead of introducing a stoichiometric amount of the amine, we can cycle through a small, catalytic quantity of amine.
  - Moreover, if we use a chiral amine, we can influence the stereocenter in the product.
  - This is what the 2021 Nobel Prize was awarded for: Asymmetric organocatalysis.

- Dave Macmillan of Princeton (one of the Nobel laureates) is a great chemist but also a master salesman, so what he realized and sold was that you can use small organic molecules as catalysts (or **organocatalysts**).
  - This was revolutionary because it was thought in the early 2000s that catalysts had to either be transition metals or enzymes.
- A common organocatalyst is proline.

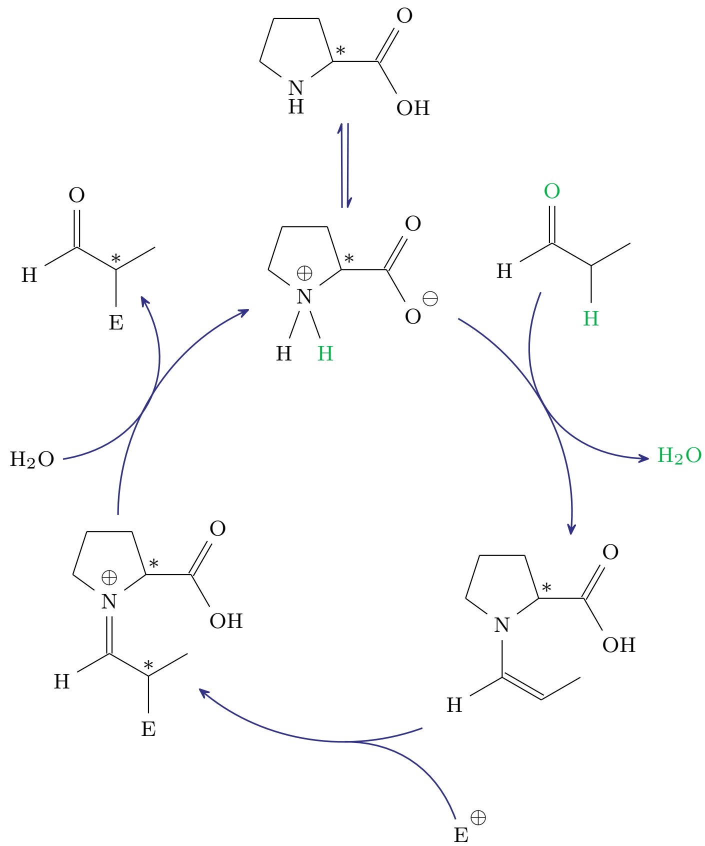


Figure 5.15: Proline organocatalysis.

  - The substrate is any simple aldehyde.
  - Because proline (a simple, cheap amino acid) is chiral, its stereocenter influences the final one by favoring one face of the substrate for electrophilic attack over the other.
  - However, you need to use a lot of it.
- **Macmillan's catalyst** is drawn as well.

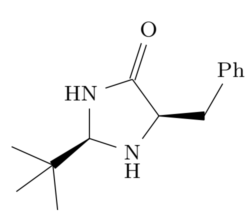
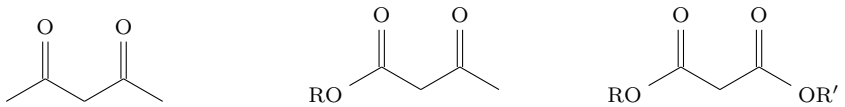


Figure 5.16: Macmillan's catalyst.

  - Macmillan's catalyst allows much lower loadings while retaining high levels of stereocontrol.

- Enamines don't solve problem 2 (regioselectivity for similar sites), however.
- Solution 2 (to problems 1 and 2): β-dicarbonyl compounds.
- β-dicarbonyl compounds.



(a) β-diketone. (b) β-ketoester. (c) Malonate.

Figure 5.17: β-dicarbonyl compounds.

  - β-dicarbonyls are referred to as such because relative to either carbonyl functional group, the other carbonyl is on the original carbonyl's β-carbon (two away along the chain from the carbon involved in the functional group).
  - Malonates could be called β-diesters, but nobody refers to them as such.
- β-dicarbonyls are useful because $9 \leq \mathrm{p}K_\mathrm{a} \leq 11$ for the hydrogens on the central α-carbon.
  - As specific examples, pentane-2,4-dione (Figure 5.17a) has $\mathrm{p}K_\mathrm{a} = 9$, dimethyl malonate has $\mathrm{p}K_\mathrm{a} = 11$, and methyl acetoacetate is somewhere in the middle.
  - The implication is that we can deprotonate β-dicarbonyls far easier than regular ketones.
- In particular, while we need LDA for acetone, we can use methoxide for β-dicarbonyls.

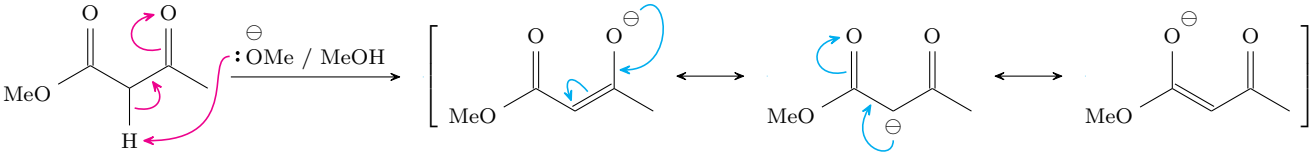
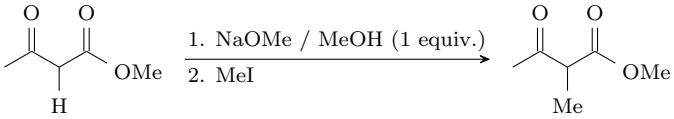


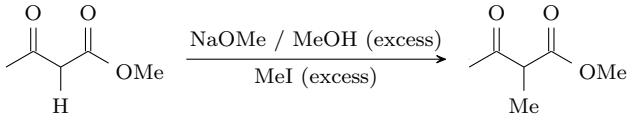
Figure 5.18: Deprotonating β-dicarbonyls.

  - It makes sense that β-dicarbonyls are more acidic than regular carbonyl compounds because their conjugate bases have three resonance forms, as above, compared to the two of regular carbonyls (as in Figure 4.1).
    - Recall that carbonyl compounds are in turn more acidic than alkanes because alkanes only have one resonance form.
  - Since $\mathrm{p}K_\mathrm{a} = 10$ for methyl acetoacetate and $\mathrm{p}K_\mathrm{a} = 15$ for MeOH, only 1 in every 10^5 β-dicarbonyls is not deprotonated, so the above equilibrium lies fairly far to the right.
  - Note that we do need to "match" the alkyl ester group(s), organic base, and solvent so that background competitive nucleophilic acyl substitution does not become observable.
    - For example, in the above reaction, we use *methyl* acetoacetate, *meth*oxide, and *meth*anol.
- The reason for performing this reaction in alcholic solvent is purely practical.
  - Sodium alkoxides can be bought, but they're air-sensitive and prone to decomposition.
  - Thus, we prefer to generate them fresh.
  - To do so, we treat some quantity of alcohol with sodium hydride or sodium metal. Either way, we form solvated sodium alkoxide in methanol and releasing H_2 gas.
  - Performing this reaction in an excess of methanol allows us to easily proceed with the reaction in liquid media, just with the necessary condition that the solvent is the alcohol.

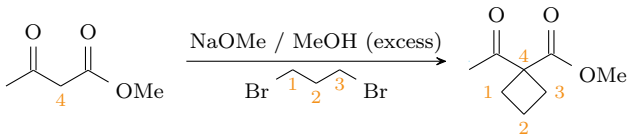
- Other ways of deprotonating β-dicarbonyls.
  - Since protonated triethyl amine has a comparable pK_a to methyl acetoacetate, mixing NEt_3 with methyl acetoacetate generates the deprotonated form reversibly.
  - In principle, we could also use LDA. It's overkill (it would lead to 10^{26}-fold deprotonation), but there's nothing chemically wrong with it.
- We now get into the reactions of β-dicarbonyls.
- Monoalkylation.
- General form.



- Mechanism.
  - We generate the enolate (as in Figure 5.18). It subsequently attacks methyl iodide from the backside via an S_N2 mechanism.
- Dialkylation.
- General form.

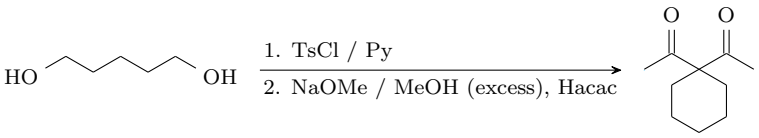


- Mechanism.
  - The first two steps are the same as the monoalkylation mechanism.
  - The third and fourth steps are deprotonation of the monoalkylated product followed by S_N2.
- Note that monoalkylation proceeds to completion (instead of generating one-half equivalent of dialkylated product) because the alkylated product is less reactive than the starting material (methyl groups are electron-donating through induction, so they destabilize the enolate intermediate).
- Cyclization (with alkyl halides).
- General form.

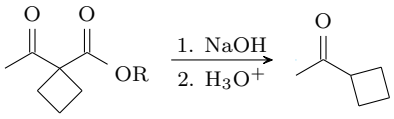


  - We use one equivalent of the dibromide.
- Mechanism.
  - The first three steps are the same as the dialkylation mechanism.
  - The fourth step is that the enolate attacks the other side of the alkyl bromide *intramolecularly* instead of attacking a new molecule.
    - The chelate effect is what prefers an intramolecular attack over an intermolecular attack.
    - There's no such thing as higher rates of collisions than intramolecular.
  - This is highly effective, great chemistry.

- Cyclization (with alcohols).
- General form.



  - This reaction has broad synthetic utility[2].
- Mechanism.
  - The first step takes place as in Figure 9.4 of Labalme (2021) and Figure 8.3 of Labalme (2022b).
  - The second step takes place as in the cyclization of an alkyl halide above, except that tosylate is our leaving group instead of bromide.
- Transforming β-diketoesters to carbonyls.
- General form.



  - We use one equivalent of sodium hydroxide.
- Mechanism.

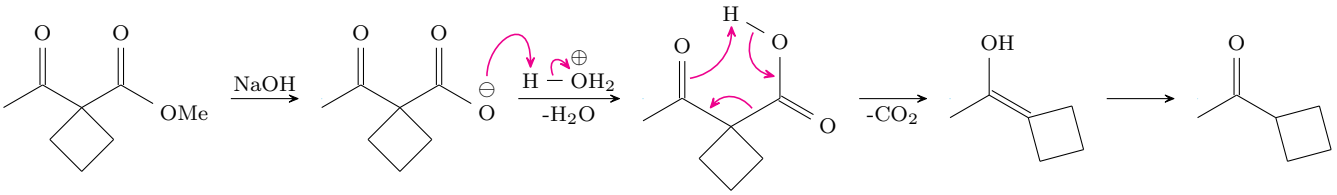
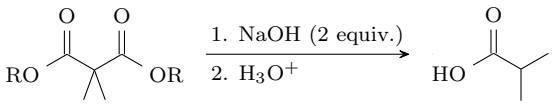


Figure 5.19: Transforming β-diketoesters to carbonyls mechanism.

  - The first step above proceeds via the saponification mechanism to yield a stable carboxylate (under the given conditions).
  - The last step above proceeds via the reverse keto-enol tautomerization mechanism (Figure 4.4 depicts the forward version), as dictated by the principle of microscopic reversibility and with H_3O^+ as the acid.
- Transforming malonates to carbonyls.
- General form.

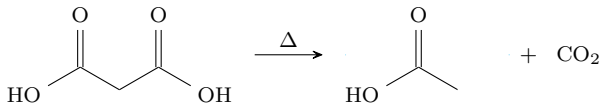


- Mechanism.
  - Double saponification yields a dicarboxylate in the first step.

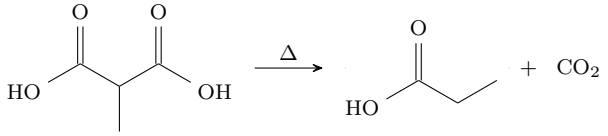
[2] We've learned a lot of reactions that make alcohols. A problem combining those reactions with β-dicarbonyl chemistry via this reactions would be great, in Levin's opinion.

  - From here, we protonate both carboxylates to form a dicarboxylic acid.
  - With free rotation about both α-β axes, one of the carboxylic acids will eventually rotate into a suitable position for step 3 of Figure 5.19 to happen.
  - We will then have a final keto-enol tautomerization.

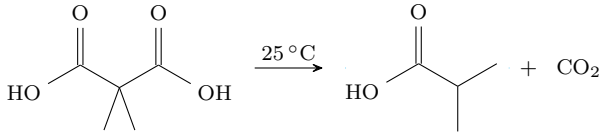
- Malonic acid reactions.



(a) Slowest.



(b) Faster.



(c) Fastest.

Figure 5.20: Decomposition of alkylated malonic acid.

  - When heated, malonic acid decomposes to release CO_2.
  - Its methylated forms, however, react much more quickly. Monomethylation confers a noticeable increase in rate, while dimethylation has the reaction proceed at rapidly at room temperature.
  - The reason for this acceleration is that the carbonyl oxygen and alcohol hydrogen that will react as per Figure 5.19 can freely rotate, but we need them close together before the reaction can happen. Indeed, the methyls squeeze the hydrogen and oxygen together because of their steric clash with the neighboring carbonyl and alcohol groups.

- Since β-diketoester enolates are less basic than normal enolates, they permit α-alkylation of secondary carbonyl compounds, solving problem 1.
- β-diketoesters are still too reactive to work with aldehydes, so they do *not* solve problem 3.
- They do solve problem 2 (regioselectivity), however.

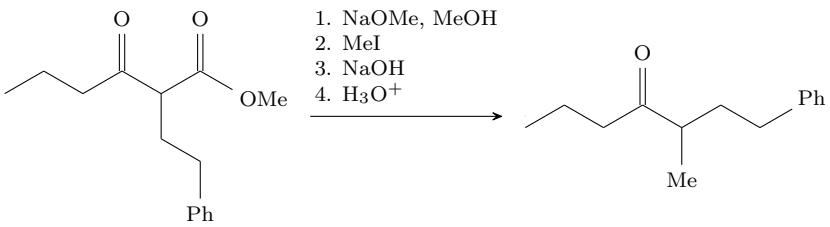


Figure 5.21: β-ketoesters and regioselectivity.

- Suppose we're asked to make the product above from MeI and any other compound(s) of our choosing.
- Performing a retrosynthetic disconnection yields 1-phenylhept-4-one, a carbonyl that would not be regioselective to LDA as discussed last lecture.
- We can, however, start from a β-ketoester, methylate once (steps 1-2), and then remove the ester (steps 3-4) to yield our final product.

- One last regioselectivity tool.

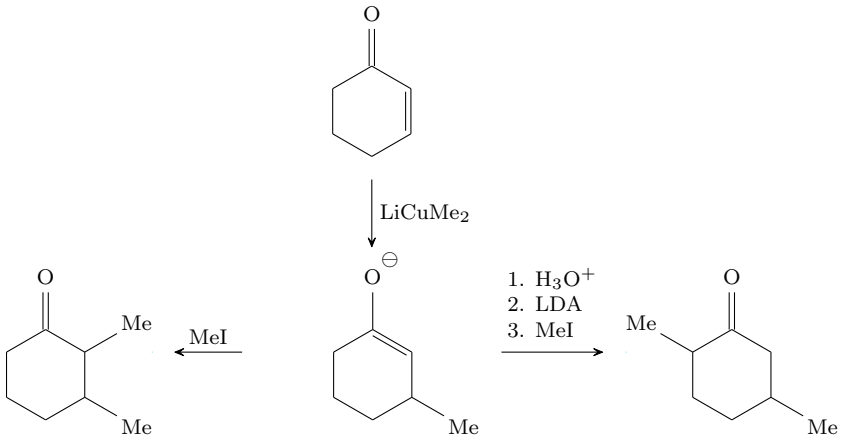


Figure 5.22: Regioselectivity with α, β-unsaturated compounds.

- When adding a cuprate to an α, β-unsaturated compound, 1,4-addition generates an enolate before aqueous workup.
- If we proceed with the aqueous workup and then use LDA, we will selectively deprotonate the less sterically encumbered hydrogens, leading to methylation on the carbonyl's left α-carbon when MeI is introduced.
- If we use the existing enolate, we methylate the carbonyl's right α-carbon when MeI is introduced.

Week 6

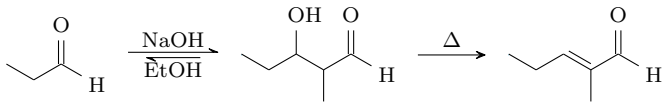
Carbonyl Condensation Reactions

6.1 Carbonyl Condensation Reactions 1

5/3:

- On Tang.
  - Teaching style.
    - For those not headed to organic chemistry grad school, this is you're last hurdle with organic chemistry. Thus, she'll try to make these last four weeks as painless as possible.
    - Additionally, she will always tell us at the beginning of every lecture which sections of Solomons et al. (2016) correspond to what will be covered today, which will be covered next time, and which practice problems we should do.
    - That being said, the class will sometimes go beyond the textbook, and it will also sometimes not cover content that is in the textbook.
    - She will also usually take the first three minutes of class to review last class's material.
  - Research.
    - Runs a chemical biology lab, with a focus on the chemistry of carbonyls and amines.
    - She cares about these functional groups and their reactions not as a way to build complexity but with an eye to how they interact in biological systems, and how we can use their reactions to understand and interpret biology.
  - Questions style.
    - Will try not to integrate reactions from previous quarters with reactions from this quarter.
    - If we want practice problems that integrate everything, look to the suggested book problems.
- Today's lecture content in Solomons et al. (2016).
  - Today: Sections 19.4-19.6 and a bit of 19.1-19.3.
  - Next time: Sections 19.1-19.3 and 19.7-19.8.
  - Practice problems: 19.23-19.37, 19.41-19.44, 19.48.
- The content from today and Thursday completes what we need for both PSet 4 and Midterm 2.
- The course up to this point.
  - Chapters 16-17 were about carbonyl chemistry.
    - These chapters focus on the carbonyl carbon, a great electrophile the reactivity of which varies depending on whether or not a leaving group is present.
  - Chapter 18 was about the acidity of carbonyls' α-hydrogens and the ensuing consequences.
  - Chapter 19 is about combining these great nucleophiles and electrophiles to form new C–C bonds.

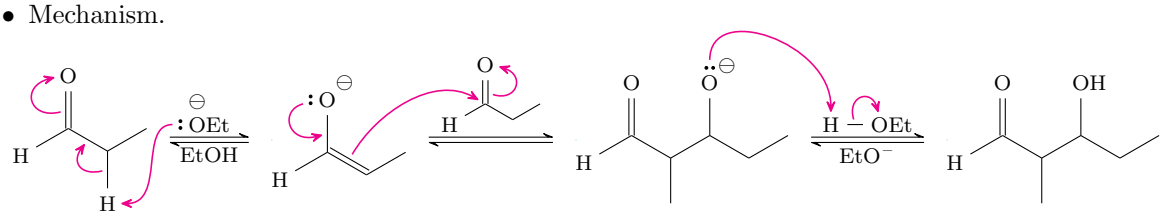
- Tang is dividing this chapter into three parts.
  I. Aldol reactions.
  II. Claisen condensation.
  III. Conjugate addition.
- Today, we will cover the following.
  I. Aldol reactions.
    A. Basic conditions.
    B. Acidic conditions.
    C. Intramolecular ketone reactions.
    D. Cross-aldol reactions.
  II. Claisen condensation.
    A. General reaction.
- **Aldol reaction**: A reaction that (before any heating) produces a product containing both an aldehyde and an alcohol functional group.
- Basic conditions.
- General form.



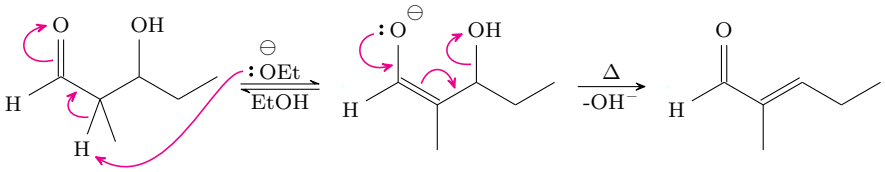
  - NaOH is a stoichiometric reagent.
  - EtOH is a solvent.
  - The full reaction from left to right can be done all at once with heat added from the beginning.
  - Notice that the first molecule (3-hydroxy-1-methylpentanal) has molecular formula exactly double that of the starting material (propanal).

$$2 \times C_3H_6O = C_6H_{12}O_2$$

    - We can easily see where the addition took place by splitting 3-hydroxy-1-methylpentanal along the C2-C3 bond.
  - The third molecule (2-methylpent-2-enal) is just 3-hydroxy-1-methylpentanal, minus a water molecule (H_2O); thus, the overall reaction is an example of a **condensation reaction**.
    - Note that 2-methylpent-2-enal is an α,β-unsaturated compound.
- **Condensation reaction**: A reaction that adds two small molecules together and is usually driven by the loss of some small molecule.
- Mechanism.



(a) Aldol reaction proper.



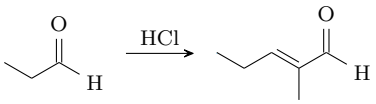
(b) Subsequent dehydration.

Figure 6.1: Basic aldol reaction mechanism.

- Dehydration is irreversible. However, hydroxide is not a very good leaving group, hence why we need heat to accomplish the last step.
- It is evident from the mechanism that two equivalents of aldehyde lead to one equivalent of the condensation product.
- Note that we use these conditions because 80% of the reactions in this chapter follow from the exact same ones. Thus, whenever you want to do a condensation reaction in a problem, it should be easy to remember the appropriate reagents.
  - Hydroxide will work here as the initial base, but it will not work in the Claisen condensation?
  - If asked to predict the products on a problem set, we will see conditions beyond ethoxide (for clarity), even though we almost never need anything else chemically.
- Equilibrium positions of the three steps in Figure 6.1a.
  - First: Slightly to the left (the SM's α-hydrogen has $\mathrm{p}K_\mathrm{a} = 17$ and ethanol's hydroxyl hydrogen has $\mathrm{p}K_\mathrm{a} = 16$; we will favor the weaker acid).
  - Second: Strongly to the right (aldehydes have *very* electron-deficient carbonyl carbons).
  - Third: Neutral (we are reacting an alkoxide with the conjugate acid of an alkoxide [specifically, ethoxide]).
- Adding up the three equilibria, we can see that the reaction favors the products without any additional external driving force.
- In both the first and second parts of this reaction (and hence in the overall reaction, too), ethoxide acts as a catalyst.
  - In Figure 6.1a, we consume one equivalent of ethoxide in the first step, and regenerate one equivalent in the last step.
  - In Figure 6.1b, we consume one equivalent of ethoxide in the first step and generate one equivalent of hydroxide in the last step. However, since hydroxide is a stronger base than ethoxide, it will quickly deprotonate one equivalent of ethanol, regenerating our one equivalent of ethoxide.

- Key points.
  1. For aldehydes, the equilibrium favors the product.
  2. For ketones, the equilibrium favors the reactants.
     - The equilibrium analogous to the first step in Figure 6.1a leans far more strongly toward the reactants for ketones.
     - If you heat the reaction up however, dehydration and Le Châtelier's principle take hold, yielding that product.
- Aldol reactions form two new chiral centers.
  - Consider the C2 and C3 carbons in the product of Figure 6.1a.
  - Thus, some more complicated SMs will yield a stereodivergent synthesis based on the mechanism.
- There is a table on Solomons et al. (2016, p. 859) that focuses on how we can take aldol products to other compounds.

- Acidic conditions.
- General form.



  - Notice that here, we directly get the α,β-unsaturated carbonyl, i.e., we do not need additional heat as with basic conditions.

- Mechanism.

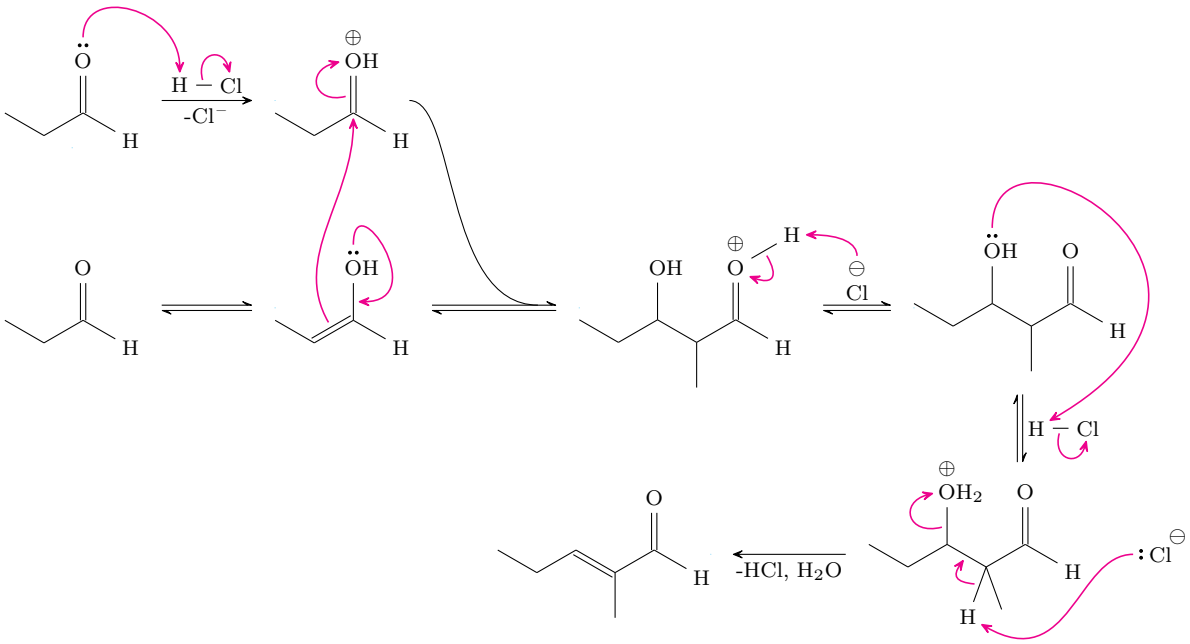


Figure 6.2: Acidic aldol reaction mechanism.

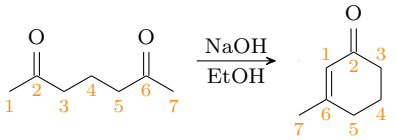
  - The first step is enol formation.
  - We also must preactivate the aldehyde before the enol can react with it.
  - In the last step, since Cl^- is a really crappy base, we have to motivate the leaving group via protonation.
    - Note that the reason that this dehydration reaction is easier than the one under basic conditions is that H_2O is a significantly better leaving group than OH^-.
  - There are many other proposed mechanisms for this reaction, but this is the one that Solomons et al. (2016) uses.

- Acetone will undergo an aldol reaction under acidic conditions even though the first four equilibria will strongly favor the reverse reaction for it. This is because the irreversible dehydration is such a strong driving force.

- A note on testable material.

  - Tang will only use the basic aldol reaction in synthesis/reagent problems; the acidic aldol reaction will only ever show up as a mechanism question.
  - She wants us to know the mechanism because knowing what it takes to get an enol to react is important. However, since we'd only ever really do a basic aldol synthetically, she'll only test us on that.

- Although ketones typically won't react under basic aldol conditions, they may cyclize intramolecularly.
- Intramolecular ketone reactions.
- General form.



  - NaOH and EtOH play the same roles as in the original basic conditions setup.

- Mechanism.

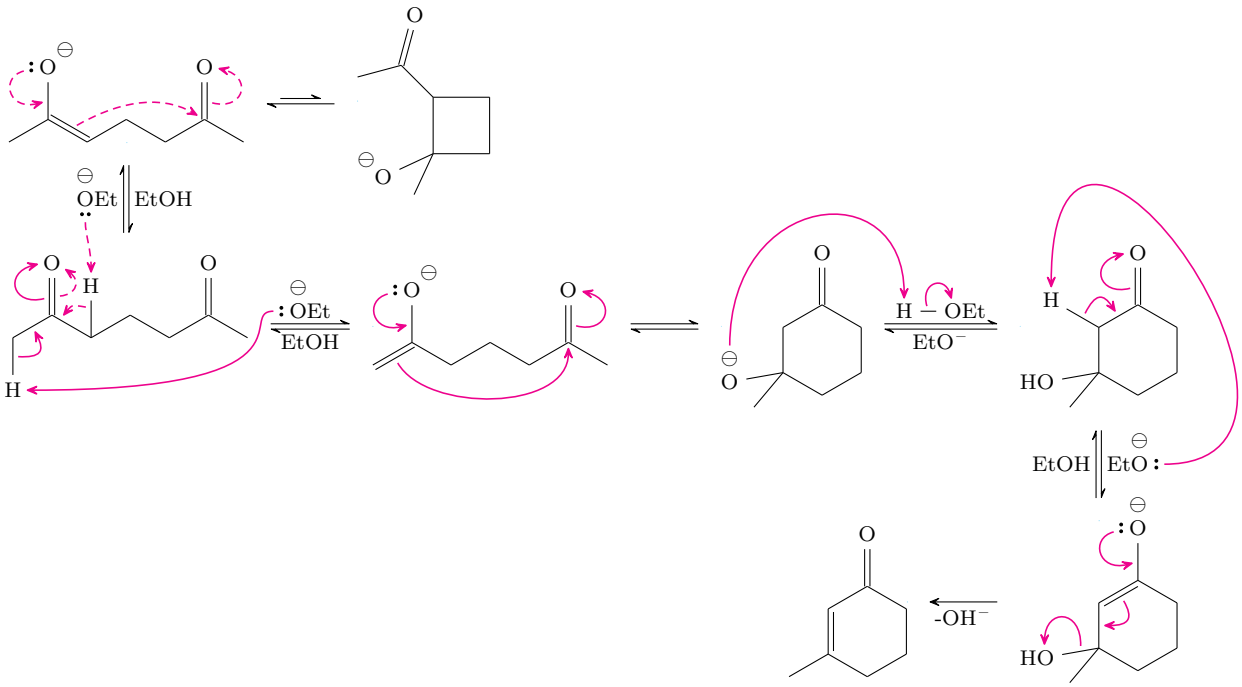


Figure 6.3: Intramolecular ketone aldol reaction mechanism.

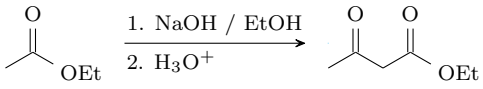
  - The diketone above is symmetric. Thus, it does not matter which side acts as the nucleophile (gets deprotonated) and which side acts as the electrophile (is attacked by the enolate). Therefore, we may WLOG deprotonate the left side of the molecule above.
  - Having chosen a ketone to deprotonate, we realize that there are two types of acidic α-hydrogens.
    - In solution, both will deprotonate.
    - However, at most one of these deprotonations can lead to a stable (5- or 6-membered) ring and thus complete the full reaction.
    - The other reversible pathway *will* occur; the product molecule will just react backwards.
  - Notice that the last three steps are entirely analogous to Figure 6.1b.

- Rules.

  1. You must be able to form a 5- or 6-membered ring for the full reaction to proceed.
  2. The diketone above is symmetric. If given an asymmetric ketone, the less hindered side will act as the electrophile, and the more hindered side will act as the nucleophile.

- Further notes on intramolecular ketone aldol reactions.
  - The above rules are not true all the time, but for the sake of the class, we will assume them to always be true.
  - Rule 2 also applies to aldehydes vs. ketones. The aldehyde portion, if it exists, is by definition less sterically encumbered and therefore will act as the electrophile.
    - The preferential use of aldehydes as electrophiles also squares with their electronics, i.e., that aldehydes are stronger electrophiles since hydrogens are worse electron-donating groups than alkyl groups.
    - Rule 2 is an empirical finding, though.
  - When looking at a cyclization retrosynthetically, break the double bond — the side of the double bond nearer the extant carbonyl will be the α-carbon of the original nucleophilic carbonyl, and the other side will be the carbonyl carbon of the original electrophilic carbonyl.
- **Cross-aldol reaction**: An aldol reaction between two different aldehydes.
  - Cross-aldol reactions are usually not productive: Given two aldehydes, they will yield a stoichiometric mix of all four products.
- Cross-aldol reactions can be useful synthetically in two main ways.
  1. When one SM cannot form enolates.
     - Think benzaldehyde.
  2. When we form stoichiometric enolate and then add the aldehyde.
- Consider the cross-aldol reaction of benzaldehyde and acetaldehyde.
  - Some acetaldehyde enolates will react with more acetaldehyde.
  - We can cut down on this however by mixing the benzaldehyde and base first and then adding acetaldehyde dropwise while stirring.
  - In this latter case, as soon as an enolate forms, it will find that it is surrounded by benzaldehyde, and likely react with it.
- Consider the cross-aldol reaction of cyclohexanone and acetaldehyde.
  - If we stoichiometrically deprotonate cyclohexanone with LDA at $-78\,^\circ\mathrm{C}$ and then add acetaldehyde, the major species will be the alkoxide (but stabilized by a Li^+ countercation).
  - This species is stable until workup.
  - Note that the molecule that we stoichiometrically deprotonate must be a ketone (i.e., not an aldehyde).
    - This is because aldehydes will dimerize, as discussed at the end of Lecture 8.
    - Another possible side reaction is partial nucleophilic acyl substitution by LDA (since aldehydes are so open sterically).
- **Claisen condensation**: A reaction analogous to an aldol reaction that uses esters instead of aldehydes or ketones.
  - Claisen condensations are electronically different from aldol reactions.
    - An ester's carbonyl carbon is less electrophilic than either an aldehyde's or a ketone's.
    - An ester's α-hydrogen is less acidic than either an aldehyde's or a ketone's.
  - Esters also have leaving groups; thus, a secondary deprotonation need not be part of the reaction pathway.
  - Claisen condensations only occur under basic conditions.

- General form.



  - Forms a β-ketoester!

- Mechanism.

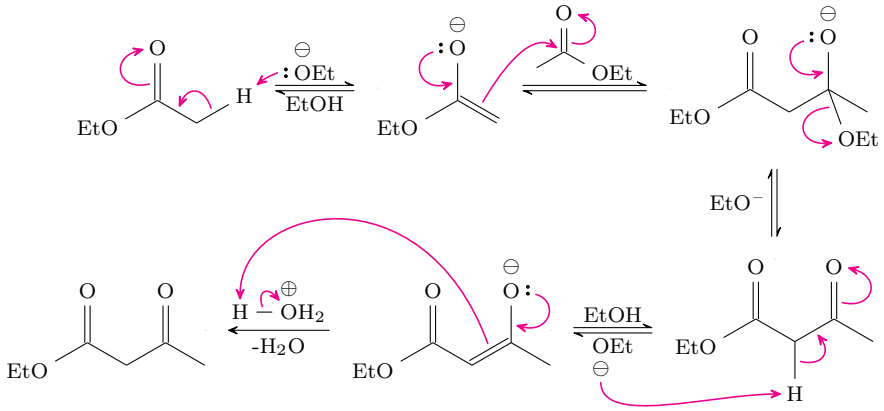


Figure 6.4: Claisen condensation mechanism.

  - The above mechanism diverges from Figure 6.1 in step 3. Here, we kick out the leaving group instead of protonating.
  - Equilibrium positions.
    - First: Strongly to the left (the SM's α-hydrogen has $pK_a = 25$ and ethanol's hydroxyl hydrogen has $pK_a = 16$; we will favor the weaker acid).
    - Second: Strongly to the left (esters are less electrophilic than aldehydes or ketones; the equilibrium position hinges on the electrophilicity of the electrophile).
    - Third: Slightly to the right.
    - Fourth: Strongly to the right (the third intermediate's double α-hydrogen has $pK_a \approx 9$ and ethanol's hydroxyl hydrogen has $pK_a = 16$; we will favor deprotonation in this case).
  - Thus, the fourth intermediate is stable until workup (i.e., is the end result of step 1 in the general form).
  - The role of ethoxide.
    - Ethoxide is a stoichiometric reagent. For every unit of product we form, we need one equivalent of ethoxide and two equivalents of SM.

- An implication of the equilibrium positions.
  - Consider subjecting ethyl isobutyrate to Claisen condensation conditions.
  - Following the mechanism in Figure 6.4, the third intermediate will have two methyl groups where the dual α-proton(s) should be.
  - Thus, the third intermediate will not be able to react forward to the stabilized form and will just react backwards to the starting material.

6.2 Carbonyl Condensation Reactions 2

5/5:

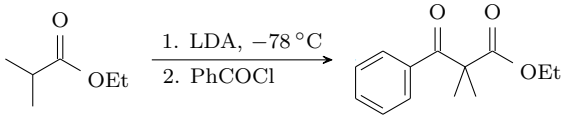
- Today's lecture content in Solomons et al. (2016).
  - Today: Sections 19.1-19.3 and 19.7-19.8.
  - Next time: Additional examples and Sections 20.1-20.4.
  - Practice problems: 19.41-19.48, 19.50-19.51, 19.58-19.59.
- Today will be mostly content and not have very many examples.
  - Tang is primarily concerned with getting us the knowledge we need to do PSet 4 and Midterm 2 today.
  - Next lecture will have a lot of examples.
- Review of last lecture.
- Today, we will cover the following.

II. Claisen condensation.
   B. Cross Claisen condensations.
   C. Intramolecular reactions.
   D. Retro-Claisen condensations.

III. Conjugate addition.
   A. Michael addition.
   B. Robinson annulation.

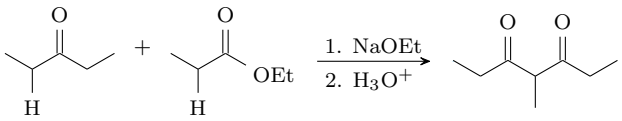
IV. Mannich reaction.

- Cross Claisen condensation.
  - A Claisen condensation between two different esters.
  - As with cross-aldol reactions, these are not usually productive.
- Cross Claisen condensations can be useful synthetically in three main ways.
  1. When one SM has no α-hydrogens.
  2. When we form stoichiometric enolate and then add an acid chloride.
  3. Between esters and ketones.
- An SM without α hydrogens.
  - Similarly to cross-aldol reactions, we can mix the non-enolate-forming species and base first and then add the enolate-forming species dropwise.
  - When given a synthesis problem, we don't have to highlight this fact; we will assume that we use the proper experimental technique.
  - Liberating CO_2 from a β-diketoester: NaOH then H_3O^+ *or* H_3O^+ and heat.
- Claisen condensations with acid chlorides.
- General form.

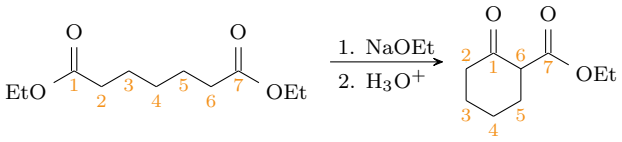


  - This reaction will not be tested; it's just for our own understanding of the fact that this is possible.

- Claisen condensations between esters and ketones.
- General form.



- Mechanism.
  - The mechanism is entirely analogous to Figure 6.4, except that we form a ketone enolate instead of an ester enolate.
  - The ketone forms the enolate since its α-hydrogens are much more acidic.
  - Why we don't have other cross Claisen condensations.
    - Ketone-ketone: As with ketone-based aldol reactions, these will not happen under basic conditions because we lack the driving force.
    - Ester-ketone: Same reason as above, plus the additional issue that ester enolates are harder to form.
    - Ester-ester: Again, the issue here is that ketone enolates form much more readily.
- Tang postulates that acid and heat is the way to liberate CO_2 from β-ketoesters?
- Intramolecular (Dieckmann) reactions.
- General form.



- Mechanism.
  - The mechanism is entirely analogous to Figure 6.4. As drawn, we deprotonate C6, and then the enolate on the right attacks the ester on the left.
- Asymmetric diesters.

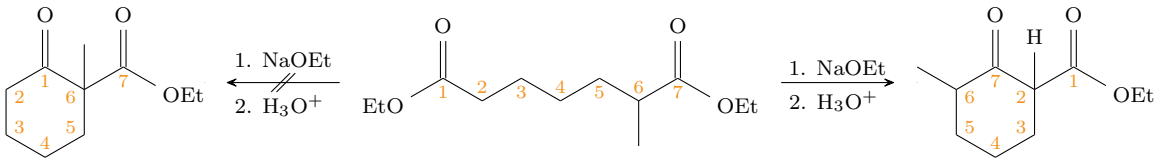
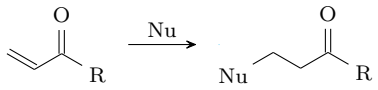


Figure 6.5: Asymmetric diesters in the Dieckmann condensation.

  - As a general rule, the more substituted side acts as the electrophile and the less substituted side acts as the nucleophile.
  - Even though the more substituted enolate is more thermodynamically stable and thus will form more readily, the product it leads to (left above) is much less stable.
    - From a mechanistic point of view (see Figure 6.4), we must form the species that still has a middle α-hydrogen (i.e., the one like the right species above).
    - This is so that we can deprotonate and create an enolate that will be stable until workup.
  - Recall that only rings of size 5-6 are stable.

- Retro-Claisen condensations.
  - Suppose we subject a β-diketoester to Claisen condensation conditions (e.g., excess EtO^-).
  - If there is a middle α-hydrogen, we will preferentially deprotonate and form a stable enolate until workup.
  - If there is *not* a middle α-hydrogen, EtO^- can add into the ketone, forming intermediate 2 of Figure 6.4. From here, we can react backwards to intermediates 2 and then the starting material.
    - The arrow pushing for the reverse is the exact opposite of the forward version, as per the principle of microscopic reversibility.
  - Note that β-ketoesters of all kinds are perfectly stable in ethanol or acid workup conditions; it is just that dimethyl substituted ones will decompose under Claisen condensation conditions.
    - Stated another way, if you put either ethyl acetate or its Claisen condensation product under NaOEt, we will get the Claisen condensation product. However, if we put either ethyl isobutyrate or its Claisen condensation product under NaOEt, we will get the ester.
    - Tang will give more examples next lecture.
- Conjugate addition.
- Tang draws three resonance structures for an α,β unsaturated compound: One neutral, the next one with the C=O bond shifted up onto the oxygen (positive carbonyl carbon), and the next one with the double bond flipped (positive β carbon).
  - This justifies why 1,2- and 1,4-addition happens at the carbons they do.
- General form.



  - The overall picture looks like we added HNu to the double bond, but mechanistically, this reaction will nor proceed without the presence of the carbonyl.
- Mechanism.

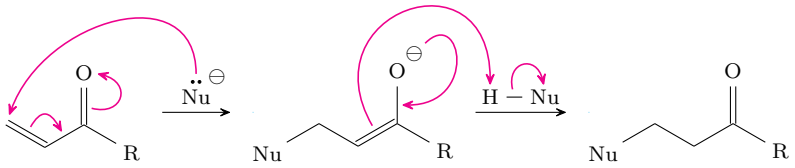
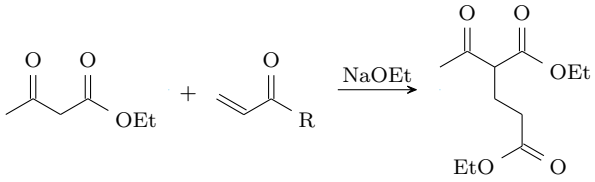


Figure 6.6: Conjugate addition mechanism.

- Review.
  - Reagents that do 1,2-addition: Lithiates, Grignards (mostly), and $LiAlH_4$.
  - Reagents that do 1,4-addition: H_2O, R–SH, RNH_2, CN^-, and R_2CuLi.
- **Michael addition**: Conjugate addition with an enolate serving as the nucleophile. *Also known as* **1,4-addition**, **Michael-type addition**.
- General form.



  - The product is a 1,5-dicarbonyl, or **Michael**.

- Mechanism.
  - We deprotonate the β-ketoester in the middle to form an enolate, which then attacks the α,β unsaturated compound as in Figure 6.6.
  - The key point here is that the β-ketoester will form the nucleophile since its double α-proton is more acidic than the enone's.

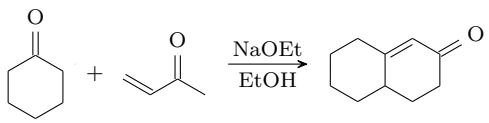
- Compounds that can serve as Michael donors and acceptors.
  - Acceptable donors: Ketones and esters yield an enolate under basic conditions.
  - Unacceptable donors: Aldehydes.
    - We will get an aldol reaction.
  - Acceptable Michael acceptors: α,β-unsaturated ketones, aldehydes, esters, nitriles, nitros, and alkyl amides.
  - Unacceptable Michael acceptors: α,β-unsaturated carboxylic acids, hydrogen amides, and acid chlorides.
    - We get initial deptotonations in basic media, or nucleophilic acyl substitution followed by deprotonation.

- We will only consider enolate-based Michael reactions in this class; in reality, Michael additions can proceed in acidic media, too, but that's beyond the scope of this class.

- **Annulation**: A ring-forming reaction.

- Robinson annulation.

- General form.



  - A one-pot reaction of Michael and aldol.
  - Methyl vinyl ketone (MVK) is a key reactant in Robinson annulations.

- Mechanism.

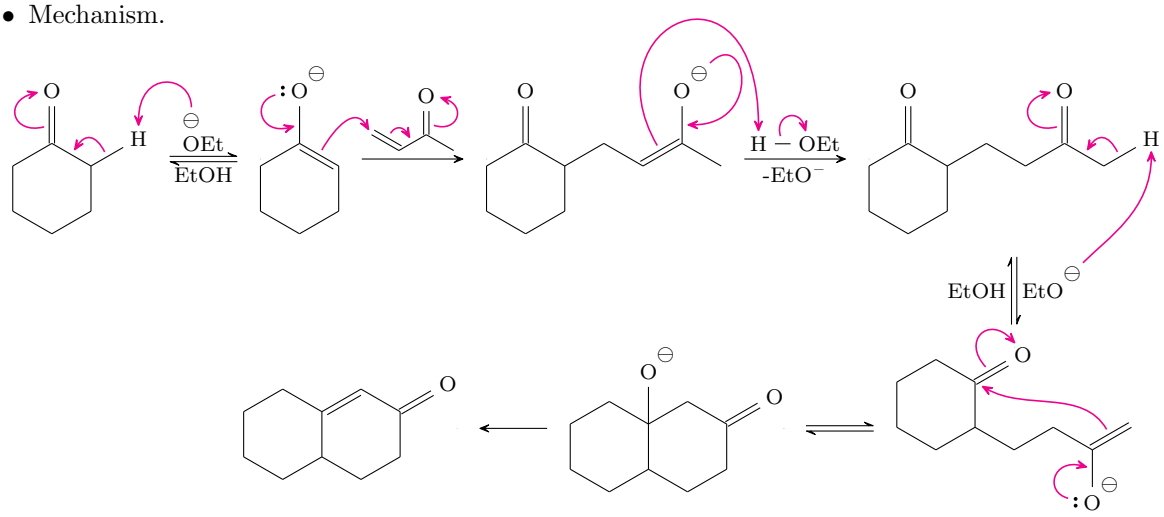
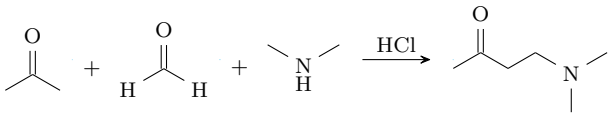


Figure 6.7: Robinson annulation mechanism.

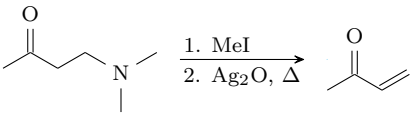
  - In this class, we assume that Michael reactions are irreversible; in reality, this is not always the case.
  - The last step is accomplished in an analogous manner to the last three steps of 6.3.
  - Tang will give more examples next lecture

- Note that Robinson was a Nobel laureate, but not for this.
- Retrosynthetic analysis.
  - Break the double bond first.
  - Then break four carbons away to recover MVK.
- Mannich reaction.
- General form.



  - The key components here are (1) a ketone, (2) an aldehyde (typically formaldehyde), (3) a *secondary* amine, (4) acidic conditions, and (5) the ability to drive off H_2O.

- Mechanism.
  - The first step is forming an iminium ion (a great electrophile; even better than formaldehyde because it's positively charged).
  - The second step is converting the ketone to an enol.
  - The enol then attacks the iminium ion and we deprotonate.
- Why we need a secondary amine.
  - If we use a primary amine, the product can react again.
  - This can be useful synthetically, but those applications are beyond the scope of this course.
    - For example, asymmetric secondary amines can tune the selectivity of the whole reaction.
- A reaction of a quaternary ammonium salt[1].



  - Nitrogen attacks MeI to form an NMe_3R^+ species. It is this molecule that reacts with silver oxide.

- Formaldehyde does not participate in aldol reactions.
  - This is because it exists as a hydrate in aqueous solution and thus cannot serve as an aldol electrophile.
  - Thus, if we want to prepare MVK, we cannot go through acetone and formaldehyde directly; we need the Mannich reaction followed by the above quaternary ammonium salt elimination.

[1] This is the Hofmann elimination. See Week 8, Lecture 1.

Week 7

Intro to Amines

7.1 Amines 1

5/10:

- Today's lecture content in Solomons et al. (2016).
  - Today: More examples for Chapter 19 and Sections 20.1-20.3.
  - Next time: Sections 20.4, 20.12, and 20.6-20.7.(review).
  - Practice problems: None.
- The exam format will be the same as Midterm 1; the difficulty will be decreased.
- Tang thinks that Chapter 19 is the hardest chapter in Organic Chemistry III.
- Problem set 4 incorporates real reactions from the literature!
- Review of Chapter 19 content.
  - Many good examples/tables/charts/summaries.
  - Carbonyl condensation calling cards.
    - A 1,3-dioxygen setup comes from a condensation reaction (aldol or Claisen).
    - Similarly, the Mannich reaction yields a 1,3-diheteroatom setup.
    - A 1,5-dioxygen setup comes from conjugate addition.
    - A cyclohexenone group comes from Robinson annulation.
  - The only alkoxide bases we will ever see for the Chapter 19 reactions are ethoxide or methoxide.
    - NaOH / EtOH and NaOEt / EtOH are equivalent conditions.
  - A trick for drawing cyclized molecules from linear molecules: The enolate side does not change.
    - For an aldol reaction, the enolate side will be the one that kept the carbonyl.
    - For a Claisen condensation, the enolate side will be the one that kept the ester.
  - Mechanics of the retro-Claisen.
    - The lack of a middle α-hydrogen implies that the ketone carbonyl carbon is much more reactive. In other words, if the ethoxide base is not attracted to an electrophilic, acidic proton, it is more likely to be attracted to the electrophilic carbonyl carbon.
    - Once ethoxide adds in, it can definitely be kicked back out again. However, we will only draw the productive route, i.e., that in which the next step is breaking the C$-$C bond.
    - Always look out for forward Claisens after performing a retro-Claisen (we are still under Claisen condensation conditions)!
    - As a particular example, if we subject the leftmost molecule in Figure 6.5 to NaOEt / EtOH, the final product will not be the middle molecule but the rightmost molecule.

  - Claisen condensation special/tricky cases.
    - A Claisen condensation will proceed with most any *single* R group on the α-carbon of the ester; in particular, we need not just have a methyl group there, but can also have bigger things, like isopropyl groups. Issues only arise when we have *two* R groups on the ester's α-carbon.
    - Ethyl cyclohexanecarboxylate cleverly disguises double R groups on the α-carbon as a ring. Regardless, if we can correctly identify it, we will see that it will only react via protonation/deprotonation under Claisen condensation conditions.
    - Claisen condensation products that can perform a retro-Claisen can sometimes continue to react in another forward Claisen. However, in such cases, we find that the retro-Claisen is preferred. There will always be a bunch of background reactions, but what determines the major product is still thermodynamics (i.e., what the most stable product is).

- Motivating Chapter 20.
  - Amines are very important in chemistry, biochemistry, and pharmaceuticals.
  - We have simple 1°, 2°, and 3° amines in chemistry.
  - In biology, amines appear in nucleotide base pairs, peptides, amphetamines, etc.
  - Amides are the least reactive (neutral) carboxylic acid derivative.

- Acid/base properties of amines.
  - Amines are our first basic functional group.

- Tang is dividing this chapter into three parts.

  I. Properties of amines.
  II. Preparation of amines.
  III. Reactions of amines.

- Today, we will cover the following.

  I. Properties of amines.
     A. Structure.
     B. Acid-base properties.

- Draws a 3D hybridized amine structure and discusses the stereochemical inversion of amines about the nitrogen center.
  - Chirality cannot be stabily maintained.
  - For the umbrealla flip, $E_a = 6\,\text{kcal}\,\text{mol}^{-1}$.
    - Recall that this is very much on the same order of magnitude as rotation from eclipsed to staggered to eclipsed in ethane (that transformation has an activation barrier of about $3\,\text{kcal}\,\text{mol}^{-1}$).
    - Note that any reaction with $E_a < 25\,\text{kcal}\,\text{mol}^{-1}$ can proceed at room temp.
    - This reaction is far below that barrier, so it proceeds readily. Perhaps we could isolate amines in one conformation at lower temperatures, though?
  - With all four substitutions different, nitrogen behaves like a carbon and does not stereoinvert.

- Acid-base properties.

- Amines are not that strong but *tend* to be good bases.
  - We say "tend" because there are cases where amines are not basic.

- Quantifying the basicity of amines.
  - We use the pK_a of the protonated amine.
  - This is so that we can consider RNH_2 species picking up a new proton (as desired). If we were to consider pK_a(RNH_2), we would be discussing that species losing a proton (or RHN^- picking up a proton).
- Simple amines have p$K_a \approx$ 9-10.
  - HCl has p$K_a = -7$.
  - BuH has p$K_a = 50$.
- Example amine pK_a's.
  - NH_3 has pK_a(NH_4^+) = 9.24.
  - $MeNH_2$ has pK_a($MeNH_3^+$) = 10.62.
    - This pK_a is higher because methyl groups are electron donating, so they make the nitrogen more nucleophilic.
  - $PhNH_2$ has pK_a($PhNH_3^+$) = 4.6.
    - The nitrogen lone pair participates in resonance with the phenyl group.
    - Thus, it is sp^2 hybridized.
    - Another consequence of this resonance/hybridization is that the whole molecule will be planar. From an orbital perspective, this promotes facile resonance among all seven p orbitals. This also presents an activation barrier to free rotation about the C–N bond.
    - The overall effect is that since the nitrogen's lone pair is delocalized into the π system and held closer to the nucleus via the sp^2 hybridization, it is less basic.
  - Substituted anilines.
    - EWGs on the ring lower pK_a.
    - EDGs on the ring raise pK_a.

Week 8

Amine Reactions and Carbohydrate Structure

8.1 Amines 2

5/17:

- Midterm 2.
  - Scores back after class.
  - Request a regrade (of your whole exam) ASAP if needed.
  - Raw score: 56 ± 24 (median 59).
  - Range: 0-99.
  - Adjusted: 70 ± 10.
- Today's lecture content in Solomons et al. (2016).
  - Today: Sections 20.4, 20.12, and 20.6-20.7.
  - Next time: Sections 22.1-22.2, 22.9A.
  - Practice problems: 20.19-20.24, 20.26, 20.34-20.36.
- Review of last lecture.
  - Basicity of amines.
  - Higher $pK_a(RNH_3{}^+)$ means more basic RNH_2.
  - Key: How willing is N to share its lone pair.
- Today, we will cover the following.

I. Properties of amines.
   B. Acid-base properties (cotd.).

II. Preparation of amines.
   A. Alkylation.
   B. Reduction.
   C. Hofmann rearrangement.
   D. Curtius rearrangement (review).

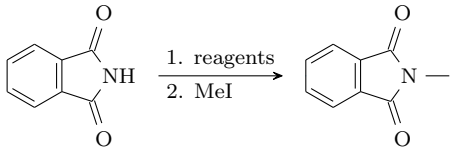
III. Reactions of amines.
   A. Hofmann elimination.
   B. Cope elimination.

- Acid-base properties (cotd.).
- Additional example amine pK_a's.
  - Py has p$K_a(PyH^+) = 5.3$.
    - Its basicity is intermediate between NH_3 and $PhNH_2$ due to its sp^2 hybridization.
  - Pyrrole has p$K_a(RH^+) = 0.4$.
    - Since nitrogen's lone pair here is fully incorporated into the aromatic system, it is not basic.
    - In fact, pyrrole has p$K_a(R) = 16.5$.
    - This means that its amine hydrogen is actually mildly acidic (about equivalent to ethanol's hydroxyl hydrogen).
  - Indole (left to us).
    - Indole is like pyrrole: To have $4n + 2$ aromatic electrons, it needs nitrogen's lone pair.
  - See the Aromaticity 2 lecture from Labalme (2022b) for more on aromatic pK_a's.
  - Amides.
    - An amide will coordinate a proton at its oxygen, not its nitrogen.
    - This protonated species will have p$K_a = 0$.
    - The reason for coordination at oxygen is that the resonance structure with a negative charge on oxygen makes a significant contribution to the overall molecule (oxygen is more electronegative than nitrogen). In fact, this resonance structure implies that the C–N bond in an amide is not rotatable, and thus the six atoms C–C(=O)–NH_2 are coplanar.
    - Additionally, the nitrogen protons are slightly acidic with p$K_a(RNH_2) = 18$.
    - Hence, if we react an amide with a Grignard, we will deprotonate the NH_2 portion.
- A note on how protonation can be used to isolate amines (and other basic species) when synthesizing them in the lab.
  - Begin by protonating the amines and performing an extraction.
  - The protonated amines will be attracted to the polar aqueous layer and all other organic compounds can be separated out with the organic layer.
  - Then we can deprotonate to recover our desired amines.
- Preparation of amines.
- Alkylation (direct).
- General form.

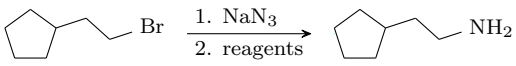
$$NH_3 \xrightarrow[2.\ NaOH]{1.\ MeI} MeNH_2$$

- Mechanism.
  - The first step proceeds via an S_N2 mechanism to yield a quaternary ammonium salt.
  - The second step (a basic workup) removes one of the three nitrogen protons, yielding $H_2O + NaI$ as side products.
- Problems with direct alkylation:
  - Even before the basic workup, we have base in solution (NH_3). This base can accomplish the second-step deprotonation, introducing $MeNH_2$ into our initial reaction mixture.
  - But adding alkyl groups (EDGs) creates more reactive amines, so $MeNH_2$ will preferentially attack CH_3I compared with NH_3.
  - Thus, with direct alkylation, we cannot stop at one particular stage; we will always get a mixture of NH_3, $MeNH_2$, Me_2NH, Me_3N, and Me_4NI.

- One potential solution.
  - In some cases, we can use excess amine and a bulky alkyl halide.
  - For example, mixing approx. 20 equivalents of $MeNH_2$ with BnCl yields fairly pure BnNMeH.
- Alkylation (Gabriel synthesis).
- General form.

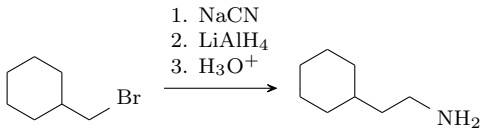


  - The Gabriel synthesis prepares primary amines.
  - The starting material is called **phthalimide**.
  - Reagents is either NaH (nice because it liberates $H_{2(g)}$ as an additional driving force) or K_2CO_3 (nice because it's not as strong as NaH).
- **Phthalimide**: A 2° amine, the lone hydrogen of which has has $pK_a = 8.3$ since it is subject to *two* EWG carbonyls and additional resonance with the aromatic ring. *Structure* see above left.
- Mechanism.
  - The first step is a deprotonation.
  - The second step proceeds via an S_N2 mechanism.
    - Thus, we preferentially use it in conjunction with primary alkyl halides.
    - Secondary, allylic, and benzylic alkyl halides will work.
    - An attempt to run this reaction with a tertiary alkyl halide will lead to elimination.
  - Notice that the product is a 3° amide and thus cannot react any further.
- There are three ways to recover the primary amine from the product above.
  1. Use H_2SO_4, H_2O, and heat.
     - This amide hydrolysis proceeds analogously to the last several steps of Figure 2.12.
     - A subsequent deprotonation of $MeNH_3^+$ will be required.
  2. Use NaOH, H_2O, and heat.
     - This amide hydrolysis proceeds analogous to the saponification mechanism.
  3. Use H_2NNH_2 and reflux.
     - See Solomons et al. (2016) for the mechanism.
- Reduction.
  - This method of preparation can proceed from a number of starting materials.
- From azides.



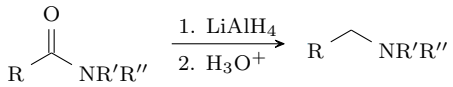
  - Begin with the desired alkyl group as an alkyl halide.
  - React it with an azide nucleophile via an S_N2 mechanism.
    - Azide is one of the few nucleophiles that is a very poor base, so it is very good for S_N2.
  - Reagents is either $LiAlH_4$ followed by an acidic workup or hydrogenation ($H_2 + Pd/C$).

- From nitriles.



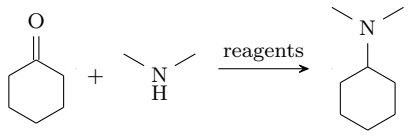
  - Take the desired alkyl group, S_N2 it with a cyanide nucleophile, and then reduce with $LiAlH_4$ as in Chapter 17.
  - Notice that this reaction adds an extra carbon before the amide, unlike with azides.

- From amides.



  - This is a review reaction; see the discussion associated with Figure 3.4.

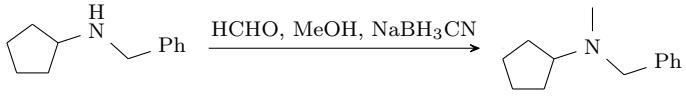
- From iminium ions (reductive amination).



  - This is a very useful reaction in the pharmaceutical industry.
  - Depending on the reagents, we can accomplish this reaction in a stepwise fashion or all at once.
  - Stepwise reagents.
    - Use mild H^+ followed by a mild hydride source, such as $NaBH_4$.
    - In the first step, we create an enamine in equilibrium with the corresponding iminium ion.
    - In the second step, hydride attacks the iminium ion's carbon, leading to the final product.
  - This set of reagents explains the name of the reaction: It is *amination* because we are replacing an oxygen with a nitrogen and *reductive* because we are reducing the iminium ion's double bond.
  - If we use these reagents, we must (in theory) perform the reaction stepwise because $NaBH_4$ can reduce any unreacted ketone.
    - In reality, there is a trick we can use to do this reaction all at once with these reagents.
  - One-step reagents.
    - Use sodium cyanoborohydride ($NaBH_3CN$) in alcoholic solvent (EtOH or MeOH).
  - $NaBH_3CN$ is a weaker hydride source (cyano groups are EWGs), so it can't react with the ketone because it's not electrophilic enough (the charged iminium ion is much more electrophilic).

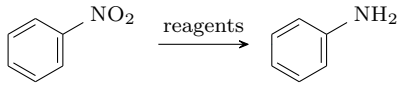
- Reductive amination describes the above reaction of a relatively complicated ketone with a relatively simple amine. If we use, instead, a relatively simple ketone and a relatively complicated amine, the reaction is called...

- Reductive alkylation.

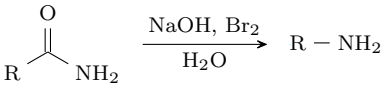


  - Remember that HCHO is formaldehyde, which is our carbon source here.

- Reductive amination/alkylation can be more controlled than alkylation.
  - This is because with alkylation, our final 3° amine could still form a quaternary ammonium salt in the presence of excess MeI.
  - However, a 3° amine can never form another iminium ion.
- From nitro groups.



  - Reagents is $H_2 + Pd/C$, $Fe + HCl$, or $Zn(Hg) + HCl$.
- Hofmann rearrangement.
- General form.



  - Whereas with azides and amides kept the number of carbons constant and nitriles added a carbon, here we lose a carbon.
  - This reaction is similar to the Curtius rearrangement.
  - The conditions are identical to those used in the haloform reaction, and we will see that there are homologies in the mechanisms, too.
- Mechanism.

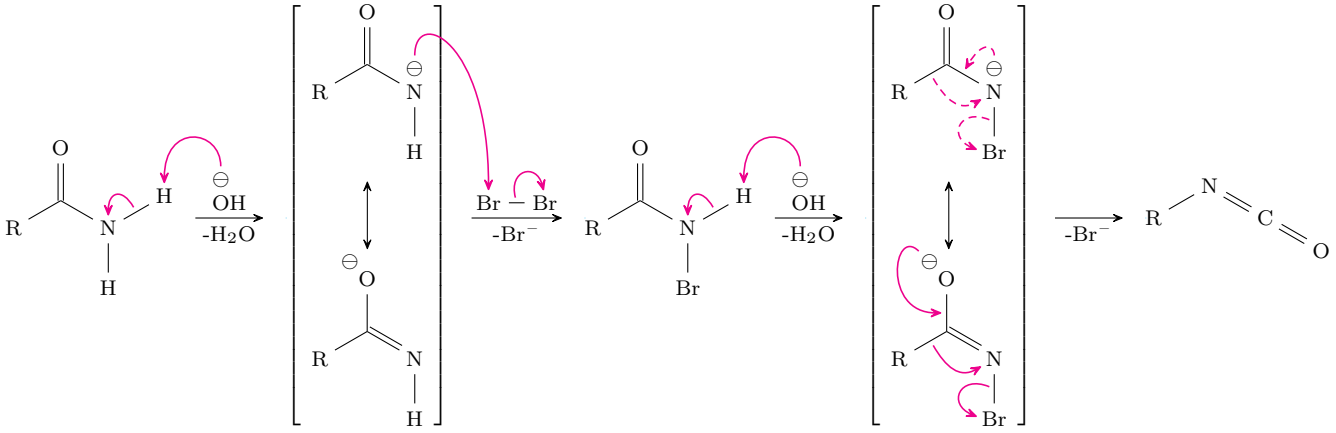


Figure 8.1: Hofmann rearrangement mechanism (isocyanate formation).

  - Many of these reactions are reversible, but the equilibria are not that important here.
  - The first two brominations proceed analogously to those in Figure 4.8.
    - Recall that the second bromination happens more readily because having bromine (an EWG) on the nitrogen makes the remaining hydrogen more acidic.
  - There are two possible rearrangement mechanisms after this for forming the isocyanate.
    - The two proceed from different resonance structures.
    - The one drawn in dashed lines is advocated for by Solomons et al. (2016). In it, the *nitrogen* lone pair kicks in, the alkyl group migrates to the nitrogen, and bromine leaves.

    - The one drawn in solid lines is advocated for by Tang. In it, the *oxygen* lone pair kicks in, the alkyl group migrates to the nitrogen, and bromine leaves.
    - Tang will accept either on a test despite her preference for the latter.
  - Once we have an isocyanate, we remove it exactly as in Figure 3.13b.
    - The NHCOOH intermediate (intermediate 2 in Figure 3.13b) is a **carbamic acid**.
    - A possible intermediate between intermediate 1 and the carbamic acid is a resonance form of the former wherein we have kicked the oxygen lone pair in and used the double bond to create a lone pair on nitrogen, negatively charging it.
    - Note that Solomons et al. (2016) uses a simplified mechanism for these first two steps (isocyanate to carbamic acid). Therein the hydroxide attacks the isocyanate carbon and kicks the N=C electrons back onto nitrogen, forming the negatively charged nitrogen intermediate described above in one go. From here, the negative nitrogen can attack water to form the carbamic acid.
    - The mechanism of Solomons et al. (2016) is inaccurate, though, because when displaced the electrons will preferentially move toward the more electronegative oxygen.
    - Regardless, both mechanisms will be accepted as correct in this course.
  - Other comments.
    - Whereas we can isolate the isocyanate intermediate in the Curtius rearrangement, the conditions of the Hofmann rearrangement are such that it will continue reacting immediately upon being formed.
    - Even though CO_2 is released by this mechanism, we will not observe bubbling in the reaction mixture because the gas is absorbed by the basic media.
    - Overall, we form isocyanate and then perform two consecutive types of nucleophilic acyl substitution.

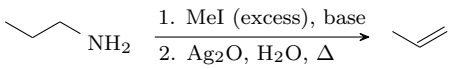
- An advantage of the Hofmann rearrangement is that it maintains the chirality in the R group.
  - In particular, we preserve the chirality at the carbon that ends up being α to the amine.
  - This differs from any of the reductive pathways that use S_N2, for instance.

- Comments on the Curtius rearrangement.
  - In the first step, heat is used to transform the (relatively stable) acyl azide into the isocyanate and liberate N_2 gas.
  - This detail was not mentioned in Lecture 6 and is not shown in Figure 3.13a.
  - You can hydrolyze the isocyanate with alcohol instead of water, leading to different products. We will explore this in PSet 5.

- Reactions of amines.

- Hofmann elimination.

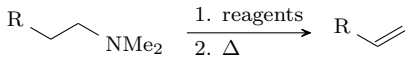
- General form.



  - This reaction solves the problem of how to turn NH_2 into a good leaving group so that we can eliminate it.
  - Example bases are NEt_3 or a NaOH pellet (it doesn't even have to be dissolved).
  - Yields the non-Zaitsev product[1] (less substituted alkene).

[1] This is why Mrs. Meer introduced the Zaitsev v. Hofmann product!

- Mechanism.
  - The first step makes the amide NH_2^- into a good leaving group by transforming it into a quaternary ammonium salt.
  - The second step causes the elimination. How it works centers around the dual role Ag_2O serves.
    - First, it relinquishes a silver cation to precipitate the iodide anion of the ammonium salt[2].
    - Second, the remaining AgO^- species acts as a strong bulky base.
- If we use a non-Hofmann elimination base (e.g., NaOEt) after forming the quaternary ammonium salt, then we get a mix of products with the Zaitsev product as the major product.
- Cope elimination.
- General form.



  - Reagents is mCPBA or H_2O_2.
  - We need heat around 150 °C in the second step.
- Mechanism.

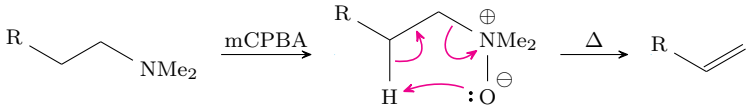


Figure 8.2: Cope elimination mechanism.

  - A concerted second step; hence, this is syn elimination.
- The Cope elimination is regioselective.

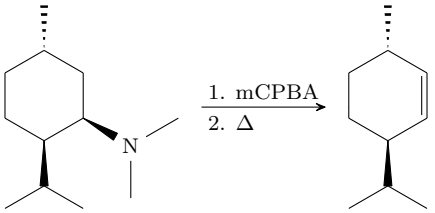


Figure 8.3: Cope elimination regioselectivity.

  - The hydrogen and oxygen need to be able to align (i.e., in the transition state). Thus, if they cannot, we will not get elimination there.
  - Guiding principle: The proton that you pull off has to point in the same direction as the nitrogen.

8.2 Carbohydrates 1

5/19:
- Today's lecture content in Solomons et al. (2016).
  - Today: Sections 22.1-22.2 and 22.9A.
  - Next time: Sections 22.3-22.4, 22.6-22.7, and 22.9B. Read Sections 22.10-22.11.

[2]Silver and iodide ions preferentially bond because of the HSAB principle from Labalme (2022a).

  - Practice problems: 22.21, 22.24, 22.28, 22.30.

- At this point, we have learned 98% of all of the reactions we'll learn for Organic Chemistry III.
  - We'll see some new reactions in this chapter, but they're all fairly obvious mechanistic analogues of previous reactions.
- Review of last lecture.
  - You don't need to be able to identify major and minor Cope elimination products for this course, just which ones can form and which ones cannot form.
- **Hydrolysis**: The addition of a water molecule to the starting material and subsequent breaking of some bond.
- **Alcoholysis**: The addition of an alcohol molecule to the starting material and subsequent breaking of some bond.
  - Note that neither hydrolysis nor alcoholysis has to involve the formation of two products from one SM (i.e., they don't need the bond broken to have been the only one holding two molecular fragments together).
- Tang is dividing this chapter into two parts.

  I. Names, structures, and properties.

  II. Reactions.
- Today, we will cover the following.

  I. Names, structures, and properties.

    A. Definitions.

    B. Structures.

  II. Reactions.

    A. Kiliani-Fischer synthesis.
- The following, up until stated otherwise, is not testable material.
- **Carbohydrate**: Sugar molecules, both simple and complicated.
- The etymology of the term, "carbohydrate."
  - Before NMR and other characterization methods, chemists determined the molecular formulas of compounds by burning them and measuring how much O_2 is consumed, how much CO_2 is formed, and how much H_2O is formed.
  - For a certain class of compounds, they determined that the formulas are of the form $(CH_2O)_n$.
  - Since these compounds all have a $1:1$ ratio of carbon to water, i.e., their unit structure is a carbon hydrate, chemists chose the name *carbohydrate*.
- The number of degrees of unsaturation of a simple sugar.
  - We can discount oxygen from the empirical formula, learning that the simple sugar $(CH_2O)_n$ has the same number of degrees of unsaturation as the hydrocarbon C_nH_{2n}.
  - Thus, since a fully saturated hydrocarbon has empirical formula C_nH_{2n+2}, we know that a simple sugar has *one* degree of unsaturation.
- Photosynthesis and cellular respiration.
  - Plants can synthesize glucose from carbon dioxide and water.

        - They us an additional special organelle with chlorophyll.
        - The energy source is sunlight.
        - Plants can also burn glucose for energy.
    - Humans cannot synthesize glucose from simpler molecules.
        - We can synthesize more complicated carbohydrates from glucose, however.
        - We solely burn glucose for energy, producing ATP and heat.

- Function of carbohydrates.

    1. An energy source for humans.
        - We can digest glucose.
        - We can also digest a number more types of sugar, e.g., sucrose (table sugar), starch (from bread), and maltose.
        - There are types of sugar that we cannot digest, e.g., cellulose.
            - Cows and sheep can digest cellulose, however, thanks to specialized bacteria in their gut.
        - The reason for the difference in digestibility between starch and cellulose hails from the type of linkage used between the sugar monomers.
    2. Other roles.
        - Structure materials (cellulose is structural in cell walls).
        - Components of nucleic acids (think ATP, as well as the sugar-phosphate backbone of DNA).
        - Many others (the following are a few specific examples).
            - The core structure of vitamin C.
            - Mediation of antibody-antigen recognition.

- Linus Pauling and vitamin C.

    - A great chemist who won (solo) the Nobel Prizes for both chemistry and peace.
    - Every day, he consumed multiple grams of vitamin C — he believed it would slow the aging process.
    - Pauling did live to 93, but one wonders if he would have lived a lot longer without such a surplus of vitamin C.
    - Modern-day vitamin doses.
        - We slightly overdose to compensate for the fact that only part of the dose will be absorbed.
        - As a particular example, shortly after taking a dose of vitamin B, your urine will become bright yellow and have a special smell. This is the excess being flushed out of your body.

- Antibody-antigen recognition.

    - This is the most important role of sugars in our body.
    - Most of the mediation is actually done by sugars instead of the primary amino-acid sequence of the antigens and antibodies.
    - Specific examples.
        - The COVID-19 vaccine gives us spike protein antibodies; having the disease gives us more. Discusses how glycoxylation of the COVID-19 spike protein allows our antibodies to recognize it and thus neutralize the virus.
        - HIV is similar.
        - A/B/O blood types also work much the same way. These work via modification of lipids. O-type blood has galactose connected to fructose as the terminal of the lipid glycin (this does not generate antibodies). A-type is the same as O-type, except with an additional galactosamine on the galactose. B-type is the same as O-type, except with an additional galactose. AB-type has both the A-type and B-type modifications to O-type.

- **Monosaccharide**: A single sugar monomer.
- **Disaccharide**: Two sugar monomers connected together.
- **Trisaccharide**: A molecule with a three sugar monomers.
- We can continue this pattern.
- **Oligosaccharide**: A chain of monosaccharides that is not too long.
  - The definition is very vague.
- **Polysaccharide**: A (longer) chain of monosaccharides.
- We now begin listing testable material.
- Structure.
- Fischer projections.

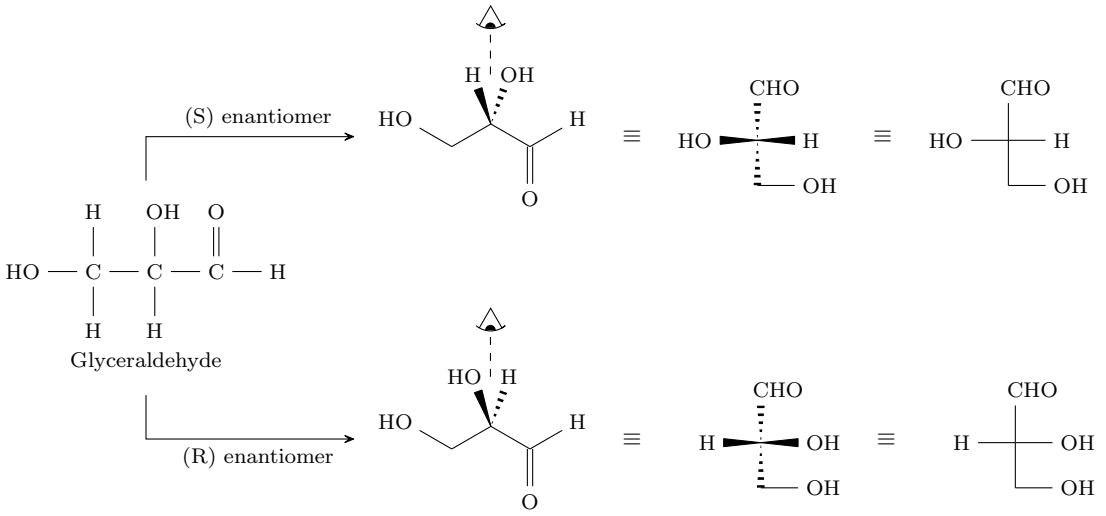


Figure 8.4: Interpreting the Fischer projections of glyceraldehyde.

  - We may have learned Fischer projections first quarter, but we've never used them up until now.
    - This makes sense because Fischer projections are only used for sugars nowadays.
  - The elements of Figure 8.4.
    - The leftmost molecule is **glyceraldehyde**. It has one chiral carbon (the central one) and thus two enantiomers.
    - The (S) enantiomer of glyceraldehyde is drawn in line-angle, in a top-view, and as a Fischer projection along the top row. The same is true of the (R) enantiomer along the bottom row.
    - The line angle drawings are fairly self-explanatory.
    - The top view is simply a redrawing of the line-angle but from the perspective of the eyes, with right being out of the page and left being into the page.
    - The Fischer projection then takes this view and simplifies all of the wedges and dashes to straight lines.
  - We canonically place the carbonyl group at the top of a Fischer projection.
  - The backbone of the hydrocarbon always curves into the page in a Fischer projection.
- **Absolute configuration** (of a molecule): The stereochemistry as denoted by R/S nomenclature.

- **D/L nomenclature**: An empirical way of describing the chirality at a carbon in a sugar. *Procedure*
  1. Identify the (bottommost) chiral carbon in the Fischer projection of a sugar.
  2. If the hydroxyl group here points to the left, we insert "L-" before the name of the sugar.
  3. If the hydroxyl group here points to the right, we insert "D-" before the name of the sugar.
- D/L nomenclature in Figure 8.4.
  - The (S) enantiomer is **L-glyceraldehyde**.
  - The (R) enantiomer is **D-glyceraldehyde**.
- All naturally occurring sugars have the D configuration.
- **Aldose**: A sugar in which the one degree of unsaturation comes from an aldehyde.
- **Ketose**: A sugar in which the one degree of unsaturation comes from a ketone.
- **Triose**: A sugar with three carbons.
- **Tetrose**: A sugar with four carbons.
- **Pentose**: A sugar with five carbons.
- **Hexose**: A sugar with six carbons.
- Examples.
  - D-glyceraldehyde is an aldose triose.
  - **D-threose** is an aldose tetrose.
  - **D-fructose** is a ketose hexose.
- **D-threose**: The following sugar. *Structure*

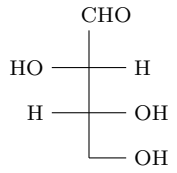


Figure 8.5: D-threose.

- D-threose has two chiral carbons.
  - As we've previously discussed, the "D" tells us the chirality at the bottom carbon.
  - The name "threose" differentiates the the chirality at the top carbon from that of this molecule's diastereomer, **D-erythrose** (see Figure 8.15).
  - Note that there also exist L-threose and L-erythrose (diastereomers of the respective D-versions with inverted chirality at the bottom carbon).
- Conformations of D-threose.
  - If we draw the conformation of D-threose indicated by the Fischer projection, we will notice that a lot of groups are eclipsed and that this is actually a very high energy conformation of the molecule.
  - This is why Fischer projections are not used beyond sugars: because normal molecules would never assume such a conformation.
  - A normal compounds gets drawn in the typical zig-zag/line-angle form.

- **D-fructose**: The following sugar. *Structure*

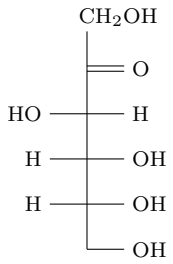


Figure 8.6: D-fructose.

- **D-glucose**: The following sugar. *Also known as* **dextrose**. *Structure*

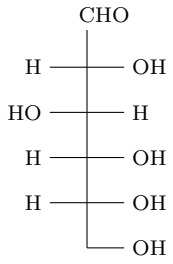
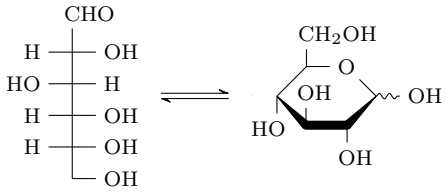


Figure 8.7: D-glucose.

  - This is the only structure Tang expects us to know by heart; every other structure will be given.
- Open and closed structures.
- General form.



  - This is how we transfer the one degree of unsaturation from an aldehyde or ketone to a ring.
  - The open and (multiple) closed forms are always in equilibrium.
    - For instance, D-glucose prefers to exist as a six-membered ring, but we can find trace amounts ($\approx 0.02\%$) of the open form and even smaller amounts of a five-membered ring form.
    - We will still never observe four-membered rings (or smaller) or seven-membered rings (or bigger).
  - The wavy line represents indeterminate chirality.
  - This is very testable material!
- Mechanism.
  - This process is just hemiacetal/hemiketal formation, as we can see by observing the similarities between Figure 8.8 and the first three steps of Figure 1.14.
  - We now know that the indeterminacy in the chirality at the one carbon comes from the fact that chirality is set by the intramolecular attack, not the prior stereochemistry.

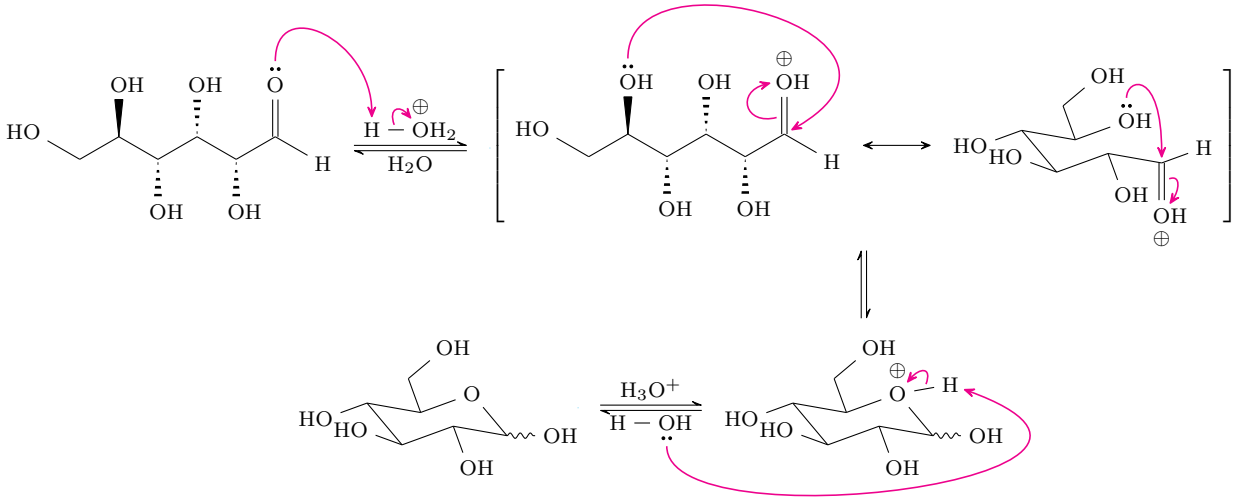


Figure 8.8: Glucose ring-closing mechanism.

  - Note that the six-membered ring of glucose is particularly favored because every substituent is in the equatorial position.

- **Anometic** (carbon): The carbon whose chirality is decided by the attack.
- **β-D-glucose**: The six-membered ring form of D-glucose wherein the hydroxyl group on the anomeric carbon is equatorial. *Also known as* **β-D-glucopyranose**.
- **α-D-glucose**: The six-membered ring form of D-glucose wherein the hydroxyl group on the anomeric carbon is axial. *Also known as* **α-D-glucopyranose**.
- **Pyran**: The following compound. *Structure*

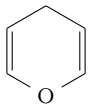


Figure 8.9: Pyran.

  - Pyran is useful in describing the cyclized form of sugars.
  - Indeed, we call six membered rings with five carbons and one oxygen **pyranose**.

- **Furan**: The following compound. *Structure*

Figure 8.10: Furan.

  - Similarly, we call five membered rings with four carbons and one oxygen **furanose**.
  - This is why we have tetrahydrofuran!

- The ratio of β-D-glucose to α-D-glucose in water is 64 : 36, owing to the former's greater stability.
- β- vs. α-linkages play a key role in determining how easy it is to hydrolyze polysaccharaides. For example, starch monomers are connected via α-linkages and thus can be easily hydrolyzed; on the other hand, cellulose monomers are connected via β-linkages and thus cannot be easily hydrolyzed.

- Reducing carbohydrates.
  - Note that the six-membered ring form of D-glucose (see the end product in Figure 8.8) contains a hemiacetal.
  - Thus, since hemiacetal formation is readily reversible, we will have some of the open form in solution with which we can perform aldehyde chemistry.
  - In particular, if we mix a solution of glucose with $NaBH_4$, we can reduce it.
  - Note that if we have a hemiketal instead, we can observe muted reactivity.
- Fun facts.
  - This is not testable content.
  - Draws the structure of **sucrose**.
    - Sucrose contains an acetal in its ring system, and fructose contains a ketal in its ring system.
    - Thus, the formation is not readily reversible, so sucrose cannot be reduced by $NaBH_4$.
    - A **glucometer** (tests blood sugar) determines whether or not the blood is oxidative.
  - Glucose is 0.75 times as sweet as glucose.
  - Fructose is 1.75 times as sweet as fructose.
  - High-fructose corn syrup (industrial synthesis).
    - Start from corn starch (cheap compared to cane sugar; mostly made of glucose).
    - Do hydrolysis to yield glucose.
    - Add an enzyme to convert some of the glucose into fructose, yielding a 55 : 45 ratio of fructose and glucose. We will also have about 20% water in solution.
- **Sucrose**: A disaccharide of glucose and fructose connected by an α-linkage. *Also known as* **table sugar**. *Structure*

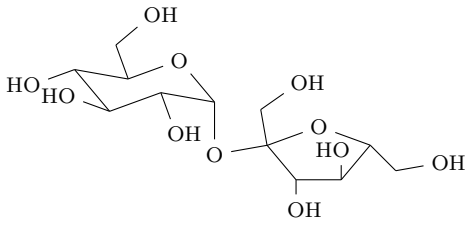


Figure 8.11: Sucrose.

- **Saccharin**: An artificial sweetener that is 350 times sweeter than table sugar. *Structure*

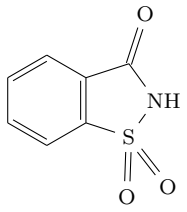


Figure 8.12: Saccharin.

- The discovery of saccharin (according to legend).
  - The chemist who first synthesized it didn't wash his hand very well after lab, went home, touched the dough of a cake that his wife was baking, and commented that it was really sweet. He later figured out that the additional sweetness was coming from saccharin.

- **Aspartame**: An artificial sweetener that is 180 times sweeter than table sugar. *Structure*

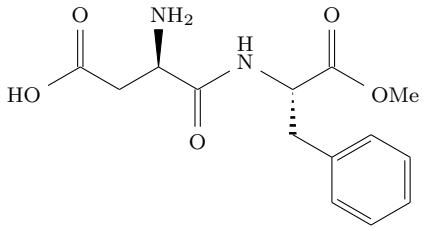


Figure 8.13: Aspartame.

- **Sucralose**: An artificial sweetener that is 600 times sweeter than table sugar. *Also known as* **Splenda**. *Structure*

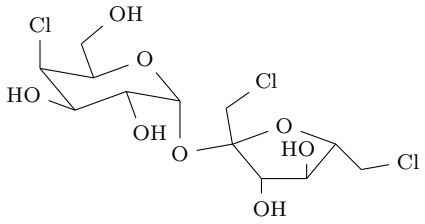
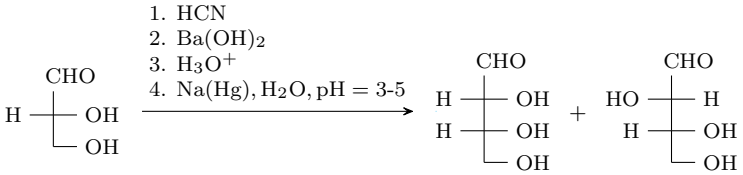


Figure 8.14: Sucralose.

- The discovery of sucralose (according to legend).
  - A PI asks his (Indian) post-doc to synthesize this chlorinated sucrose analogue. The post-doc reports the complete synthesis and the PI ask him to "test it," as in characterize spectroscopically. However, the post-doc hears "taste it," is confused but goes and does so, and reports, "sir, it's very sweet."
- All artificial sweeteners were discovered by accident — there's no reason you'd think they're sweet just by looking at the structure.
- Artificial sweeteners are dangerous in extreme excess, but not in any ordinary amount.
  - Tang goes over an experiment on mice and their kidneys to support this claim.
  - If we use a sugar alcohol, however, (e.g., sorbitol), we can get diarrhea for eating too much.
    - This is because these are not as sweet, so we use more; but since they are not digestible, consuming too much does not bode well for the digestive system.
- Kiliani-Fischer synthesis.
- General form.



  - This is a **chain-elongation reaction**.
- **Chain-elongation reaction**: A reaction that takes a simple sugar and extends it by one carbon.

- Mechanism.

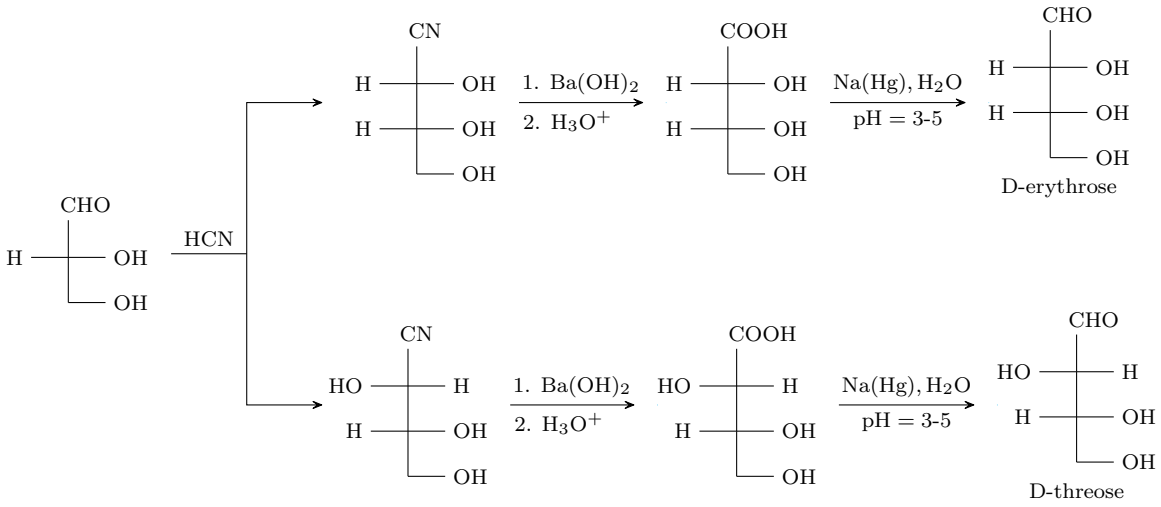


Figure 8.15: Kiliani-Fischer synthesis mechanism.

  - In the first step (cyanohydrin formation), the cyanide ion can attack either face. Thus, the first step leads to the formation of two diastereomers.
  - In the second and third steps, it is an empirical finding that barium hydroxide is a better base source than NaOH or something else of the sort, but it is hard to say that any of these alternatives flat-out would not work. What we are basically accomplishing here, though, is nitrile hydrolysis (see Figure 2.12).
    - Tang indicates that the $Ba(OH)_2$ generates a carboxylate from our nitrile and then the acid protonates it to a carboxylic acid.
  - The last step is a reduction.

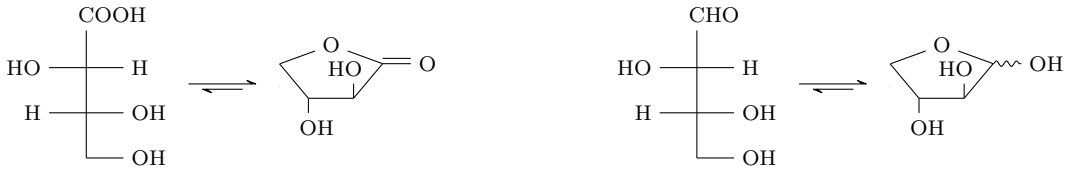
Week 9

Intro to Biological Molecules

9.1 Carbohydrates 2

5/24:

- Today's lecture content in Solomons et al. (2016).
  - Today: Sections 22.3-22.4, 22.6-22.7 and 22.9A-22.9B. Read Sections 22.10-22.11.
  - Next time: Sections 25.1-25.2, 25.4-25.5, 24.11, and more.
  - Practice problems: 22.20, 22.31, and 22.43.
- Final exam info.
  - The final exam will be 2.2 times longer than the midterm (so slightly more than twice as many problems).
  - This should help us as we won't lose so many points if we can't get a mechanism this way.
  - The final is cumulative, though Tang will try to test more on new content.
  - The practice exam is almost as hard as the real final exam.
- Review of last lecture.
  - In the Kiliani-Fischer synthesis, the carboxylic acid intermediate can cyclize into a lactone and the final product can cyclize into a sugar.



(a) Intermediate 2. (b) Product.

Figure 9.1: Extra Kiliani-Fischer cyclizations.

  - D-threose is now used in biology to mimic ribose.
- Today, we will cover the following.

II. Reactions.

B. Mutarotation.

C. Glycosides.

D. Oxidation/degradation.

- Differences between α-D-glucopyranose and β-D-glucapyranose.

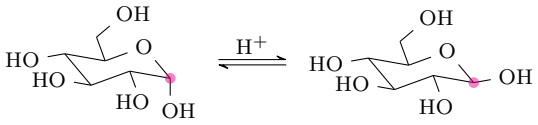
$$\text{MP}_\alpha = 146\,^\circ\text{C} \qquad [\alpha]_\alpha = \pm 112.2^\circ$$
$$\text{MP}_\beta = 150\,^\circ\text{C} \qquad [\alpha]_\beta = \pm 18.7^\circ$$

  - The **anomers** differ in their melting point (MP) and optical rotation ($[\alpha]$).

- Crystallization of a D-glucose solution at different temperatures can isolate either one of them.
  - α can be crystallized at room temperature; β can be crystallized at 100 °C.

- If the α and β anomers (in any proportion) are added to H_2O, over time, the optical rotation tends toward 52.6°.
  - This is because of **mutarotation**, which will always make the $\beta : \alpha$ ratio tend to 64 : 36.
  - If we now take a weighted average of the specific rotations of the pure anomers, we will get approximately 52.6°.

- General form.



  - We use an acid catalyst to simplify the mechanism, but it may not be necessary?

- Mechanism.

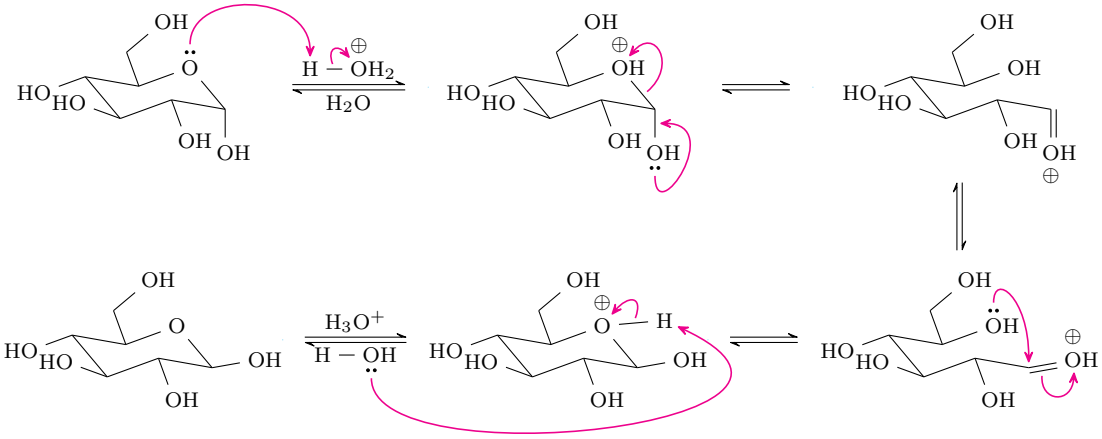


Figure 9.2: Mutarotation mechanism.

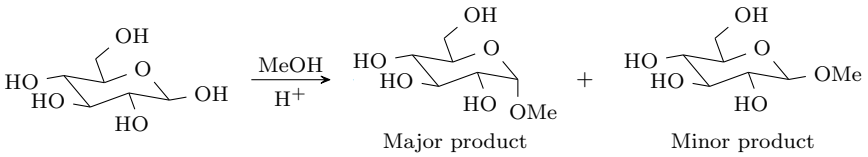
  - When we recyclize, we can form either anomer once again.
  - Note that if we lose a proton from the second intermediate, we can create the linear form of glucose.

- Key: Rapid interconversion of the α, β forms.

- The equatorial, β anomer is not always energetically preferred.
  - For example, α-D-mannose (or α-D-mannopyranose) is preferable to β-D-mannose (or β-D-mannopyranose).
  - The mechanism is not fully understood, but the current assumption is that on the α-anomer, the σ^* orbital of the axial C−O bond accepts electrons from the oxo lone pair via hyperconjugation in a stabilizing fashion.

- α or β case-by-case prediction is not testable material.

- **Glycoside**: A cyclic acetal/ketal of a sugar.
- Glycoside formation.
- General form.



  - We notably do not form the open hemiacetal from the open form of a sugar.
  - The two anomers of the product are called **methyl α-D-glucopyranoside** (major) and **methyl β-D-glucopyranoside** (minor).

- Mechanism.

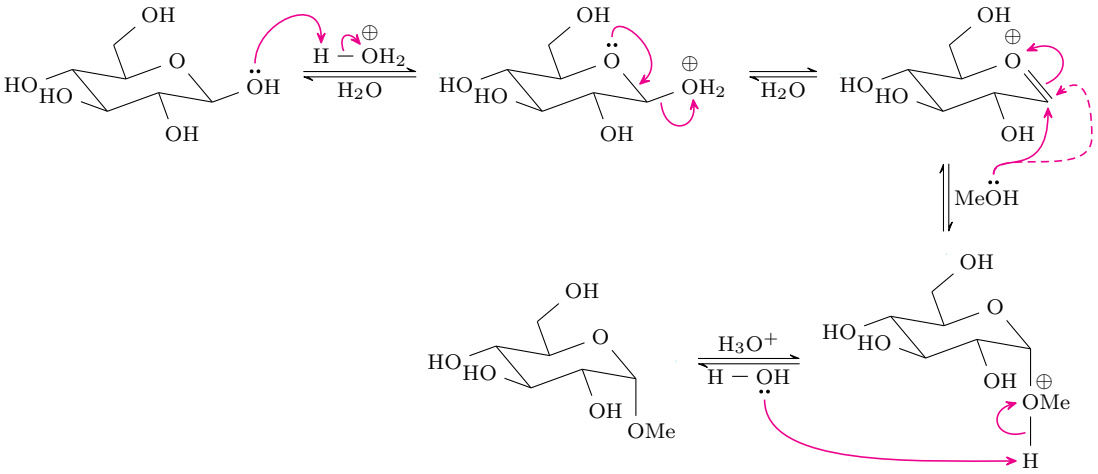


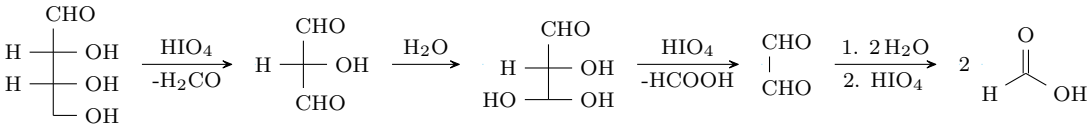
Figure 9.3: Glycoside formation mechanism.

  - Note that the mechanism is symmetric for α-D-glucose.
  - Which anomer of the product is formed depends on the side from which the MeOH nucleophile attacks. Indeed, if we use the dashed attack in step 3 instead of the solid attack, we will get the β product.

- Note that mutarotation and glycoside formation proceed through different intermediates.
  - We use the mutarotation intermediate because it is much likelier to form in water. The glycoside formation one is just what we need for glycoside formation to proceed, so we have no choice but to go through it.

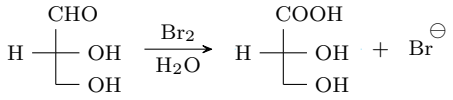
- Oxidation/degradation.
- Periodic acid.
- Consider periodic acid (HIO_4).
  - Recall diol cleavage (see Figure 1.3).

- General form.



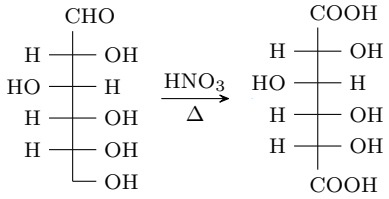
  - Applying it to sugars cleaves repeatedly.
  - We get formic acid and formaldehyde in multiple equivalents?
  - We have to see aldehydes as hydrates here.

- Tang works through D-fructose as an example.
- Bromine water.
- General form.



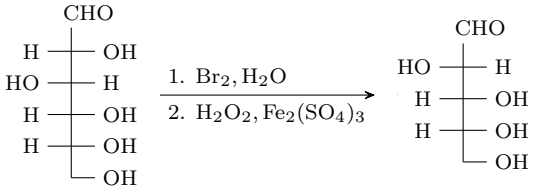
  - This is a good, mild way to convert aldehydes to carboxylic acids.

- Mechanism. *picture; email Tang.*
- Nitric acid and heat.
- General form.



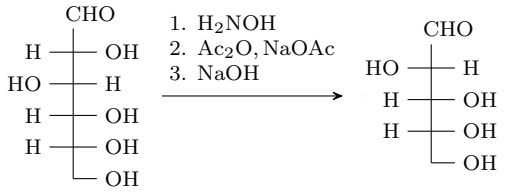
  - The product is **glucaric acid**.

- Mechanism. *picture; email Tang.*
- Ruff degradation.
- General form.



  - Read 22.11 for ??
  - The first step is bromine water again.
  - The second step is the exact opposite of Kiliani-Fischer synthesis.

- Mechanism. *picture; Google it.*
- Wohl degradiation.
- General form.



  - The reactant is hydroxylamine and forms an oxime.
  - Ac_2O is acetic anhydride very reactive.
  - The product is **D-arabinose**.

- Mechanism.
  - Essentially, we form an oxime from the top aldehyde.
  - Then we turn the hydroxyl portion of the oxime into AcO, a good leaving group. AcO^- engages in an E2 elimination on the oxime hydrogen, forming a cyano group.
  - Base then eliminates the cyano group, giving us an aldehyde one carbon down.
- What Tang expects us to know from Chapter 22.
  - The mechanisms she showed us (only a few).
  - No synthesis problems with sugars.
    - Tang has shown us some good reactions, but modern sugar synthesis does not use any of these reactions; these are all decades old.
    - Modern sugar chemistry is very hard; these reactions are just classic ones.

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