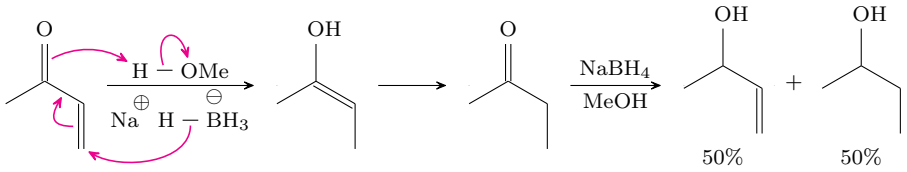
Week 3

Reactions of Carboxylic Acid Derivatives

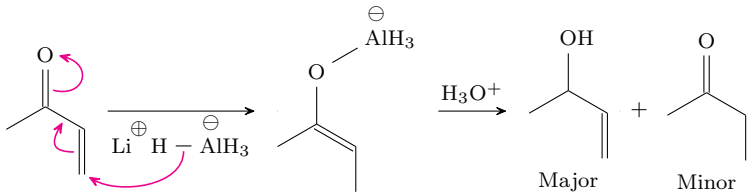
3.1 Office Hours (Levin)

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 (2022), although he has a different way of deriving them.
  - The 1,2-reduction product is the same in both. But for the $NaBH_4$, you get full reduction as the other major byproduct.
  - We will never be asked to use this reaction synthetically because it is not selective.
  - We're most likely to encounter alkyllithiums or cuprates. The thing to keep in mind with the messy ones is that they're messy. We're more just interested in introducing enolate chemistry with these.

- Problem Set 1, Question 3a: We form one bond with the best stereochemistry and then do an S_N2 to simultaneously form the epoxide and kick out SPh_2.
- Problem Set 1, Question 2f: Cyclic systems are one of the only places you see hemi-acetals.

- Problem Set 1, Question 3b: The transition state has too much ring strain, so show proton transfers as being mediated by solvent molecules.
- n-butyl lithium stands for "normal"-butyl lithium; s-butyl lithium is sec-butyl lithium.

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 (2022) for the mechanism.
  - The fact that we observe double addition means that the **overaddition product** is the major product.
  - If you only add one equivalent of lithiate, the major products will be the overaddition product and unreacted ester; the ketone will only be a very minor product.
    - This is because esters are less electrophilic due to donation from the ether oxygen, so the lithiate will selectively go for the ketone as soon as it becomes available.
    - Ester resonance essentially partially protects it from nucleophilic addition.
- **Overaddition product**: A nucleophilic addition product in which the nucleophile adds more than once.
  - So named because we typically only want monoaddition.

- Hydride addition to...
  1. Esters ($NaBH_4$, $LiAlH_4$, and DIBAL-H).
  2. Amides ($LiAlH_4$ and DIBAL-H).
- Esters ($NaBH_4$).
  - $NaBH_4 + MeOH$ does not react with esters (for the purposes of this class).
- Esters ($LiAlH_4$).

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

  - See Figure 9.2 of Labalme (2022) for the mechanism.
  - Mechanistically, the aldehyde intermediate is much more reactive than the ester, once again.
  - Is it the lithium cation that bonds to the alkoxide or the AlH_3 species?
- Selecting for addition to the ester instead of addition to the aldehyde intermediate.
  - We are going to change the structure of our reducing agent.
  - We'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*

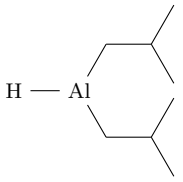


Figure 3.2: Diisobutylaluminum hydride (DIBAL-H).

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

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

- Mechanism.

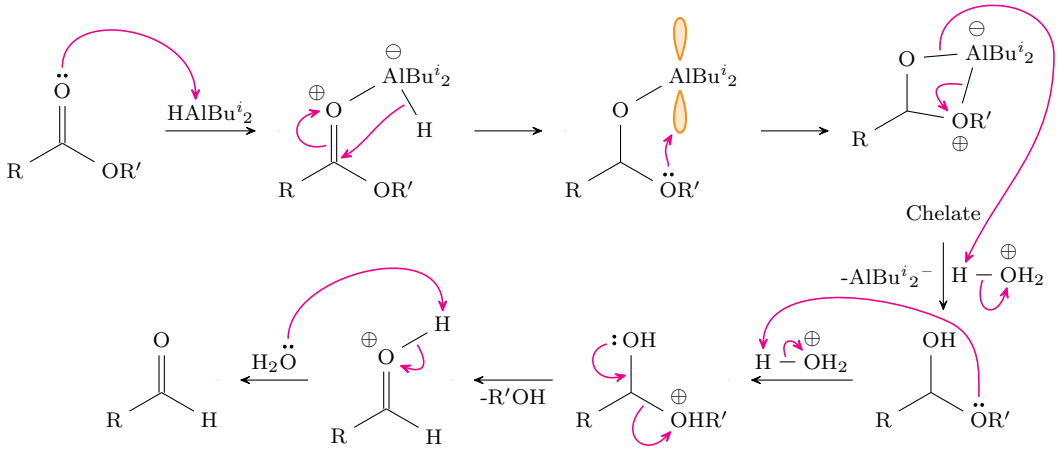


Figure 3.3: Monoreducton of esters mechanism.

  - 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.

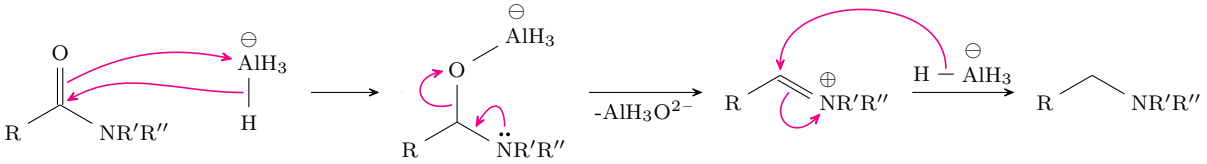


Figure 3.4: Reduction of amides mechanism.

  - 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.

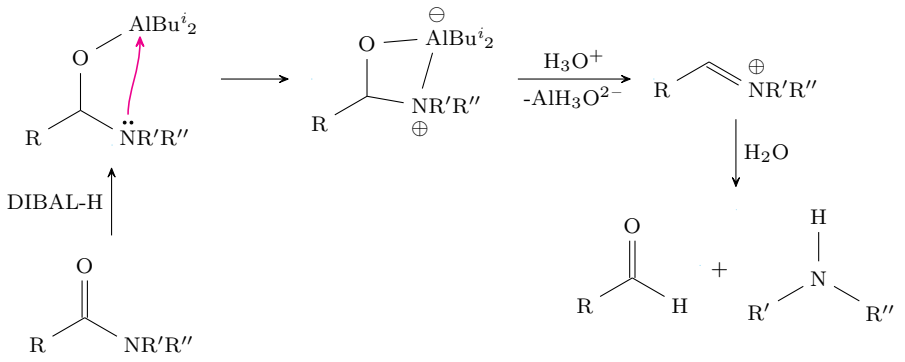


Figure 3.5: Monoreducton of amides mechanism.

- 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.

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

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

- Mechanism.

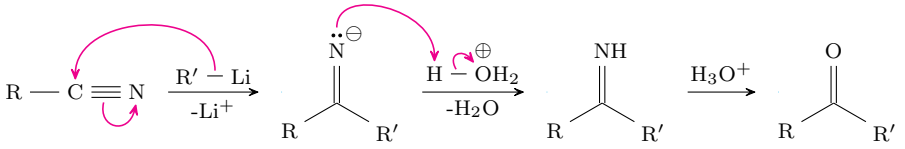


Figure 3.6: Nitrile alkylation mechanism.

  - 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.

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

- 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.

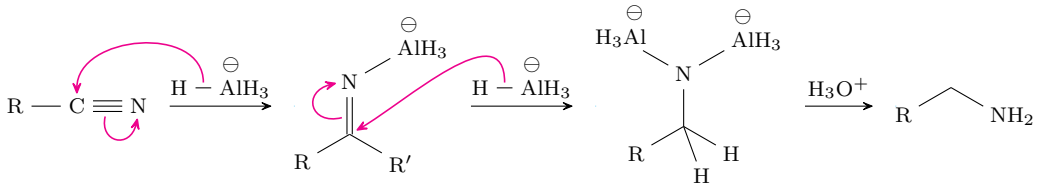


Figure 3.7: Nitrile reduction mechanism.

  - 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.

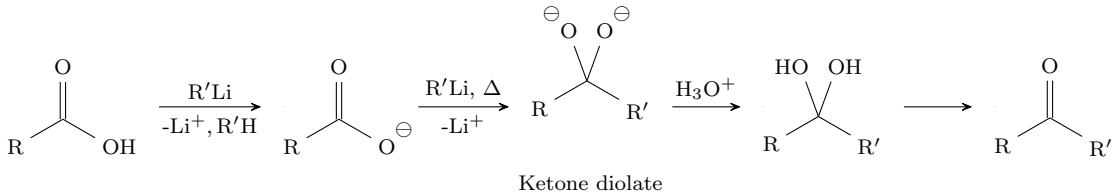
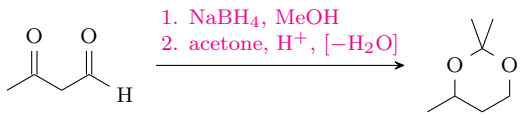


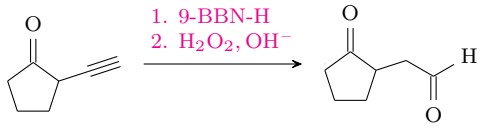
Figure 3.8: Carboxylic acid to ketone mechanism.

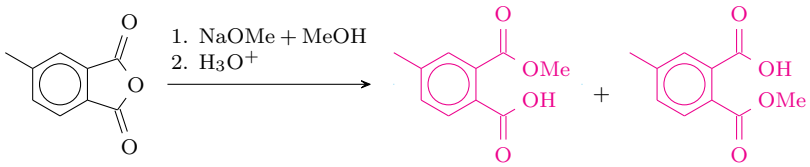
  - The excess lithiate is used to both deprotonate the carboxylic acid and alkylate the carboxylate that gets formed.
  - The heat is used to overcome the low electrophilicity of the carboxylate.

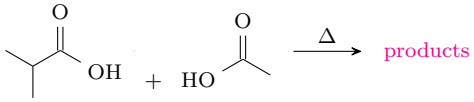
3.3 Problem Session

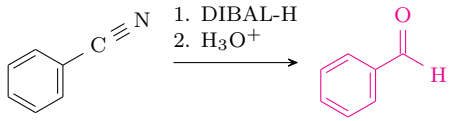
- Practice problems.

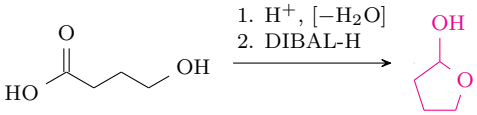
1. 

   - 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. 

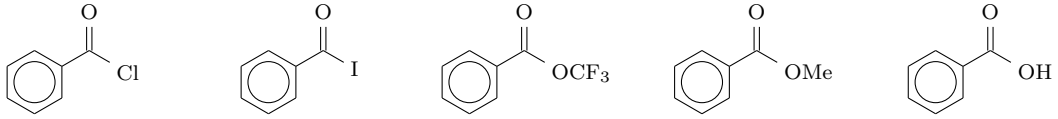
   - The products are a whole variety of coupled anhydrides.
   - We can do this selectively by transforming one of the carboxylic acids into an acid chloride with $SOCl_2$.
     - Note that we don't *have* to turn the other carboxylic acid into a carboxylate, but we can catalyze/accelerate the reaction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

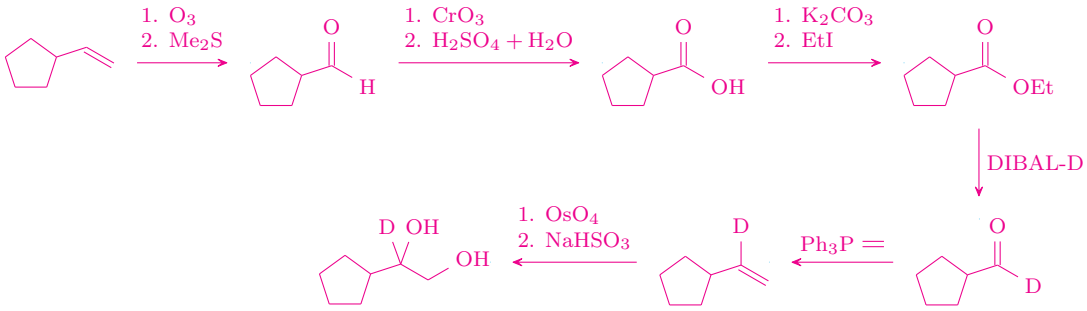
7. Rank the following in order of rate of nucleophilic acyl substitution with an alkoxide nucleophile.



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^+).

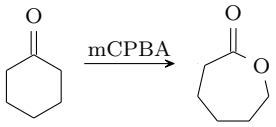
3.4 Carboxylic Acids and Derivatives 3

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.

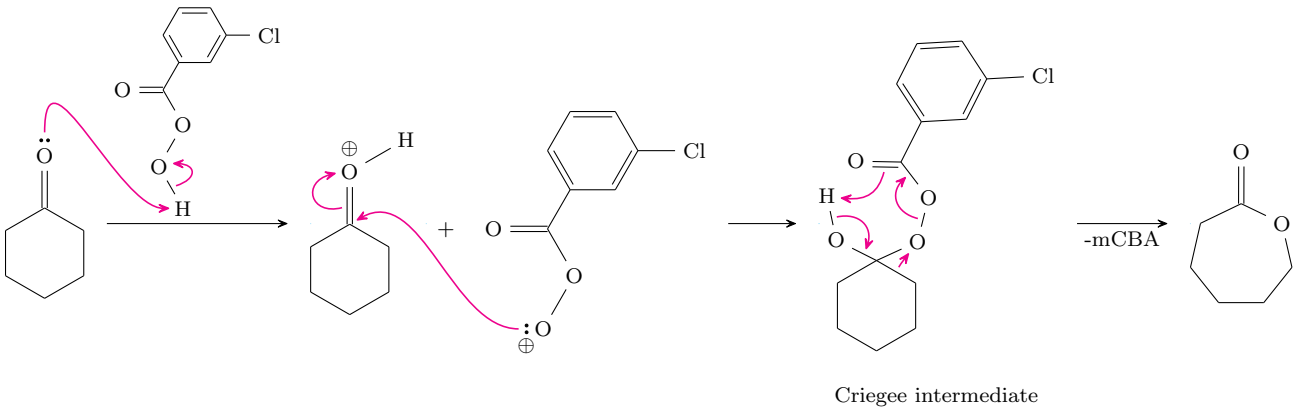
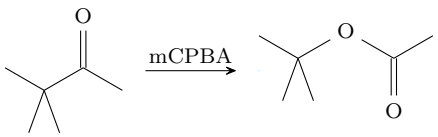


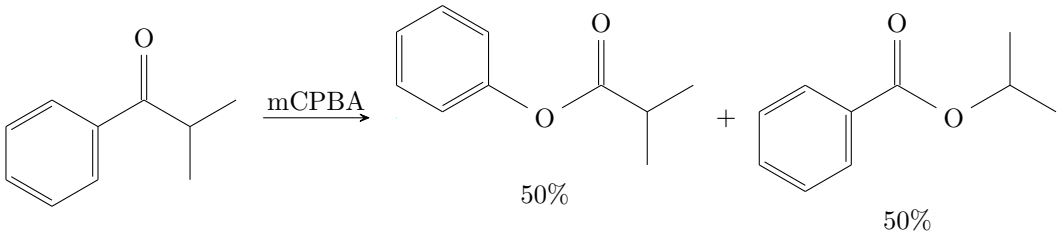
Figure 3.9: Baeyer-Villiger mechanism.

  - 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 hydroboration/oxidation (Figure 1.6) and the formation of the enol boronate.
  - Additionally, the O–O bond is pretty weak and can be displaced.
    - However, because this is mCPBA (with its electron withdrawing carbonyl), the O–O electrons can swing around and facilitate the attack of the carbonyl electrons on the substrate's acidic proton.
  - Last step arrow pushing chronology: The O–H electrons swinging down. Reforming the carbonyl provides the oomph that breaks the C–C bond. The C–C electrons migrate. This makes everything else just swing around.
    - Note that this chronology is not technically accurate; curved arrows are a human invention we assert overtop a concerted step. However, this is a good trick to think of for memorization purposes.

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



(a) A selective case.



(b) An unselective case.

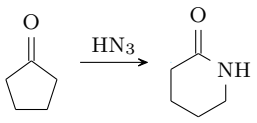
Figure 3.10: Asymmetric ketones in the Baeyer-Villiger.

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

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



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

- **Hydrazoic acid**: A toxic, volatile, and explosive substance. *Structure* $HN{=}N^{+}{=}N^{-}$
  - This is useful industrially, but less useful in the lab (because of all the associated hazards).
- Mechanism (See Figure 3.11).
  - 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.

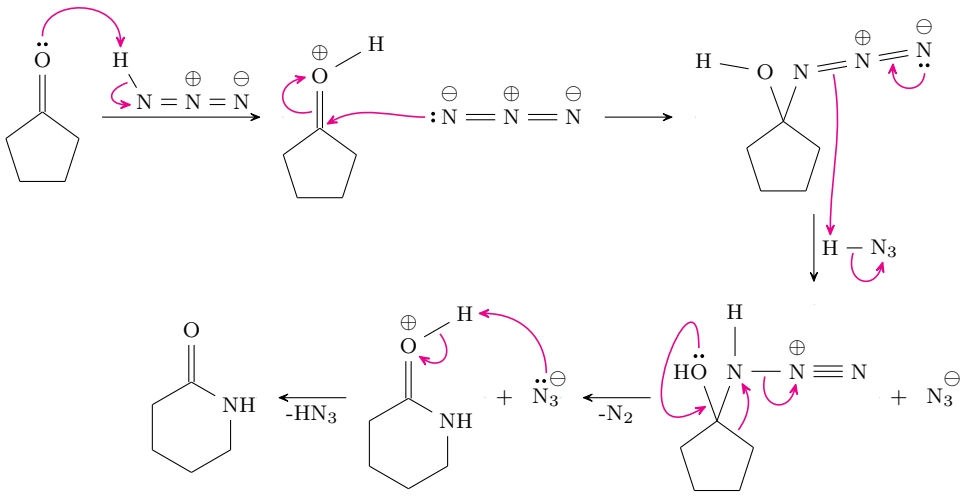


Figure 3.11: Schmidt reaction mechanism.

- Using an alkyl group in place of the hydrogen on the hydrazoic acid *requires* catalytic acid (the new acid isn't strong enough to catalyze its own chemistry). The alkyl group just gets added to the nitrogen in the product.
- The Schmidt reaction also works intramolecularly.

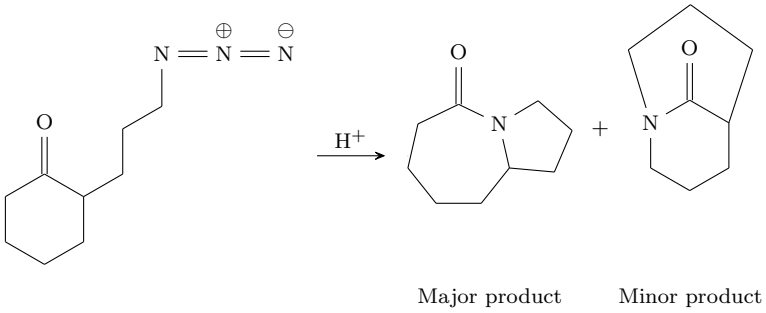
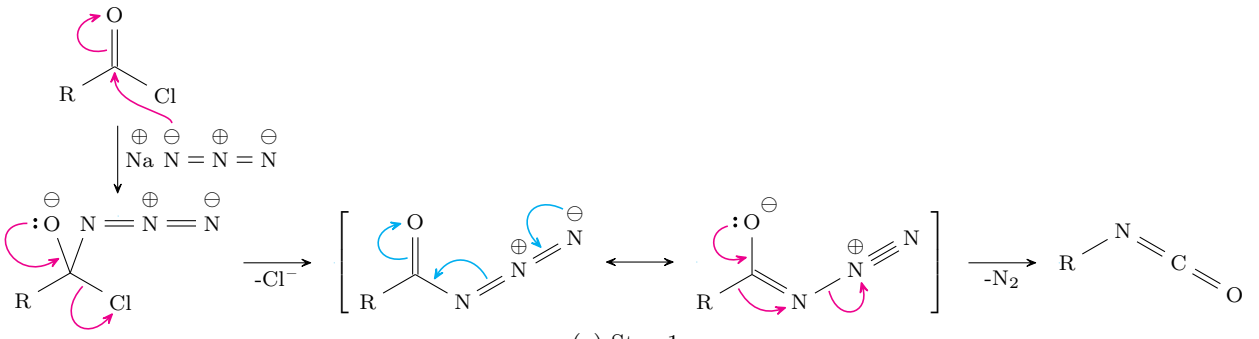


Figure 3.12: Intramolecular Schmidt reaction.

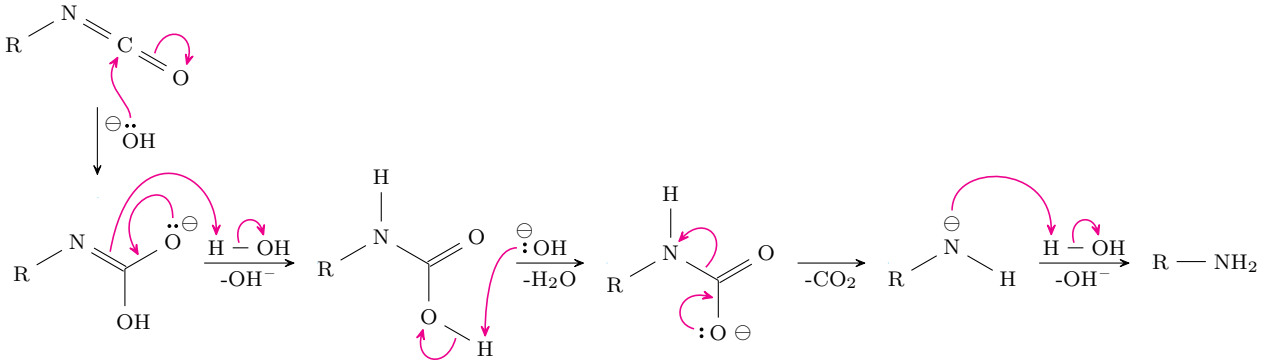
  - The intramolecular Schmidt builds complexity really quickly.
  - When you're building natural molecules, it allows you to get up from simple cheap starting materials to complex polycycles quite quickly, which you want.
- The Curtius rearrangement.
- General form.

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

  - 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.

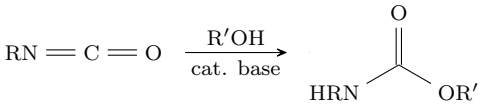
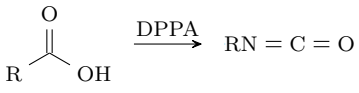


Figure 3.14: Carbamate formation.

  - 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*

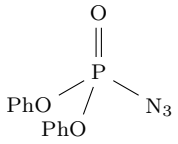
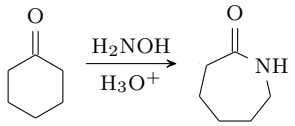


Figure 3.15: Diphenylphosphoryl azide (DPPA).

  - 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.

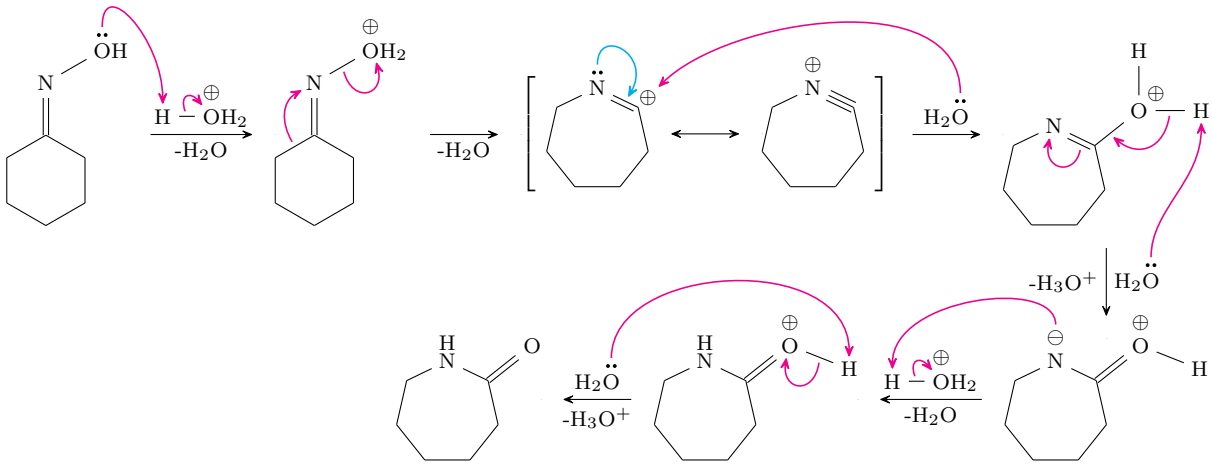


Figure 3.16: Beckmann rearrangement mechanism.

  - 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.