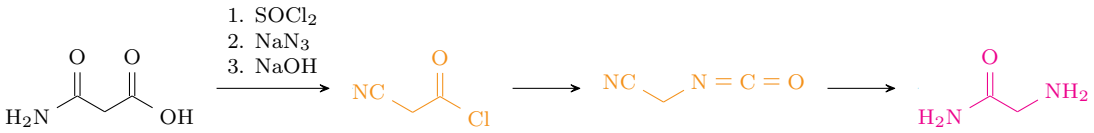
Week 4

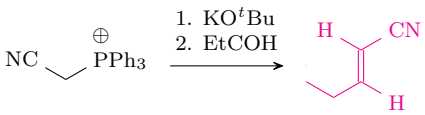
Exam and Enol(ate) Reactivity

4.1 Problem Session

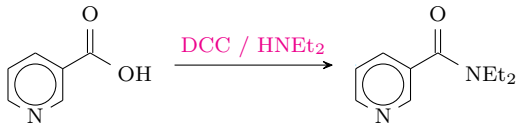
4/19:

- Practice problems.

1. 

2. 

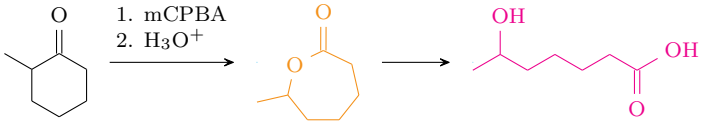
   – This reaction involves a stabilized ylide, hence the formation of the *trans* product.

3. 

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

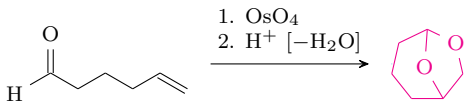
4. 

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

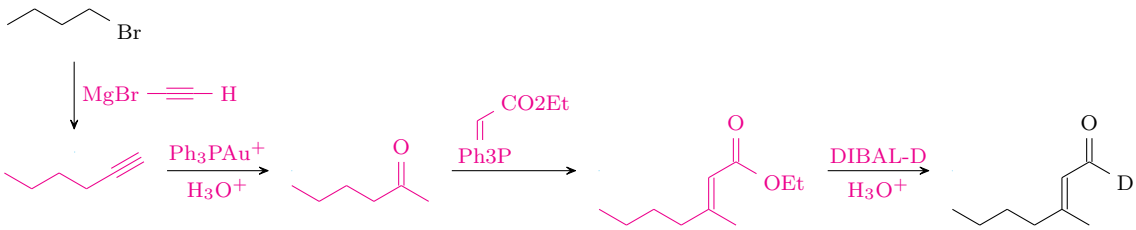
5. 

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

6.

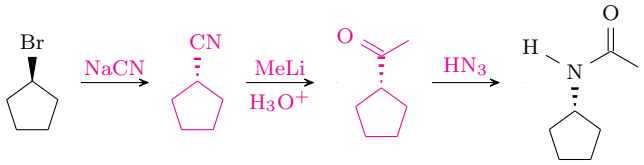


7. Mechanism: Goes over the Curtius rearrangement.
8. Retrosynthesis.

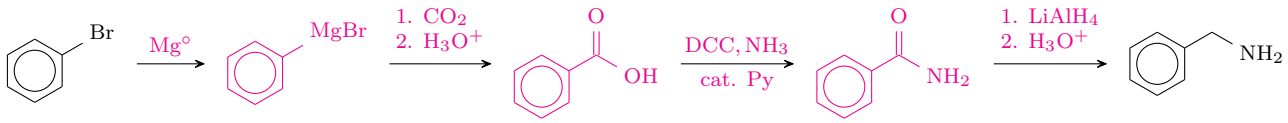


   - That deuterated aldehyde should indicate DIBAL-D.
   - COOEt is an EWG, and we will get the desired trans product in a Wittig with it.

9. Retrosynthesis.



10. Retrosynthesis.



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

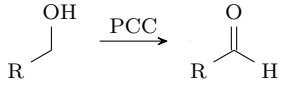
- For mechanism questions, if we're struggling, think back to the sentence trick from the very beginning of the course.
- For synthesis questions, just throw as many reactions out there as we can think of.

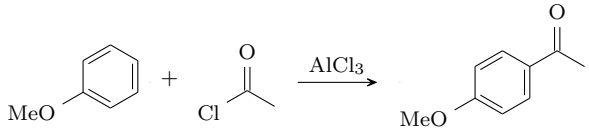
4.2 Midterm 1 Review Sheet

Reactions

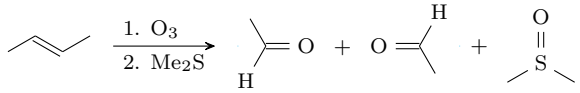
Carbonyl Synthesis

4/20:

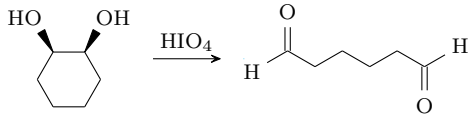
1. 

2. 

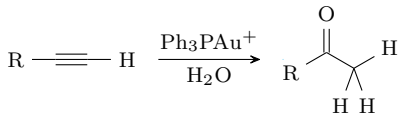
   – Recall ortho/para selectivity.

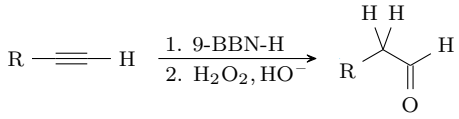
3. 

   – Not adding Me_2S traps the ozonide intermediate.

4. 

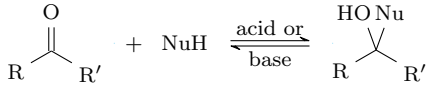
   – *cis*-diols react faster, but are not required.

5. 

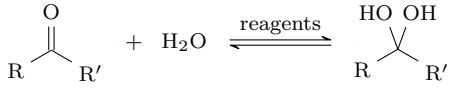
6. 

Nucleophilic Addition to Carbonyls

General

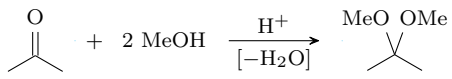
1. 

Oxygen Nucleophiles

1. 

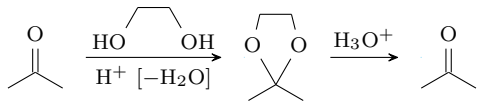
   – Reagents is either H_3O^+ or OH^-.

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

2. 

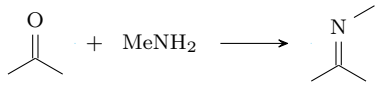
   – Remove water with a Dean-Stark apparatus (and toluene) or 3 Å aluminosilicates.

   – 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.

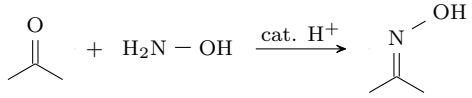
3. 

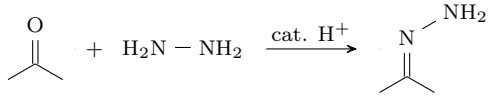
   - We use ketals as protecting groups when we want our ketone to be able to withstand basic conditions (remember, ketals need acid to form and be unformed).
   - We can also protect 1,2- and 1,3-diols from basic conditions with acetone.

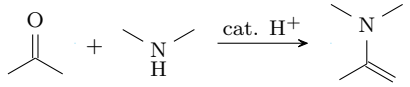
Nitrogen Nucleophiles

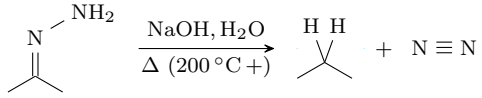
1. 

   - 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. 

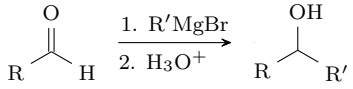
4. 

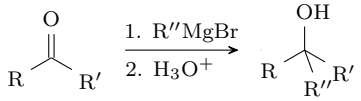
5. 

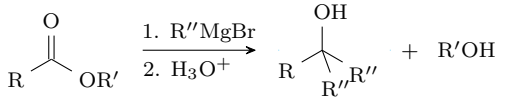
Hydride Nucleophiles

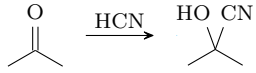
1. $NaBH_4 + MeOH$ reduces aldehydes and ketones to alcohols.
2. $LiAlH_4$ followed by H_3O^+ reduces an ester to its two component alcohols.

Carbide Nucleophiles

1. $RBr \xrightarrow[Et_2O]{Mg^\circ} RMgBr$
2. $RBr \xrightarrow[Et_2O]{2\,Li^\circ} RLi + LiBr$
3. 

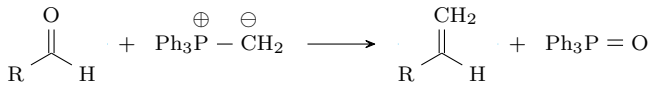
4. 

5. 

6. 

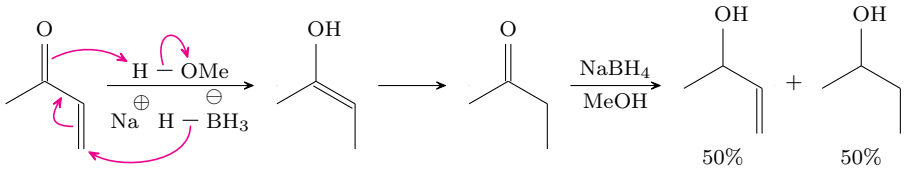
   - Can be accelerated by an acid/base catalyst, but no catalyst is necessary. Acid catalysts are more common.

Ylide Nucleophiles

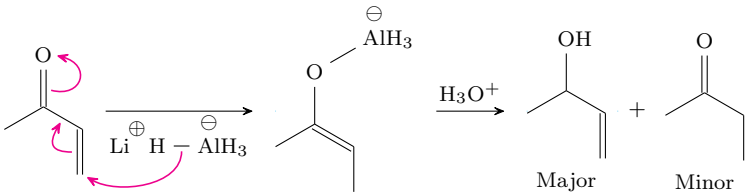
1. $Ph_3P \xrightarrow{MeBr} Ph_3BrP{-}CH_3 \xrightarrow{KO^tBu} Ph_3P{=}CH_2$
2. 

   – 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



$NaBH_4$.

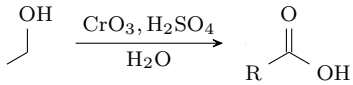
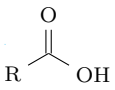
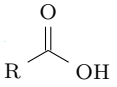


$LiAlH_4$.

Reduction of α, β unsaturated compounds.

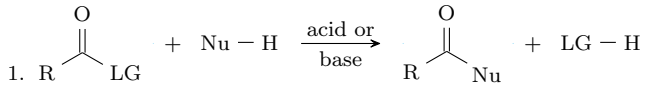
1. Organolithiums select for 1,2-addition.
2. Grignards are intermediate.
3. Cuprates select for 1,4-addition.
   – $2\,MeLi \xrightarrow{CuI} LiCuMe_2$

Carboxylic Acid Synthesis

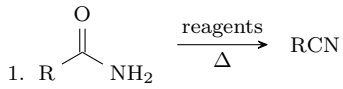
1. 
2. $RMgBr \xrightarrow[2.\ H_3O^+]{1.\ CO_2}$ 
   – Either lithiates or Grignards will suffice.
3. $RCN \xrightarrow{H_3O^+}$ 

Nucleophilic Acyl Substitution

General



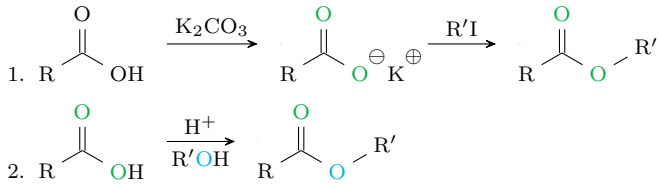
Dehydration of Amides



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

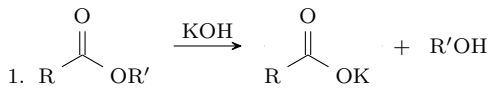
S_N2 Nitrile Formation

Ester Synthesis

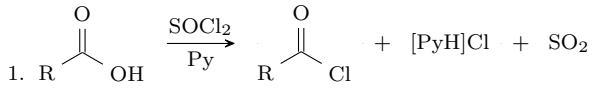


- The acid is a catalyst.
- The alcohol usually doubles as the solvent, esp. since we need it in excess.
- Removing water can drive the forward reaction; excess H_3O^+ reverses it.

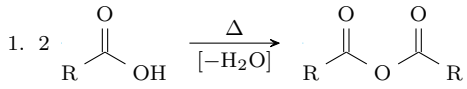
Ester Reactions



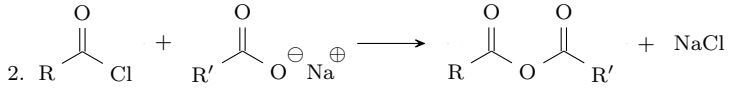
Acid Chloride Synthesis



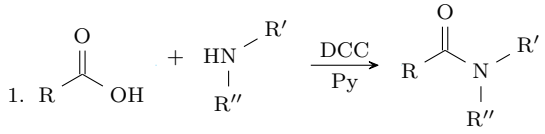
Anhydride Synthesis



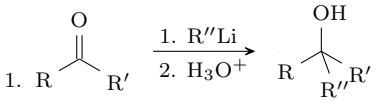
- Also works intramolecularly.
- Combining different carboxylic acids leads to a statistical mixture of products.

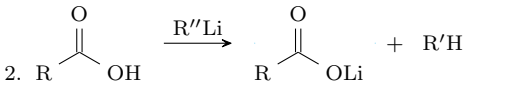


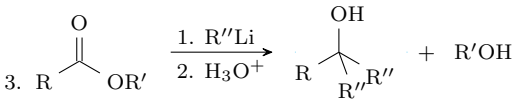
Amide Synthesis



Carbide Nucleophiles

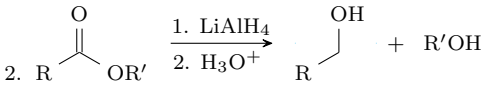
1. 

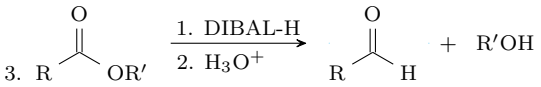
2. 

3. 

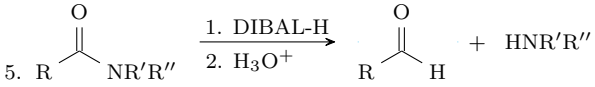
Hydride Nucleophiles

1. Esters and $NaBH_4$ do not react.

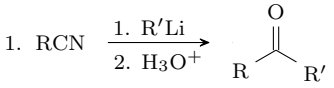
2. 

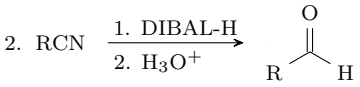
3. 

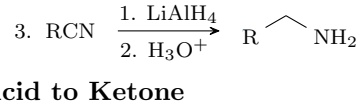
4. 

5. 

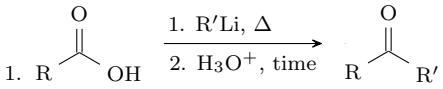
Nitrile Reactions

1. 

2. 

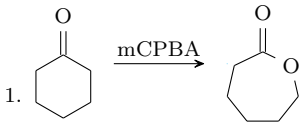
3. 

Acid to Ketone

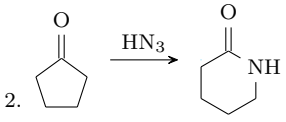
1. 

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

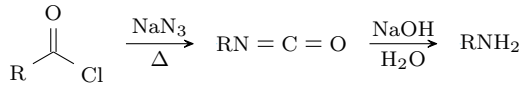
Insertion Reactions

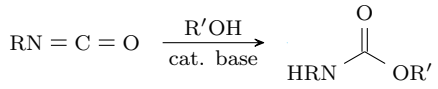
1. 

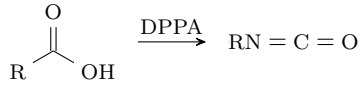
   - Migratory aptitude favors bulkier groups.

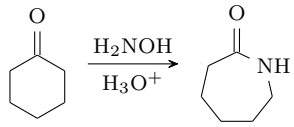
2. 

– 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*

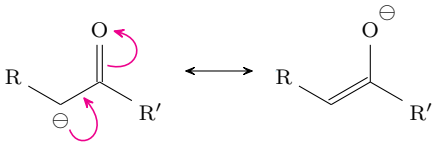


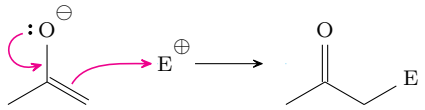
Figure 4.1: Enolate.

  - 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.

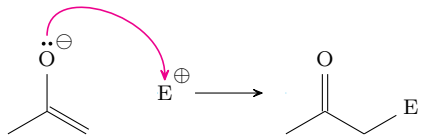
$$C_2H_4 \xrightarrow[CH_2I_2]{Zn/Cu} C_3H_6$$

  - 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$K_a \approx 15$) is 10^{10} times more acidic than ethanol (p$K_a \approx 5$) due to resonance stabilization of the conjugate base in the former.
  - Deprotonating a C–H bond: A hydrogen on the 1-carbon of propane (p$K_a \approx 50$) is 10^{25}-10^{30} times more acidic than a hydrogen on acetone (p$K_a \approx$ 20-25) once again due to resonance stabilization (note that deprotonated acetone constitutes an enolate).

- Enolates have two main modes of reactivity.



(a) Adding an electrophile at the carbon.



(b) Adding an electrophile at the oxygen.

Figure 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*

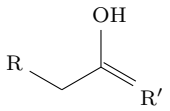
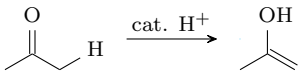


Figure 4.3: Enol.

- **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.

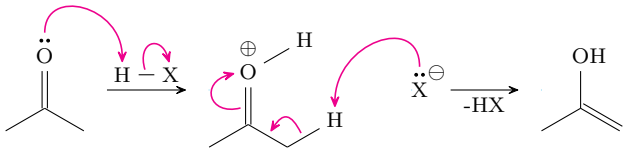
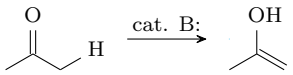


Figure 4.4: Acid-catalyzed enol formation mechanism.

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



- Mechanism.

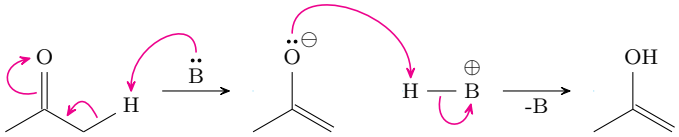


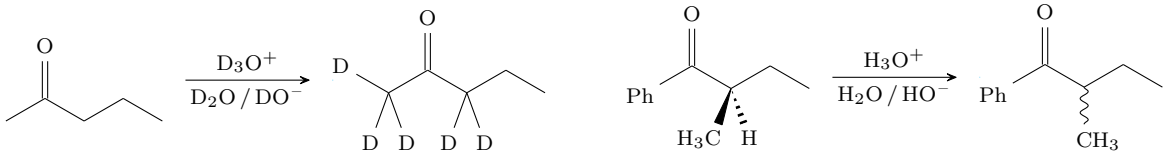
Figure 4.5: Base-catalyzed enol formation mechanism.

  - 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).

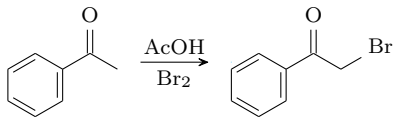


(a) Deuteration. (b) Racemization.

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 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.

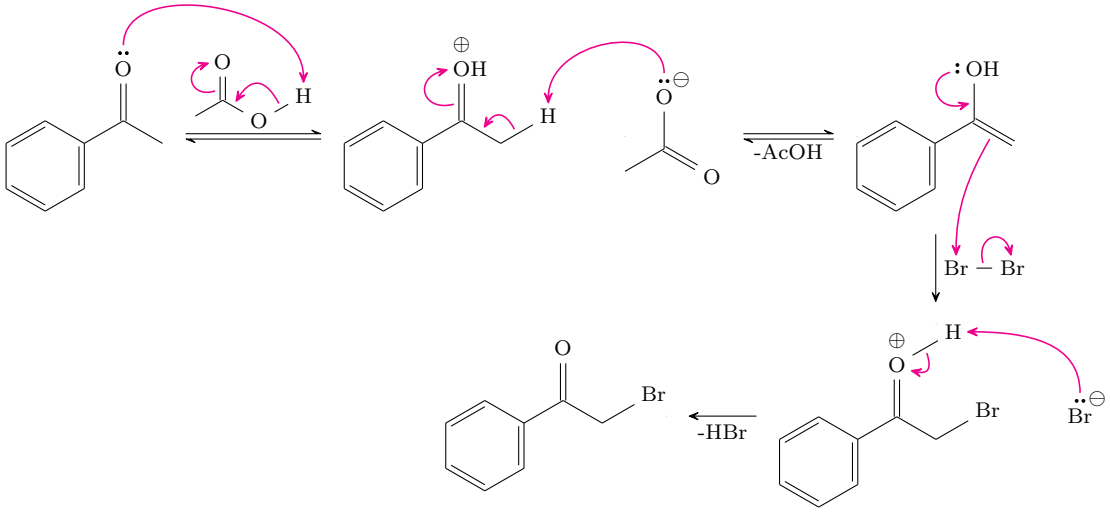
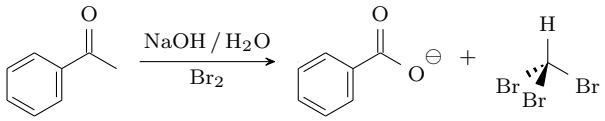


Figure 4.7: Acid-catalyzed halogenation of enols mechanism.

  - 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 alo 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.

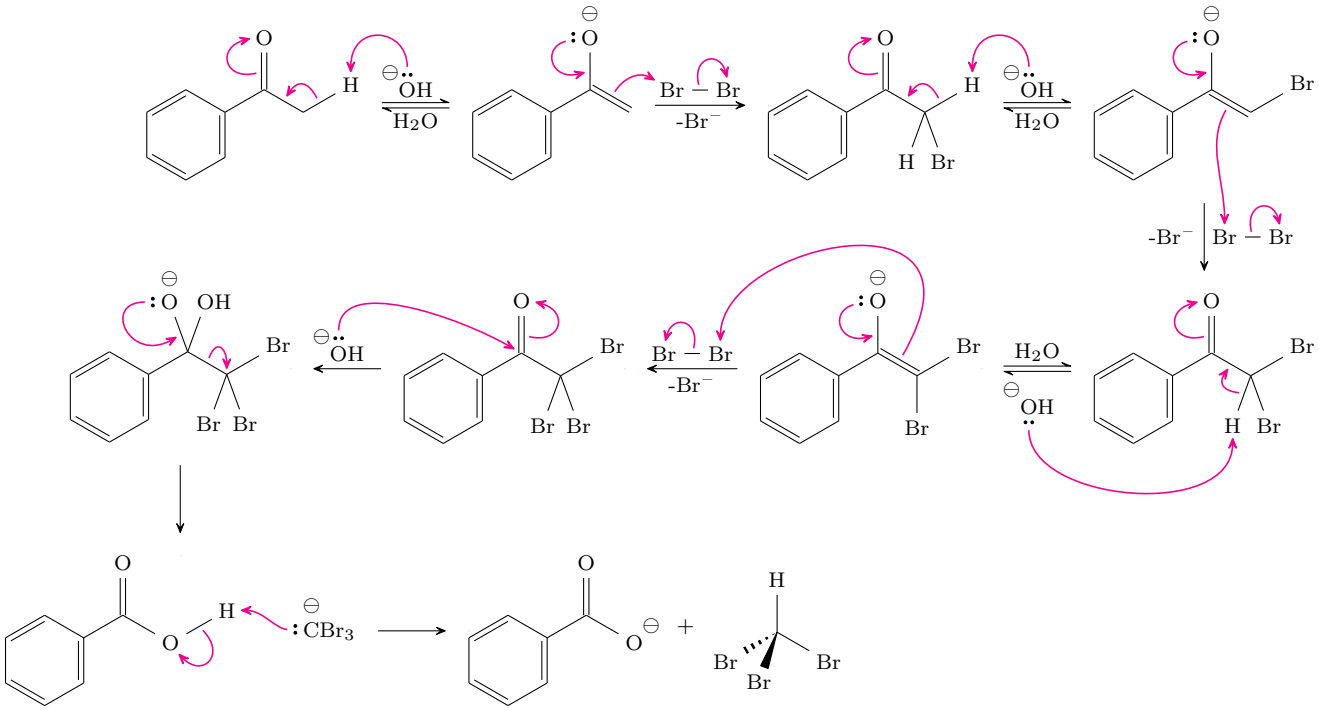


Figure 4.8: Haloform reaction mechanism.

  - 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.
  - 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.

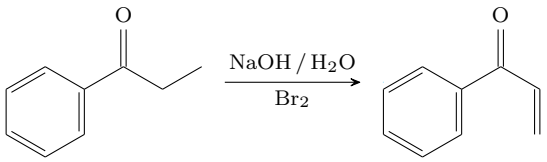


Figure 4.9: β-hydrogens in the haloform reaction.

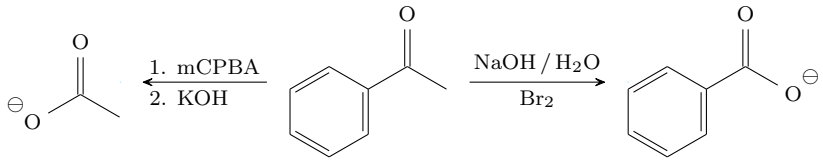


Figure 4.10: Synthetic uses of the haloform reaction.

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