

# Unit 5

## Enolate Chemistry

### 5.29 Enols and Enolates

11/15:

- Grade cutoffs on Exam 3.
  - A: 85-100.
  - B: 70-84.
  - C: 63-69.
  - < C: < 57.
  - If you are considering dropping this class, the drop date is 11/20.
    - It does not count as a drop if you just stop showing up and stop submitting assignments.
    - Go to the Registrar's site and fill out an add/drop form.
  - If you are doing less well than you had hoped or expected, talk to your TFs about options!
    - You may be eligible for tutoring.
    - It is *your responsibility* to reach out for help.
- Fun (or scary) Friday: Prof. Buchwald sings the elements song!
- Announcement: Unit 5 study guide posted.
- We now begin the first of four lectures in Unit 5: Enols and enolates.
  - Readings: Chapters 20, 25, 26 of Clayden et al. (2012).
- Lecture outline.
  - A. Background.
    - Enolate definition.
    - Keto-enol tautomerization (base-catalyzed and acid-catalyzed).
    - Evidence: Deuterium exchange.
  - B.  $\alpha$ -halogenation of ketones.
    - Base-promoted mechanism (and complications).
    - The iodoform reaction.
    - Acid-catalyzed mechanism.
  - C.  $\alpha$ -alkylation.
    - Lithium diisopropylamide.
    - Malonate ester synthesis.
    - Kinetic vs. thermodynamic enolates.

- We'll begin with Topic A: Background.
  - Defining enolates.

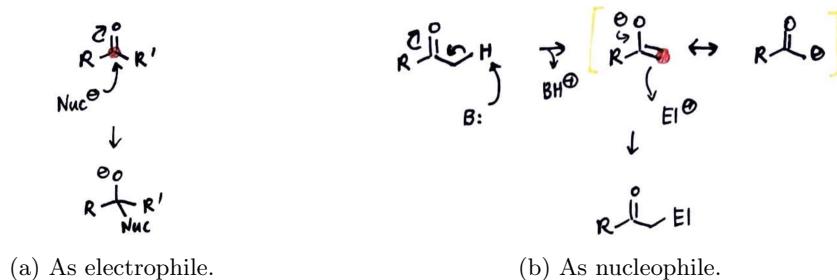


Figure 5.1: Carbonyl-based chemical reactions.

- Carbonyls have two important modes of reactivity.
  - We've already discussed how carbonyls can act as electrophiles (Figure 5.1a).
    - This yields a tetrahedral intermediate, as we've discussed.
  - The other mode of reactivity — which is new and our focus — is that we can deprotonate at the  $\alpha$ -carbon to make a nucleophilic species (Figure 5.1b).
    - The major resonance structure will be the oxygen-centered one (because oxygen is more electronegative).
    - However, most reactions we're interested in proceed at carbon.
  - Key concept: Oxygen *enables* this mode of reactivity stabilizing the negative charge.

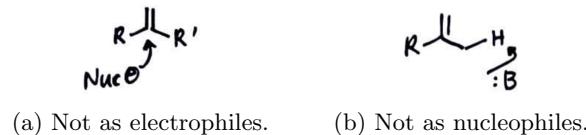


Figure 5.2: Alkenes do not react via carbonyl-analogous pathways.

- For the purposes of 5.13, analogous addition to alkenes (Figure 5.2a) and  $\alpha$ -deprotonation of alkenes (Figure 5.2b) is very rare.
  - Let's now discuss tautomers.

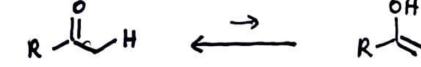


Figure 5.3: Keto-enol tautomerization.

- Ketones can tautomerize to **enols** (a portmanteau of alkene and alcohol).
  - The keto and enol form are known as **tautomers**.
  - The equilibrium favors the keto form by far (about a million to one; we'll only have 0.001% enol).

• Catalysts can speed up the interconversion, but they can't change the equilibrium.

  - Let's discuss the mechanism by which bases and acids speed this process up, though.

- Base-catalyzed keto-enol tautomerization mechanism.

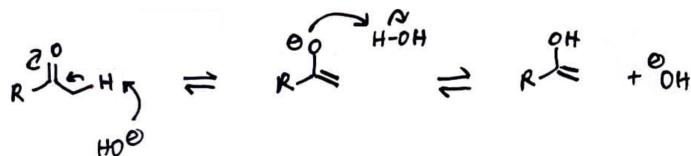
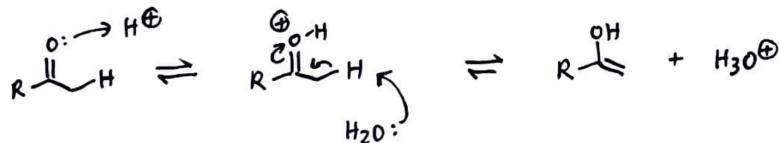
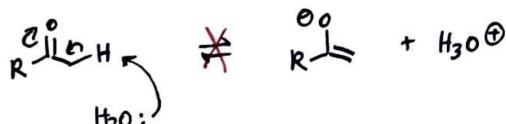


Figure 5.4: Keto-enol tautomerization mechanism (base-catalyzed).

- The  $\alpha$ -carbon of a ketone has  $pK_a \approx 20$ .
  - This is a good number to memorize, not because you'll ever be tested on it but because understanding relative  $pK_a$ 's will aid your chemical intuition.
- Hydroxide can speed up this process by deprotonating the  $\alpha$ -carbon.
  - Then we just protonate the oxygen.
- Recall that we still have  $K_{\text{eq}} \ll 1$ .
- Acid-catalyzed keto-enol tautomerization mechanism.



(a) Correct mechanism.



(b) Incorrect mechanism.

Figure 5.5: Keto-enol tautomerization mechanism (acid-catalyzed).

- We can either write the reagents equivalently as  $\text{H}^+/\text{H}_2\text{O}$  or  $\text{H}_3\text{O}^+$ .
- As we've been doing, we begin by protonating the carbonyl.
- Then the best base in solution comes and deprotonates the  $\alpha$ -carbon.
  - Water isn't a great base, but it's all we've got.
- Note that we do *not* do deprotonation first and protonation second, as drawn in Figure ??b.
  - Remember that anions cannot exist in acidic solution!
- So this is all great, but what if we don't believe Prof. Buchwald that tautomerization occurs?
  - It's good to question things in science!
  - Many times, we've assumed things that later experiments have proven incorrect.

- We can find evidence for enolization via an isotopic labeling study.

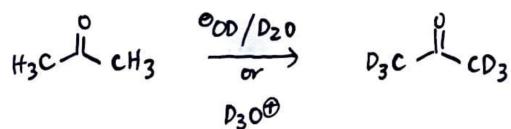


Figure 5.6: Isotopic labeling provides evidence for keto-enol tautomerization.

- If we dissolve acetone in basic deuterated water and deuterioxide (or acid), we will eventually obtain deuteroacetone.
- The mechanism proceeds analogously to Figure 5.4 or 5.5a, except that our reagents are all  $\text{DO}^-$  and  $\text{D}_2\text{O}$ .
  - In particular, we replace each of the six hydrogens one at a time with deuterium, eventually leading to the product.
  - We form the fully deuterated product instead of a H/D-mixed product because we assume that the concentration of deuterated acid or base and water is *much* greater than the concentration of acetone. This is similar to the swamping effect in Figure 4.31a.
- We now move onto Topic B:  $\alpha$ -halogenation of ketones.
  - We can do this with chlorine, bromine, or iodine.
- Base-promoted  $\alpha$ -halogenation mechanism.

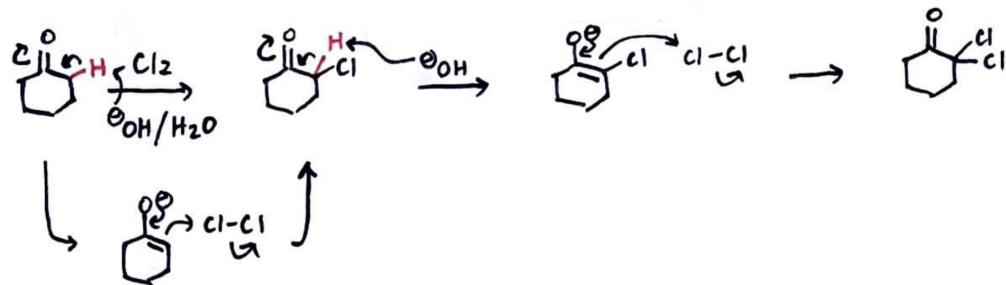


Figure 5.7:  $\alpha$ -halogenation mechanism (base-promoted).

- Imagine we mix cyclohexanone with chlorine gas under basic conditions. What's going to happen?
- We'll form a small amount of enolate, and then chlorinate to form  $\alpha$ -chlorocyclohexanone.
  - We declare victory!
  - Except that the world is a harsh place and — like in Figure 3.17a — we can get further reactivity.
- In particular, the hydrogen geminal to the  $\alpha$ -chlorine is now *more* acidic (proximity to an EWG, so anion is stabilized).
  - Thus, we can react again to get  $\alpha$ -dichlorocyclohexanone.
  - Thus, this reaction is not good... except in one case.

- The iodoform reaction.

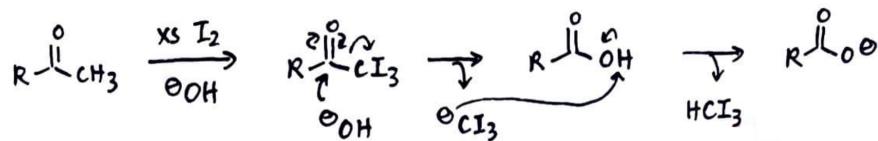
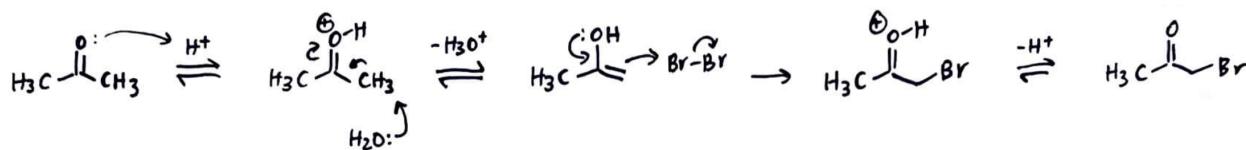


Figure 5.8: Iodoform reaction.

- In the first step, we have three successive iodinations to yield the triiodomethylketone.
- This is such a strong EWG and good leaving group that the triiodomethylketone acts kind of like an acid chloride.
  - In particular, we get an addition-elimination mechanism that kicks out the triiodomethanide anion.
  - This anion can then be protonated by the resultant carboxylic acid to yield iodoform ( $\text{HCl}_3$ ) and a stable carboxylate.
- Iodoform precipitates as a yellow solid.
  - In the olden days, it used to be a test for a ketone.
  - Before we had NMR, mass spec, and other kinds of spectroscopy, we had a bunch of test reagents that we would add to our compounds to determine what it was.
  - Essentially, if we had a compound and we didn't know what it was but thought it was a ketone, we could confirm or deny this by adding iodine and base to our mixture!
- What does it mean when Prof. Buchwald draws a circular arrow from a carbonyl  $\pi$ -bond back to it?
  - They use this in Clayden et al. (2012)!
  - This is a shorthand for the two-step addition-elimination process, in which electrons kick up in a first step and then kick back down in a second step.
  - This is similar to how we shorthand a two-step proton transfer as "PT!"
- So how do we make mono- $\alpha$ -haloketones, if that's our goal?
  - Use acid-catalyzed  $\alpha$ -halogenation!
- Acid-catalyzed  $\alpha$ -halogenation mechanism.

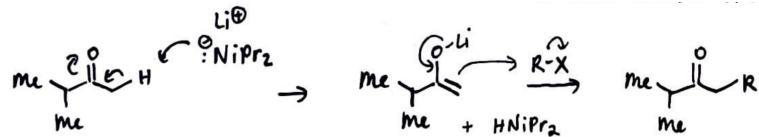
Figure 5.9:  $\alpha$ -halogenation mechanism (acid-catalyzed).

- Acids encourage the rate of formation of the enol.
- Then if we do this in the presence of bromine, we'll get  $\alpha$ -bromoacetone (following deprotonation).
- Now the product is *less* reactive than the starting material (because the bromine EWG stabilizes the carbonyl and disfavors protonation of it).
- Takeaway: Acid-catalyzed  $\alpha$ -halogenation is selective for monohalogenation.
- This process is used to synthesize a lot of medicines and drug molecules.

- We now move onto Topic C:  $\alpha$ -alkylation.
  - This is the heavy hitter; a really, really important reaction of ketones.
- General form.

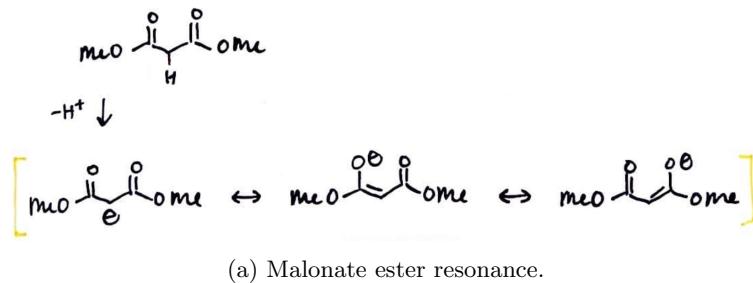
Figure 5.10:  $\alpha$ -alkylation.

- Suppose we want to convert a ketone into a new compound where we've formed a C–C bond.
- The other reagent is a primary or secondary alkyl halide.
- Drawing a mechanism for this doesn't seem too bad at first.
  - We may deprotonate to the enolate and attack the alkyl halide to start.
  - But there is a complication.
    - We get lots of side reactions!
  - In 5.13, we're all about efficiency and elegance, so this is not good.
- There are several solutions to this issue, which we'll discuss presently.
- Solution 1: Use lithium diisopropylamide (LDA).

Figure 5.11:  $\alpha$ -alkylation with lithium diisopropylamide.

- See Figure 3.3b for the structure and synthesis of LDA.
- Helpful characteristics of LDA.
  - LDA is a strong base.
  - It is secondary and hence hindered (therefore a poor nucleophile).
  - The conjugate acid of LDA has  $\text{pK}_a \approx 35$ .
  - Thus, it will only deprotonate and not do any competitive addition chemistry!
- We begin with an essentially irreversible deprotonation to the enolate.
- This is followed by 100% conversion to the alkylated product.
- Using LDA is a relatively modern solution — only about 50 years old.
  - However, organic chemistry has been around for close to 250 years!
  - The roots of organic chemistry are in the old German dye industry, which morphed into the present-day pharmaceutical industry.
  - So how did people do this stuff before LDA? Via solution 2.

- Solution 2: Malonate ester synthesis.



(b) Regular ester resonance.

Figure 5.12:  $\alpha$ -alkylation with malonate esters.

- The starting material has esters on both sides (either ethyl or methyl; it doesn't matter).
- The important thing is that for the malonate ester,  $pK_a \approx 13$ .
  - In contrast, a regular ester has  $pK_a \approx 25$ .
  - Why this drastic difference in  $pK_a$ ?
    - The deprotonated malonate ester's anion has more resonance forms (two adjacent carbonyls into which to delocalize!) than the deprotonated ester (only one adjacent carbonyl).
  - This difference leads us to call the deprotonated malonate ester a **soft enolate**.
  - These characteristics make it very easy and safe to work with, so it's often used at scale.
- We'll now quickly introduce a topic that we'll also discuss more next time.
- Kinetic vs. thermodynamic enolates.
- Kinetic** (enolate): The enolate generated by deprotonation at the less-substituted position, all else being equal.
- Example: LDA (really big and bulky) will selectively form the kinetic enolate at the unsubstituted position of  $\alpha$ -methylcyclohexanone.



Figure 5.13: Kinetic enolate formation.

- This enolate could then be used — for example — to attack methyl iodide ( $MeI$ ) and alkylate.
- Note that this process would most likely form a mixture of stereoisomers.

- **Thermodynamic** (enolate): The enolate that is more stable.
- Example: Potassium *t*-butoxide ( $\text{KO}^t\text{Bu}$ ) has  $pK_a \approx 16-18$ , so it deprotonates  $\alpha$ -methylcyclohexanone reversibly until we get the more stable one.

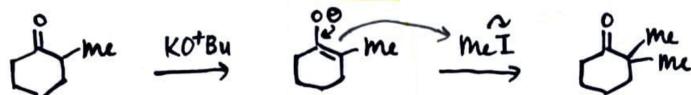


Figure 5.14: Thermodynamic enolate formation.

- Treating this with  $\text{MeI}$  then generates the  $\alpha$ -dimethylated form of cyclohexanone.
- You can add in  $\text{Me}_3\text{SiCl}$  to trap enolates as silyl enol ethers.

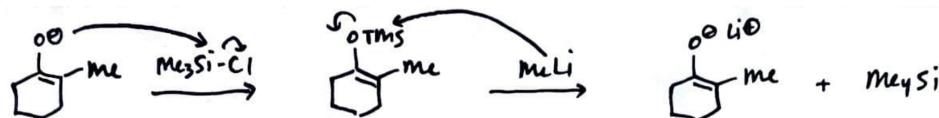


Figure 5.15: Trapping enolates as silyl enol ethers.

- This silyl protecting group could then be removed with  $\text{MeLi}$ , regenerating the enolate and yielding tetramethylsilane ( $\text{SiMe}_4$ ) as a byproduct.
- In the deprotection step, the methyl anion attacks the silicon atom in the TMS group, engaging in an  $S_N2$  displacement.

## 5.30 Enolate Alkylation

11/18:

- We will not begin with a line-by-line review of last lecture; rather, we will clarify some things.
- Lecture 29 recap.
  - Recall kinetic vs. thermodynamic enolates (Figures 5.13 & 5.14).
  - When we use a strong, hindered base (like LDA), we abstract the unhindered proton to form the kinetic enolate.
    - This process is irreversible, and yields 100% of the kinetic enolate.
    - The process is irreversible because  $pK_a \approx 35$  for the conjugate acid of LDA (lithium diisopropylamide), so this conjugate acid cannot react backwards.
  - Use of a somewhat strong, somewhat bulky base (like  $\text{KO}^t\text{Bu}$  in  ${}^t\text{BuOH}$ ).
    - This process is highly reversible, so we'll abstract the unhindered proton first. But then the enolate can react backwards with  ${}^t\text{BuOH}$  to reform the ketone!
    - This process is highly reversible because  $pK_a \approx 19$  for  ${}^t\text{BuOH}$ , so this conjugate acid *can* react backwards.
    - However, when we eventually deprotonate the hindered proton, we form a more stable enolate that is *less likely* to react backwards.
    - Thus, the net result is that we form the *thermodynamic* enolate under these conditions.
  - Both of these enolates can then be trapped with  $\text{MeI}$  into the corresponding  $\alpha$ -alkylation product.

- Lecture outline.

C.  $\alpha$ -alkylation.

- Enolate-forming bases.
- Enolates from esters (hard to form) and aldehydes (don't form).
- Enolate-alkylation electrophiles.
- Synthesis of  $\alpha$ -substituted acetic acid derivatives.
- Synthesis of  $\alpha$ -substituted 1,3-diols.

- We return to Topic C:  $\alpha$ -alkylation.
- Let's consider the properties of several strong bases.

<u>Base</u>	<u>Conjugate Acid (of Base)</u>	<u>pK<sub>a</sub> of Conjugate Acid</u>
NaOEt/EtOH	EtOH	~16
KOtBu/ <sup>t</sup> BuOH	<sup>t</sup> BuOH	~19
LDA/THF	iPr <sub>2</sub> NH	~35

Table 5.1: pK<sub>a</sub>'s of typical enolate-forming bases.

- The left column shows a base and the solvent in which you use it, not necessarily the base and its conjugate acid!
- It follows from the table that NaOEt and KO<sup>t</sup>Bu are reversible bases, and LDA is an irreversible base.
- The difference between the first two is that KO<sup>t</sup>Bu is bulkier and less nucleophilic.
  - So if we're worried about nucleophilic attack as a side reaction, use this!
- Otherwise, NaOEt is cheaper and more pleasant to work with.
- So what happens when we do enolate formation with different bases?
  - Suppose that the conjugate acid B<sub>1</sub>H has pK<sub>a</sub> > 22.
    - Then the reaction is irreversible.
    - Example: LDA!
  - Suppose that the conjugate acid B<sub>2</sub>H has 16 < pK<sub>a</sub> < 22.
    - This reaction is reversible.
    - Examples: NaOEt and KO<sup>t</sup>Bu!
  - Suppose that the conjugate acid B<sub>3</sub>H has pK<sub>a</sub> < 16.
    - Nothing happens! The base isn't strong enough.
  - Note: We'll read in Clayden et al. (2012) that we can use bases with pK<sub>a</sub> < 16 *if* we pair it with a Lewis acid.
    - Example: Trimethylsilyl chloride (TMSCl) and NEt<sub>3</sub>.
  - Generalizing this.
    - Consider the pK<sub>a</sub> of our  $\alpha$ -proton.
    - If the base is 3 pK<sub>a</sub> units weaker or stronger, we get reversible enolate formation.
    - If the base is more than 3 pK<sub>a</sub> units stronger, we get irreversible enolate formation.
    - If the base is more than 3 pK<sub>a</sub> units weaker, no reaction occurs because the base is too weak.

- Example: Consider methyl isopropyl ketone.
  - Use LDA to deprotonate at the methyl group and form the kinetic enolate.
  - Use  $\text{KO}^t\text{Bu}$  in  $t\text{BuOH}$  to form the thermodynamic enolate.
- How about forming enolates from esters?
  - We need LDA because  $pK_a \approx 25$  for the ester's  $\alpha$ -proton.
  - Indeed, esters have significantly less acidic  $\alpha$ -protons than ketones.
  - We also need low temperatures to prevent self-condensation.
- How about forming enolates from aldehydes?
  - For the purposes of this class, we'll say that aldehyde enolates don't exist.
  - In reality, aldehyde enolates *do* exist, but they are *so* reactive that even at low temperatures, there is lots of competitive self-condensation.
- We now return to alkylations of enolates in more depth.
  - There are parallels to  $\text{S}_{\text{N}}2$  reactivity here.
  - Enolates are more hindered than, for example, cyanide nucleophiles ( $\text{CN}^-$ ), azide nucleophiles ( $\text{N}_3^-$ ), etc.
    - They are also more basic.
  - For the purposes of 5.13...
    - We'll say that primary alkyl, methyl, benzyl, and allyl halides react with enolates to do  $\alpha$ -alkylation.
      - The TFs will discuss in recitation why benzyl and allyl halides are "activated!"
    - We'll also say that secondary alkyl halides do not react with enolates.
      - This is because it's more hindered, so we get more competitive elimination.
  - Tertiary, vinyl, phenyl, and neopentyl halides *never* react with enolates.
    - Note that neopentyl is bad (even though it's primary) because it's *super* bulky.
- We now discuss the synthesis of  $\alpha$ -substituted malonate esters.

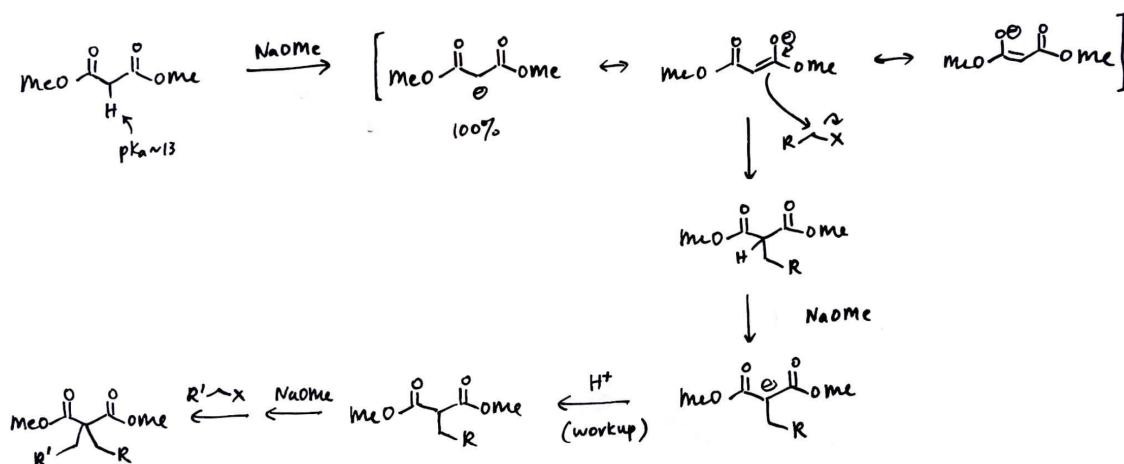


Figure 5.16: Malonate ester synthesis.

- Recall malonate esters from last class (see Figure 5.12a).
- Since these compounds have  $pK_a \approx 13$  at their  $\alpha$ -protons, NaOMe can do 100% deprotonation.
  - Note that we match the base to the ester: Dimethyl malonate should be paired with NaOMe in MeOH and diethyl malonate should be paired with NaOEt in EtOH.
  - This is because we'll have competitive transesterification (see Figure 4.32), so matching the base ensures that we don't get a mixture of products.
- Our deprotonated malonate ester can then attack some C–X bond, alkylating the  $\alpha$ -position.
- But we're still in basic solution, so our species will be deprotonated until water workup.
  - Do assume that we will *not* get competitive dialkylation.
  - However, alternatively, we could add more base and another C–X species to yield a dialkylated species.
- These reactions are collectively known as the **malonate ester synthesis**.

- TTQ: Given propane-1,3-diol, MeI, and EtI, make the product shown in Figure ??a.

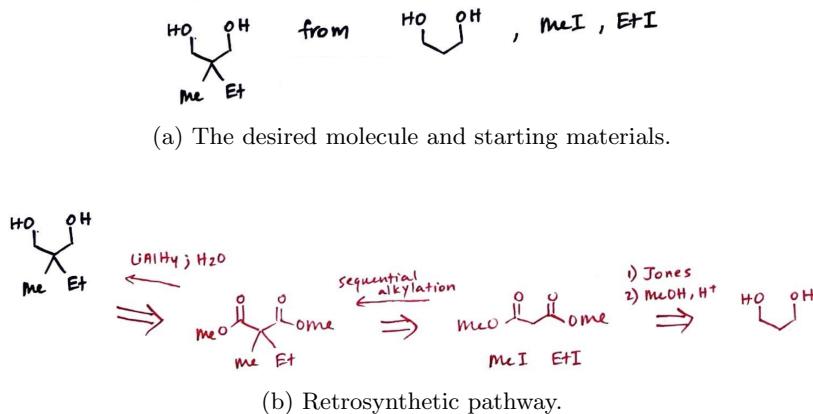


Figure 5.17: TTQ: Synthesis of an  $\alpha$ -substituted 1,3-diol.

- You might get greedy and start thinking about how to deprotonate the middle carbon directly, but we can't do that; we have to go back to something more reasonable first.
- Indeed, we can do a malonate ester synthesis with sequential alkylations followed by LAH reduction to the diol!
- Tip: Whenever you see a 1,3-diol, you should ask yourself if a malonate ester can be used!
- Note that we make the malonate ester from the 1,3-diol via Jones oxidation (see Figure 4.6a) followed by Fischer esterification (see Figure 4.34).
- We now discuss a related process called the **acetoacetate synthesis**.

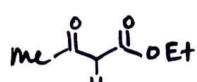


Figure 5.18: Ethyl acetoacetate.

- Here, we have a *ketone* next to an ester group.
  - The reason that one is an ethyl ester and the other is a methyl ester is historical; we are totally fine to use ethyl or methyl esters wherever, as long as we're consistent.
- $pK_a \approx 11$  for ethyl acetoacetate.

- Let's now begin the synthesis.

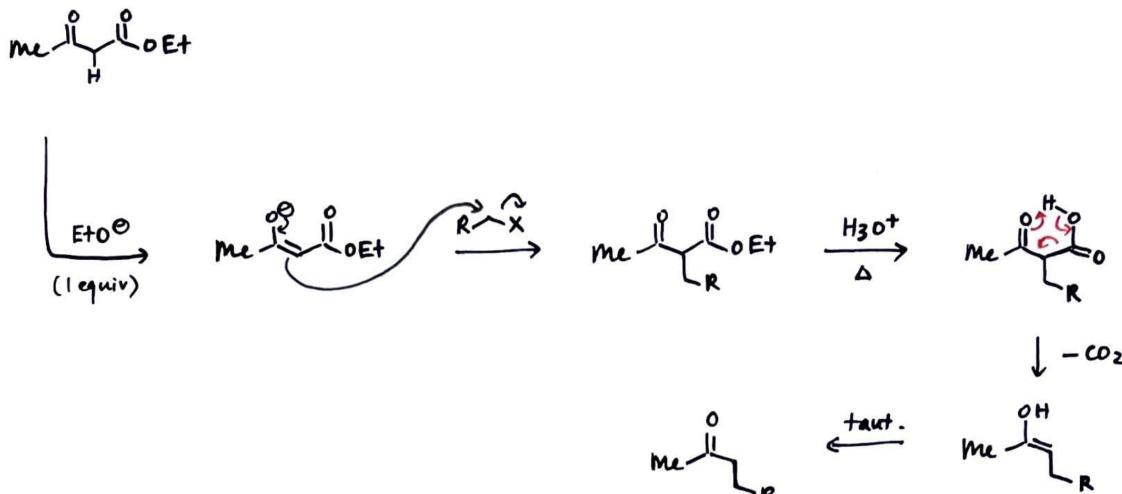


Figure 5.19: Acetoacetate synthesis.

- Adding 1 equivalent of  $\text{EtO}^-$  deprotonates to the enolate.
  - Note that the resonance will be primarily with the ketone, *not* the ester!
- Then we can do our alkylation.
  - We could even do a second alkylation, but we're just not going to show that here.
- Next step: We heat our intermediate in acid, which first gives ester hydrolysis to the  **$\beta$ -ketoacid**.
  - $\beta$ -ketoacids are known to undergo decarboxylation to yield enols!
- However, in acidic solution, our enol will quickly tautomerize to a ketone.
- Takeaway: This reaction is equivalent to enolate alkylation with LDA (see Figure 5.13).
  - However, LDA is pyrophoric and hence nasty to work with.
  - The acetoacetate synthesis, however, is **bucket chemistry** (easy, safe, and scalable).

- TTQ: Make 2-methylhexa-1,5-diene from ethyl acetoacetate, allyl bromide, any other reagent we want with two or fewer carbons, and any other non-carbon reagent.

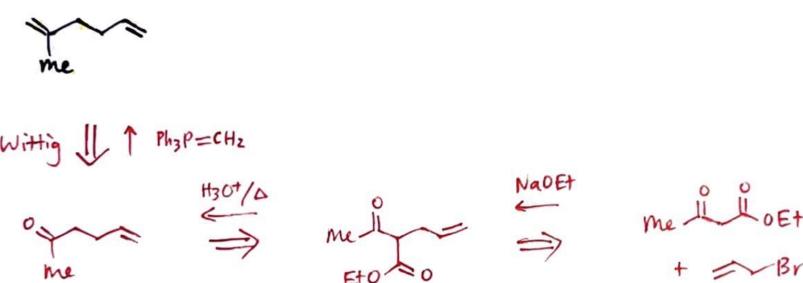
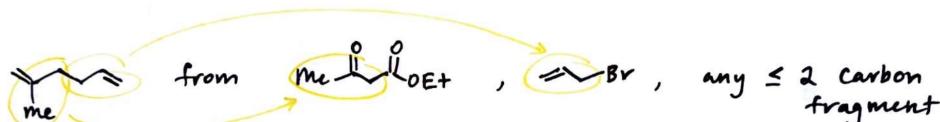


Figure 5.20: TTQ: Using the acetoacetate synthesis.

- Match up the carbons as we've done previously.
- A Wittig would yield the product.
- Next step: We can go back to the acetoacetate.
- Next step: Do alkylation from the starting materials.

## 5.31 Aldol Reactions

11/20:

- Announcements.
  - PSet 7 is due before Thanksgiving so that you don't have to spend the break thinking about it! However, you should feel free to turn it in the Saturday of Thanksgiving by noon if it's too hard to get it in before the break.
  - On PSets and exams, please only use reactions covered in 5.12 and 5.13!! Using knowledge from your research only makes grading more difficult for the TFs, and will not score you any more points.
  - The practice exams for Exam 4 will go up next Monday.
    - They will *not* cover material that hasn't been covered in class this time around.
- Lecture 30 recap.
  - Prof. Buchwald redraws Table 5.1, Figure 5.13, and Figure 5.14.
    - Note that whenever we use LDA, we need *at least* 1 equivalent of it to ensure irreversibility.
  - Good enolate alkylating agent include primary alkyl, methyl, benzyl, and allyl groups.
    - $X = \text{Br}, \text{I}, \text{OTs}$ .
    - There are other alkylating agents, but we're just not discussing them.
  - $\beta$ -dicarbonyl species are called "soft enolates," because they do less competitive chemistry.
- Today: Aldol reactions.
  - Etymology: Aldehyde starting material and alcohol product.
  - We'll discuss more named reactions later on this semester (Dieckmann, Michael, Claisen), but this one is not named after a person.
- Lecture outline.
  - D. Aldol reactions.
    - General form.
    - Acid-catalyzed mechanism.
    - Base-catalyzed mechanism.
    - Dehydration of aldol adducts.
    - Complications.
  - General form.

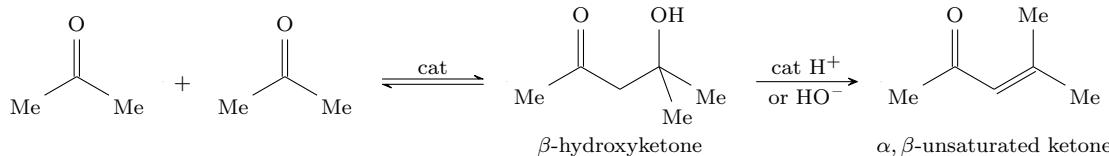


Figure 5.21: Aldol condensation.

- The catalyst is typically an acid or base.
- The first step is a condensation, and the second is a dehydration.
- Tip: If we see a  $\beta$ -hydroxyaldehyde or  $\beta$ -hydroxyketone in a synthesis question, think aldol!
  - If you see an  $\alpha, \beta$ -unsaturated carbonyl, you should also think aldol.
- Review: How does the ketone appear in acidic solution? It exists in a few forms.

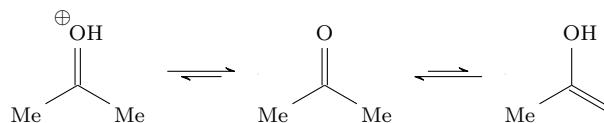


Figure 5.22: Forms of a ketone in acidic media.

- The majority is as the ketone.
- It can also be protonated.
  - This protonated species is a great electrophile, but there's only a little bit of it.
  - It is in equilibrium with the regular ketone.
- The ketone can also form the enol in very small amount.
  - This is a moderate nucleophile.
- Recall that there is *no* enolate in acidic media!
- Acid-catalyzed mechanism.

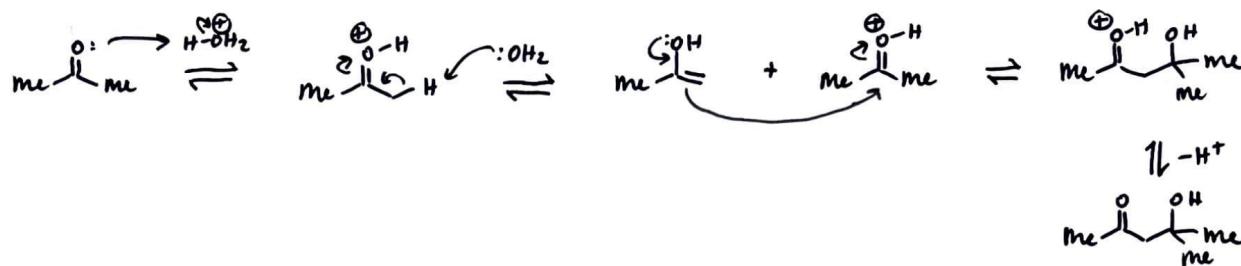


Figure 5.23: Aldol reaction mechanism (acid-catalyzed).

- In the first step of the mechanism, we protonate the ketone to its protonated form.
- We then deprotonate at the  $\alpha$ -position to form the enol.
- The enol can then nucleophilically attack another molecule of protonated ketone.
- Finally, we deprotonated to the aldol.
- Important note: Every step is reversible!
- Review: How does the ketone appear in basic solution? It also exists in a few forms.

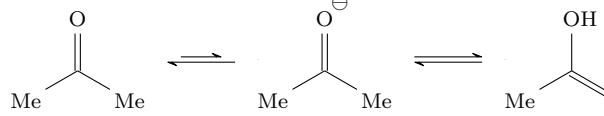


Figure 5.24: Forms of a ketone in basic media.

- The majority is as the ketone, once again.
- It can exist as the enolate.
  - This species is a great nucleophile, but there's only a little bit of it.
- The ketone can also form the enol in very small amount.
  - This is a moderate nucleophile.
- Recall that there is *no* protonated ketone in basic media!
- Base-catalyzed mechanism.

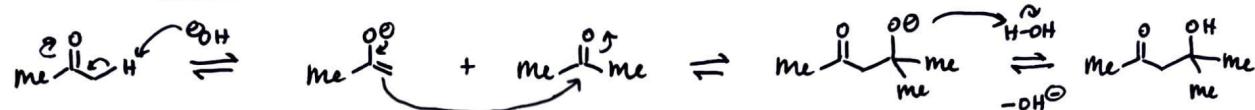


Figure 5.25: Aldol reaction mechanism (base-catalyzed).

- In the first step of the mechanism, hydroxide comes in to form the enolate.
- The enolate then adds nucleophilically into a molecule of (regular, nonprotonated) ketone.
- We then protonated the oxyanion to form the aldol.
- Important note: Every step is reversible, once again!
- This is a very efficient process: Base-catalyzed, with no cationic intermediates.
- How do we get from the aldol adduct to the  $\alpha,\beta$ -unsaturated ketone?
- Via the **dehydration** of aldol adducts!
- **Dehydration** (reaction): A reaction that involves the loss of  $\text{H}_2\text{O}$ .
- A possible (but incorrect!) acidic mechanism.

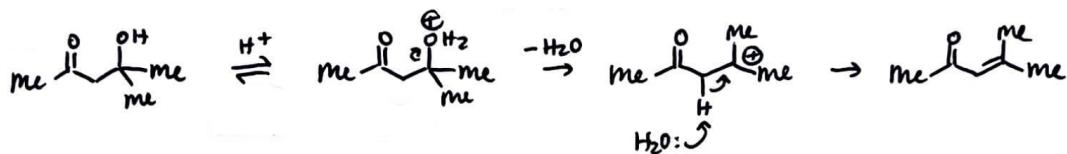
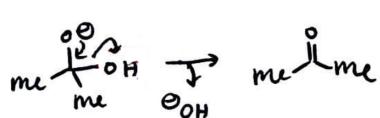
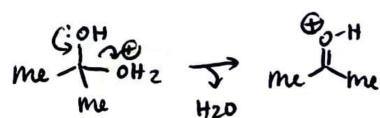


Figure 5.26: Incorrect acid-catalyzed aldol dehydration mechanism.

- In acidic media, we protonate the alcohol, which then leaves to give a tertiary carbocation.
- Tertiary carbocations are ok here because we have all that hyperconjugation stabilization.
- Then we get subsequent elimination to the  $\alpha,\beta$ -unsaturated ketone product.
- To understand the real mechanism, consider the tetrahedral intermediates.



(a) Pushing hydroxide.



(b) Pushing water.

Figure 5.27: Push groups in tetrahedral intermediates.

- Hydroxide is a bad leaving group, but if we have a **push group** (ideally an anionic species) in the tetrahedral intermediate, we can kick it out (Figure 5.27a).
  - In acidic media, OH is typically not that good of a push group, but it is able to push out water, which can then come back and remove the proton (Figure 5.27b).

• In aldol reactions, alkenes act as “electron conduits.”

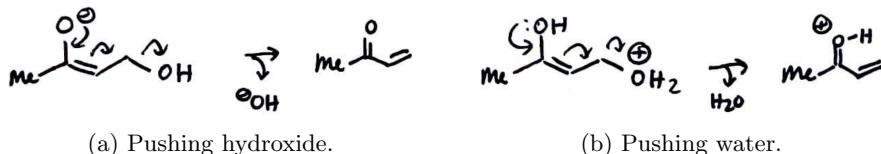


Figure 5.28: Push groups can act from distant positions through electron conduits.

- This allows the (protonated or unprotonated)  $\beta$ -alcohols to feel the effect of the oxyanion or hydroxyl group even from further away!
  - With push groups in mind, let's now discuss the *correct* acid-catalyzed aldol dehydration mechanism.

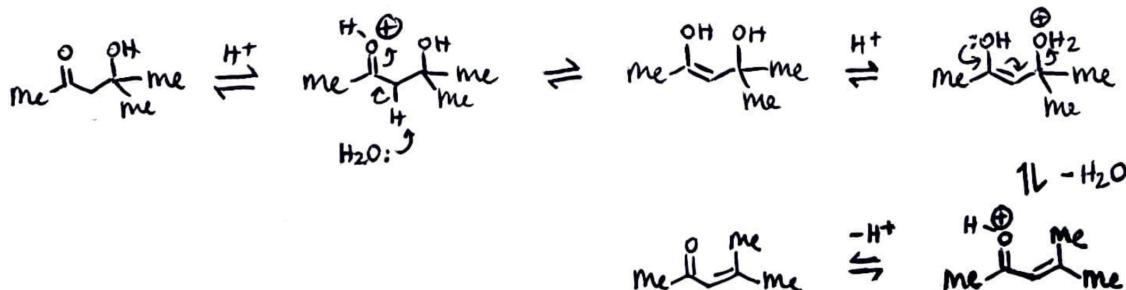


Figure 5.29: Aldol dehydration mechanism (acid-catalyzed).

- The first two steps are keto-enol tautomerization.
  - We then protonate the  $\beta$ -alcohol.
  - Next, we push it out through our electron conduit.
  - Finally, we deprotonate our reformed ketone.
  - To drive these reactions in the forward direction, we often need to remove water.<sup>[1]</sup>
    - We can remove water with some kind of dehydrating agent, though we don't need to show this on PSets or exams.
  - A story from Prof. Buchwald's undergrad years.
    - Running a reaction in acetone on a 200 mg scale, but isolated 9 g of product!
    - What happened?
    - Someone had added a dehydrating agent to the bottle of acetone, turning it all into the aldol condensation product! So Prof. Buchwald hadn't used acetone as his solvent; he'd used the above aldol condensation product.
  - Complications that arise in aldol reactions.

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<sup>1</sup>Think Le Châtelier's principle! Removing one product drives the equilibrium to the right.

- Complication #1: Mixed aldols.

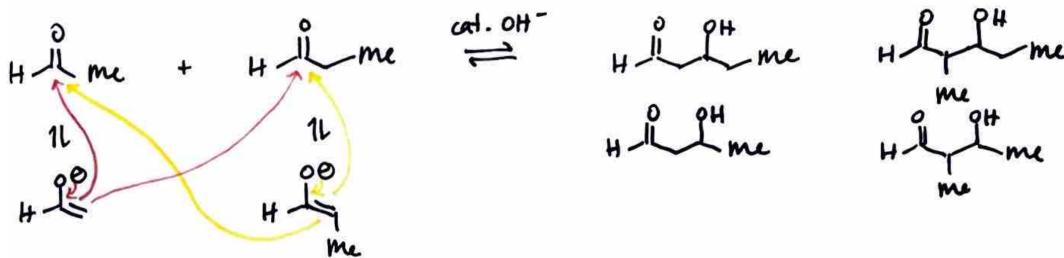


Figure 5.30: Mixed aldol reaction product distribution.

- This is what happens if we have two kinds of potential enolate-forming species in solution.
- We'll get a mixture of cross-condensation and self-condensation products! There's no way to do this selectively.
- And we're all about *efficiency* and *elegance* in 5.13, so we need ways around this.
- So how can we pick substrate combinations in which only one component can act as a nucleophile?

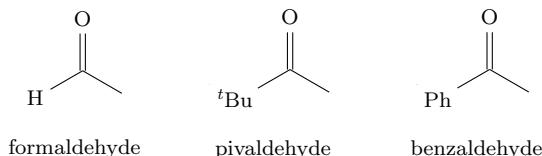


Figure 5.31: Non-enolizable carbonyl compound examples.

- Carbonyls aren't inherently nucleophiles; we make them *into* nucleophiles via deprotonation of an  $\alpha$ -proton.
- But if we make a carbonyl without any  $\alpha$ -protons, we have a non-enolizable species that can *only* react as an electrophile!
- Examples: Formaldehyde, pivaldehyde (smells terrible), and benzaldehyde (smells like almonds).
  - Aldehyde protons have high  $pK_a$ 's and won't be deprotonated.
  - Note that formaldehyde is a gas, but for the purposes of 5.13, we'll say that we can treat it as a liquid reagent like any other. This isn't entirely false because we can buy liquids that react like they're liquid formaldehyde (i.e., they decompose to formaldehyde *in situ*).
- Thus, if we mix acetophenone with formaldehyde, we will only get one aldol product!

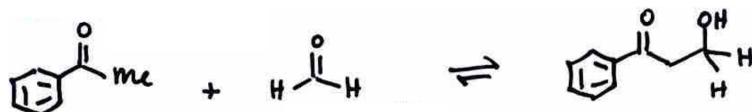


Figure 5.32: Cross-aldol reaction with only one enolizable species.

- Note that we don't get competitive dimerization of acetophenone because aldehydes are *much* more electrophilic, so they'll react with an enolate *much* faster.

- Complication #2: Intramolecular aldol reactions.



Figure 5.33: Intramolecular cross-aldol reaction.

- Here, we'll form the  $\beta$ -hydroxy cyclohexanone.
- Why did we deprotonate the methyl group? Indeed, we're under equilibrating conditions, so shouldn't we deprotonate at the other side to form the thermodynamic enolate?
  - We can form that enolate, but it won't react! The proposed product is a cyclobutane derivative.
  - Cyclobutanes have 25 kcal/mol of ring strain.
  - 1.4 kcal/mol means 10-fold selectivity, so this cyclobutane product is like 19-orders of magnitude disfavored.
  - We'll just go from the thermodynamic enolate back to the ketone, until we deprotonate to form the kinetic enolate.
- Complication #3: A modern strategy for cross-aldol reactions between multiple enolizable products.

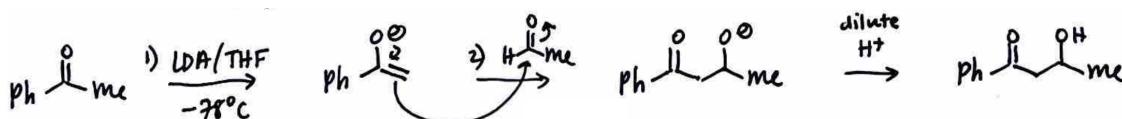


Figure 5.34: Modern cross-aldol reaction.

- Deprotonate with cold LDA to form the kinetic enolate selectively.
- Then add the other coupling partner for quick reactivity.
- Note that *p*-TsOH is a good acid catalyst for dehydration!

## 5.32 Claisen Condensations and Conjugate Additions

11/22:

- Lecture 31 recap.
  - Recall Figure 5.21.
    - In an aldol reaction (not the dehydration part), every step is reversible.
    - Good aldol reactions are those in which...
      - Cross-aldols in which only one molecule can enolize;
      - Self-condensation/dimerization.
      - Intramolecular;
      - Use of LDA (1 equivalent) to selectively form the kinetic enolate, then add to an aldehyde.
  - Lecture outline.
    - E. Claisen condensations.
    - F. Michael additions.
      - 1,4-additions.

- We'll begin with Topic E: Claisen condensations.
  - These were discovered by Ludwig Claisen.
- General form.

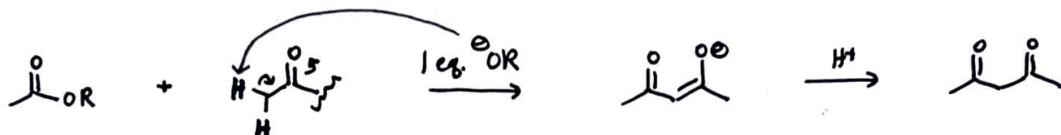


Figure 5.35: Claisen condensation.

- This is a reaction between an ester and an ester/ketone to form a 1,3-dicarbonyl.
- The ester/ketone will become the enolate and attack the other ester.
  - It must have at least two protons on its  $\alpha$ -carbon in order for this reaction to work.
  - One of these protons will be picked off for the initial condensation, and the second will be picked off to form the enolate drawn above (which is stable until workup).
- To prevent (noticeable) transesterification, we use an alkoxide base ( $RO^-$ ) matching the ester.
- Unlike aldol reactions (see Figure 5.21), the first step is irreversible here.
  - This is because the reaction is driven forward by the formation of a stable enolate in the pre-workup step.
- Claisen condensation mechanism.

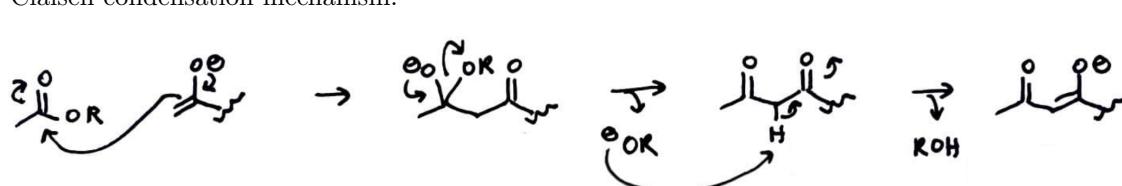
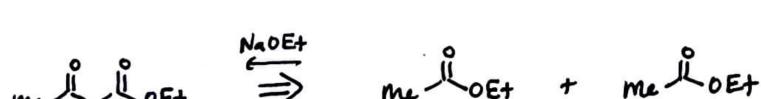


Figure 5.36: Claisen condensation mechanism.

- The first step forms a tetrahedral intermediate.
- The third step is driven by a  $pK_a$  difference: The 1,3-dicarbonyl has  $pK_a \approx 9$  and ROH has  $pK_a \approx 16$ , so the alkoxide base will very much favor deprotonating the 1,3-dicarbonyl.
- Note again the two different hydrogens that get picked off, and the enolate that is stable until workup.
- Under workup conditions, why won't we protonate at the oxygen?
  - This would form a  $\beta$ -ketoenol, and enols are unstable!
  - Even if we did form this, it would quickly tautomerize to a 1,3-dione.
- Self-Claisen condensations.

Figure 5.37: Self-Claisen condensations synthesize  $\beta$ -ketoesters.

- For the PSet, you will need to be able to make ethyl acetoacetate as above!!
- Tip: If you ever need to synthesize a  $\beta$ -ketoester, think Claisen!
- This is especially easy to do if you can start from two equivalents of the same starting material for pseudodimerization, as above.
- What about intramolecular Claisen condensations? This is the Dieckmann condensation.
  - Walter Dieckmann developed this while in München at BASF.
- General form.

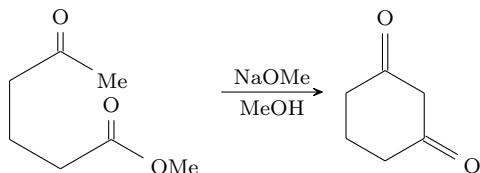


Figure 5.38: Dieckmann condensation.

- As per usual, the solvent is the alcohol that is the conjugate acid of the base used, which in turn is determined by the type of ester used in the starting material.
  - For example, here we use  $\text{MeOH}$  and  $\text{NaOMe}$  because our starting material contains a methyl ester.
- This reaction can be used to make 5- or 6-membered rings.
- Mechanism.

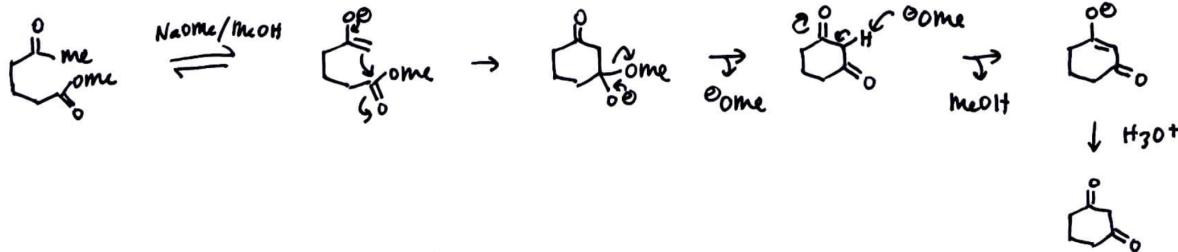


Figure 5.39: Dieckmann condensation mechanism.

- Making 1,3-diones is a topic that will probably be on the exam!! Prof. Buchwald likes these questions.
- Crossed or mixed Claisen condensations.

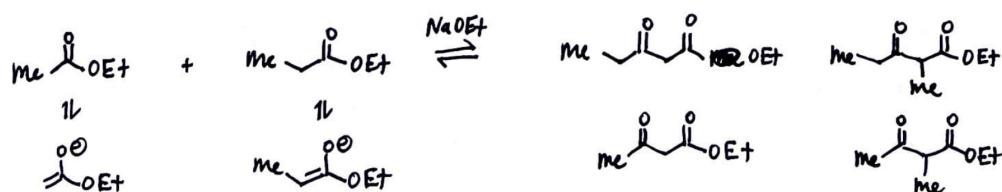


Figure 5.40: Mixed Claisen condensation product distribution.

- Claisen reactions don't have to be dimerizations!
- If we mix two esters, we will not get the coupled product selectively.
  - Instead, we will get a mixture, and *we do not like mixtures.*
- Recall that NaOEt only yields a small amount of enolate, so once it's formed, it can react with either compound.
- Effective mixed Claisen.

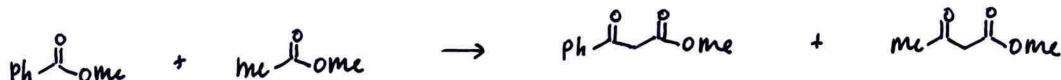


Figure 5.41: Cross-Claisen condensation with only one enolizable species.

- Analogously to Figure 5.32, we can use a mixture containing only one enolizable position.
- One side product we'd see is the dimerization product of the enolizable species.
  - If we were desperate to make this compound, though, we could do this and then purify out just the heterocoupled product.
- Thus, this is still inelegant.
- Solution #1 to mixed Claisens.

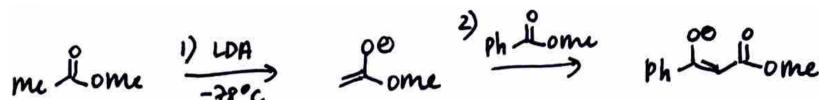


Figure 5.42: Modern cross-Claisen condensation.

- Analogously to Figure 5.34, use LDA!
- One-pot, two-step process: To a container of your first ester in THF at  $-78^{\circ}\text{C}$ , add LDA. Then add your other ester.
- Solution #2 to mixed Claisens.

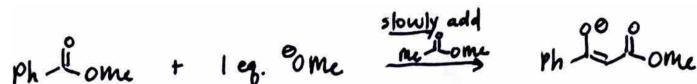


Figure 5.43: Dropwise cross-Claisen condensation.

- Mix your nonenolizable ester and base. Then add your other ester slowly/dropwise.
- This makes it so that as soon as a molecule of your enolizable ester forms the enolate, it is surrounded by many more molecules of the nonenolizable ester and thus is more likely to react with one of them!
- Reactions between ketones and esters are usually clean.



Figure 5.44: Ketone-ester condensation.

- Here, we take advantage of the difference in  $pK_a$ 's.
  - Essentially, we will form  $10^6$  times more ketone enolate than ester enolate because  $pK_a \approx 19$  at the  $\alpha$ -position of a ketone, and  $pK_a \approx 25$  at the  $\alpha$ -position of an ester.
- Takeaway:  $\Delta pK_a$ 's control the selectivity.
- However, there is one complication.
  - Because ketones are more electrophilic than esters, the (non-dehydrogenated) aldol will form in solution more readily than the Claisen condensation product.
  - However, the aldol product forms reversibly, and the Claisen one does not!
  - Thus, the quick reversible equilibrium to the aldol product gives way to a slow, steady, and irreversible conversion to the Claisen condensation product, forming it exclusively in the end.
- This concludes our discussion of Claisen condensations.
- We now move onto Topic F: Michael additions.
  - These are also known as 1,4-additions.
- General form.



Figure 5.45: Michael addition.

- We run these reactions with catalytic base.
- In retrosynthesis, look for 1,5-dicarbonyls! This is a big clue that Michael addition was used.
- The left compound (the enolizable ketone) is called a **Michael donor**.
  - It is nucleophilic.
  - Examples: The enolates of esters, ketones, and 1,3-dicarbonyl compounds.
- The right compound (the  $\alpha, \beta$ -unsaturated ketone) is called a **Michael acceptor**.
  - It is electrophilic.
  - Examples:  $\alpha, \beta$ -unsaturated acyl X groups, where X = H, alkyl, aryl, OR, NR<sub>2</sub>, etc.  $\alpha, \beta$ -unsaturated nitriles and nitro-compounds work, too.
- Why do we get nucleophilic attack at the  $\alpha, \beta$ -unsaturated ketone's  $\beta$ -carbon?

Figure 5.46: Resonance forms of an  $\alpha, \beta$ -unsaturated ketone.

- Because of resonance, that  $\beta$ -carbon has a  $\delta^+$  partial charge on it!
- Michael addition mechanism.



Figure 5.47: Michael addition mechanism.

- The Michael donor gets converted to its enolate form, which then attacks the Michael acceptor.

- Example Michael addition.

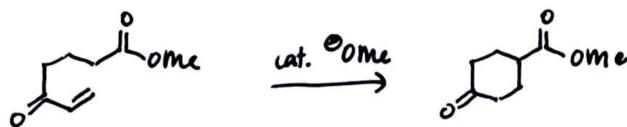


Figure 5.48: Intramolecular Michael addition.

- This type of reaction leads into another important reaction!
- The Robinson annulation.

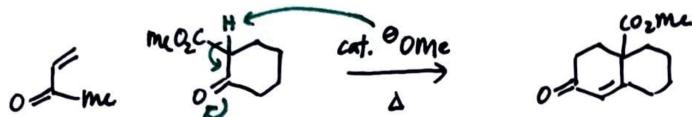


Figure 5.49: Robinson annulation.

- This reaction is a Michael addition, followed by an aldol condensation, followed by a dehydration.
- A historically important reaction that is still used today to synthesize pharmaceuticals at scale.
- 1,4-additions are a broader class of reactions than just Michael additions.
  - Recall Figure 4.52: Gilman reagents can do a kind of 1,4-addition, too!
  - Note that we can synthesize a broader class of Gilman reagents called **cuprates** by combining 2 equivalents of an alkyl lithium reagent RLi with CuI; these  $R_2CuLi$  reagents will then add R instead of Me!
- If we have an  $\alpha, \beta$ -unsaturated ketone, a Grignard or alkyl lithium reagent could be used to do 1,2-addition to the ketone.

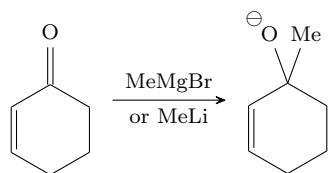


Figure 5.50: 1,2-addition with Grignards and alkyl lithium reagents.

- This is called 1,2-addition because we add a metal (Mg or Li) to the 1-atom (the oxygen), and an R group to the 2-atom (the carbon).
- If we have an  $\alpha, \beta$ -unsaturated ketone, a Gilman reagent can do 1,4-addition to the entire enone system!

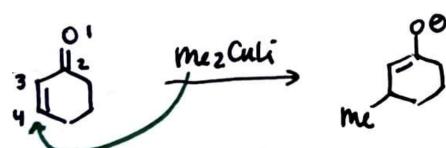


Figure 5.51: 1,4-addition with the Gilman reagent.

- This is called 1,4-addition because we add a metal (Cu) to the 1-atom (the oxygen), and an R group to the 4-atom (the  $\beta$ -position).
- 1,4-addition also gives us an enolate, and an enolate is a terrible thing to waste.
  - We can work this up directly to get rid of it, *or* we can use it.
  - For instance, we could trap it as a silyl enol ether (as in Figure 5.15).
    - Recall that we could then regenerate the enolate later with MeLi.