Week 6

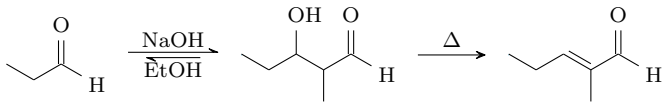
Carbonyl Condensation Reactions

6.1 Carbonyl Condensation Reactions 1

5/3:

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

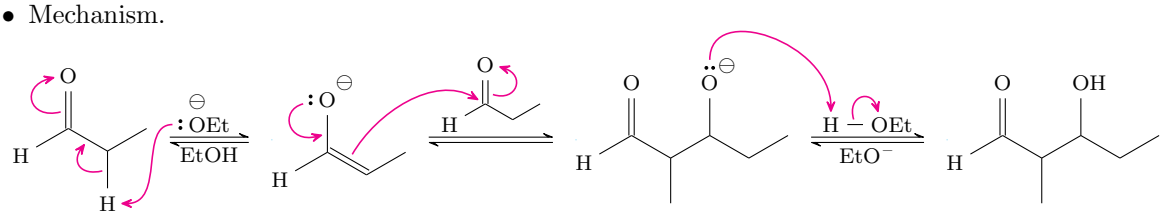
- Tang is dividing this chapter into three parts.
  I. Aldol reactions.
  II. Claisen condensation.
  III. Conjugate addition.
- Today, we will cover the following.
  I. Aldol reactions.
    A. Basic conditions.
    B. Acidic conditions.
    C. Intramolecular ketone reactions.
    D. Cross-aldol reactions.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



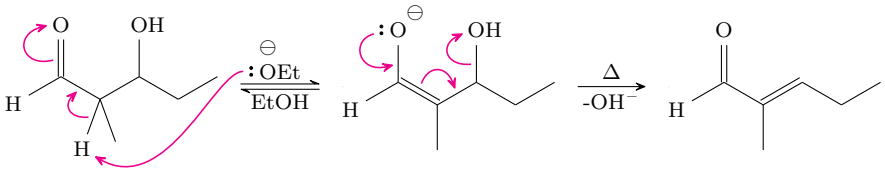
  - NaOH is a stoichiometric reagent.
  - EtOH is a solvent.
  - The full reaction from left to right can be done all at once with heat added from the beginning.
  - Notice that the first molecule (3-hydroxy-2-methylpentanal) has molecular formula exactly double that of the starting material (propanal).

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

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



(a) Aldol reaction proper.



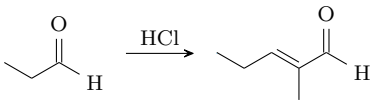
(b) Subsequent dehydration.

Figure 6.1: Basic aldol reaction mechanism.

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

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

- Acidic conditions.
- General form.



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

- Mechanism.

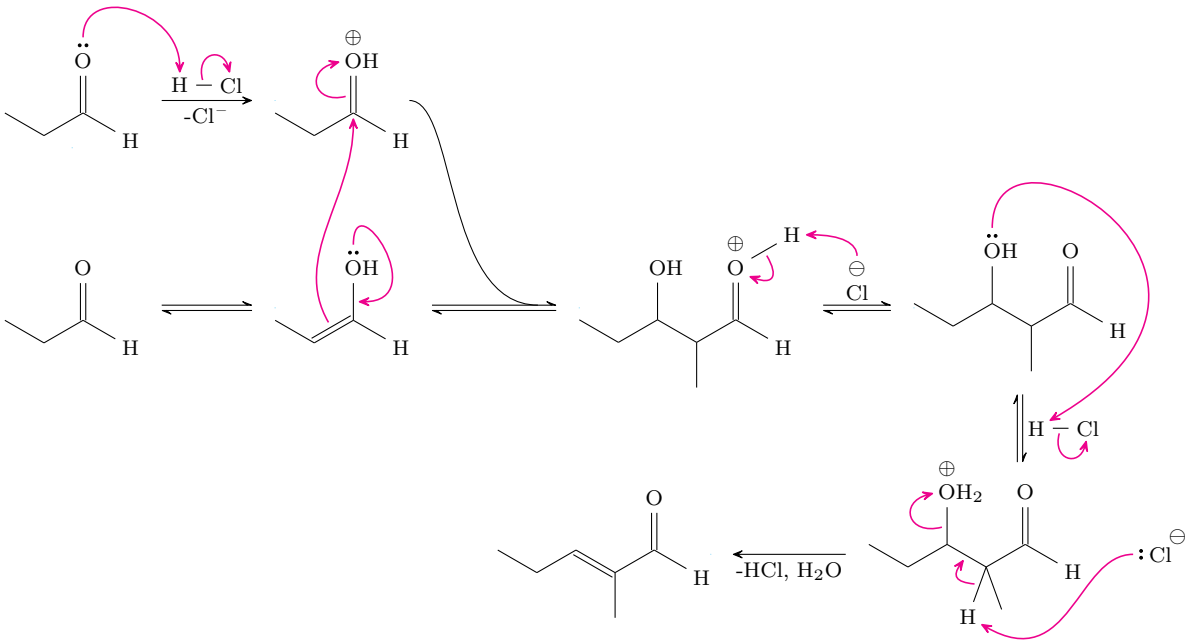


Figure 6.2: Acidic aldol reaction mechanism.

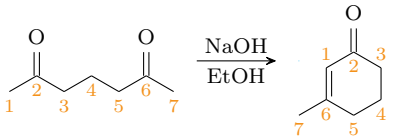
  - The first step is enol formation.
  - We also must preactivate the aldehyde before the enol can react with it.
  - In the last step, since Cl^- is a really crappy base, we have to motivate the leaving group via protonation.
    - Note that the reason that this dehydration reaction is easier than the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

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

- A note on testable material.

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

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



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

- Mechanism.

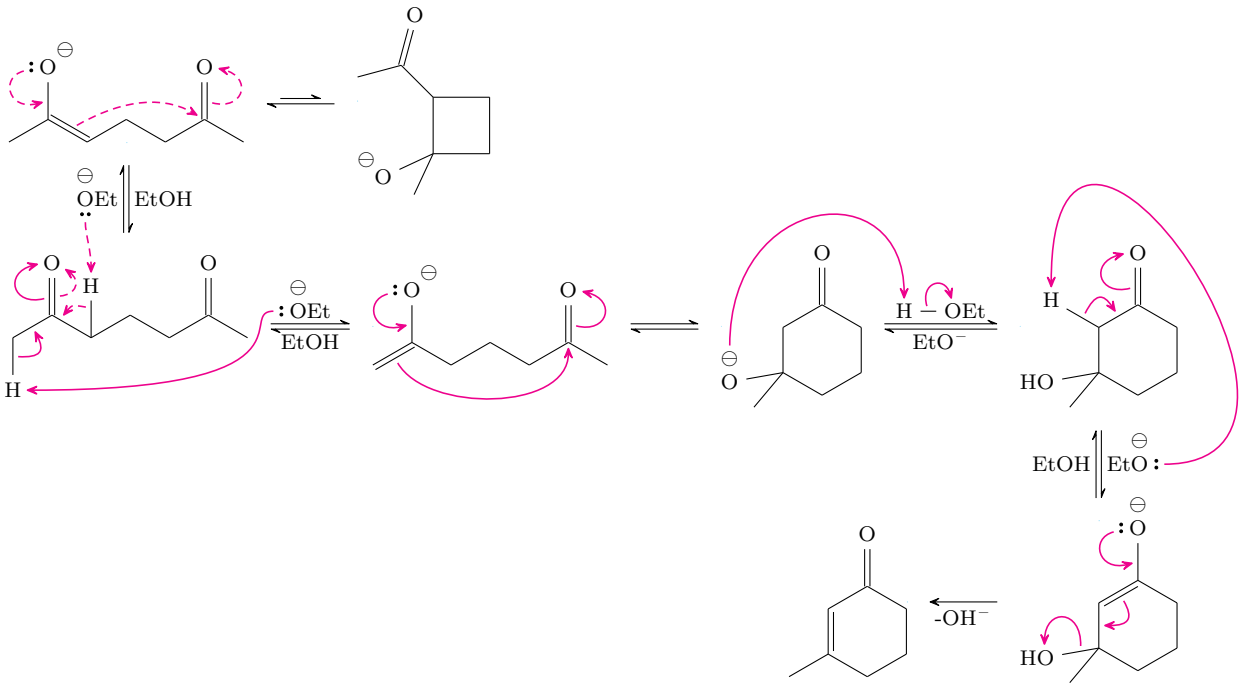


Figure 6.3: Intramolecular ketone aldol reaction mechanism.

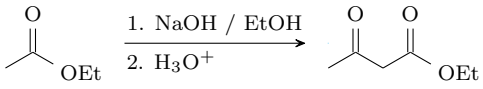
  - The diketone above is symmetric. Thus, it does not matter which side acts as the nucleophile (gets deprotonated) and which side acts as the electrophile (is attacked by the enolate). Therefore, we may WLOG deprotonate the left side of the molecule above.
  - Having chosen a ketone to deprotonate, we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

- Rules.

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

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

- General form.



  - Forms a β-ketoester!

- Mechanism.

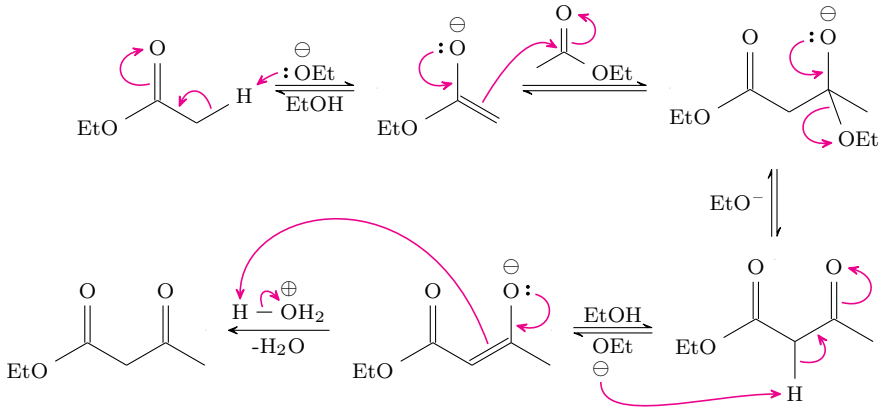


Figure 6.4: Claisen condensation mechanism.

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

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

6.2 Carbonyl Condensation Reactions 2

5/5:

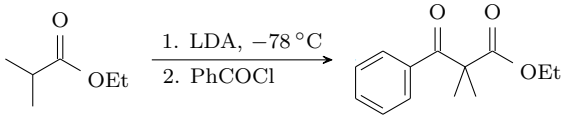
- Today's lecture content in Solomons et al. (2016).
  - Today: Sections 19.1-19.3 and 19.7-19.8.
  - Next time: Additional examples and Sections 20.1-20.4.
  - Practice problems: 19.41-19.48, 19.50-19.51, 19.58-19.59.
- Today will be mostly content and not have very many examples.
  - Tang is primarily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

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

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

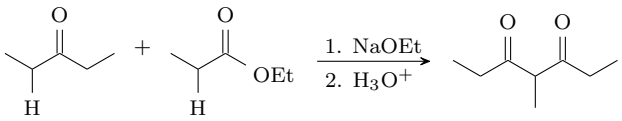
IV. Mannich reaction.

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

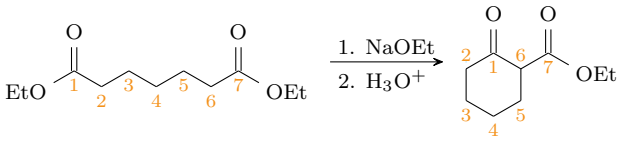


  - This reaction will not be tested; it's just for our own understanding of the fact that this is possible.

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



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



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

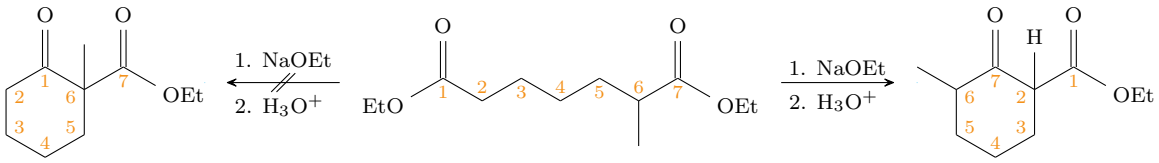
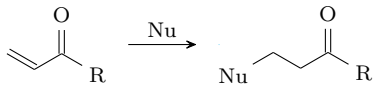


Figure 6.5: Asymmetric diesters in the Dieckmann condensation.

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

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



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

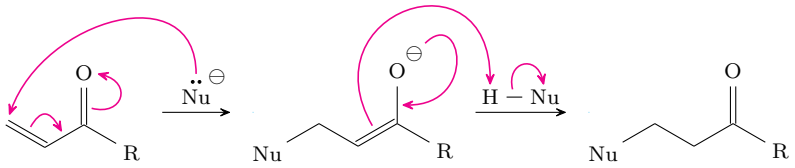
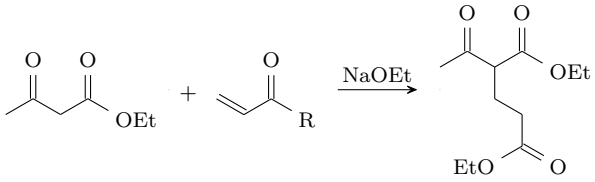


Figure 6.6: Conjugate addition mechanism.

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



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

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

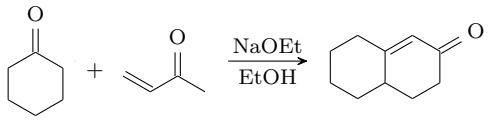
- Compounds that can serve as Michael donors and acceptors.
  - Acceptable donors: Ketones and esters yield an enolate under basic conditions.
  - Unacceptable donors: Aldehydes.
    - We will get an aldol reaction.
  - Acceptable Michael acceptors: α,β-unsaturated ketones, aldehydes, esters, nitriles,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

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

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

- Robinson annulation.

- General form.



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

- Mechanism.

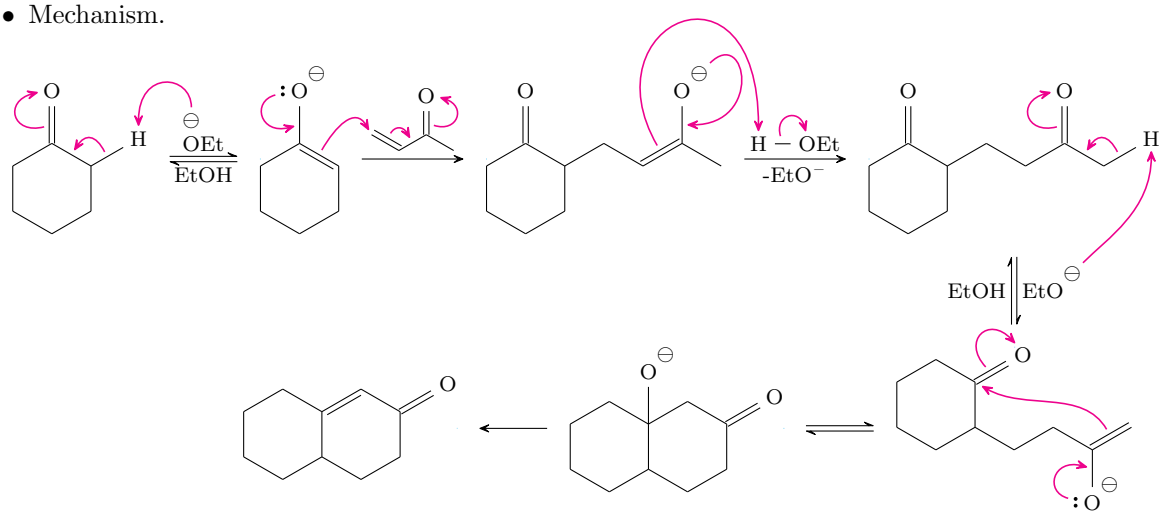
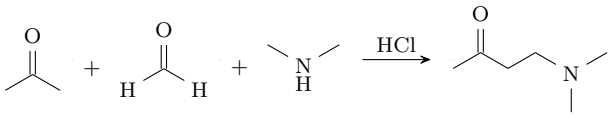


Figure 6.7: Robinson annulation mechanism.

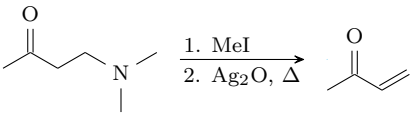
  - In this class, we assume that Michael reactions are irreversible; in reality, this is not always the case.
  - The last step is accomplished in an analogous manner to the last three steps of 6.3.
  - Tang will give more examples next lecture

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



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

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



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

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

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