

- 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.

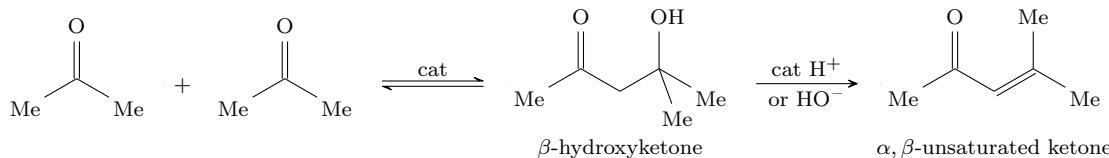


Figure 5.21: Aldol condensation.

- 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.

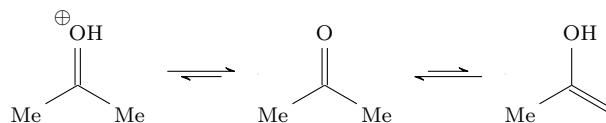


Figure 5.22: Forms of a ketone in acidic media.

- 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.

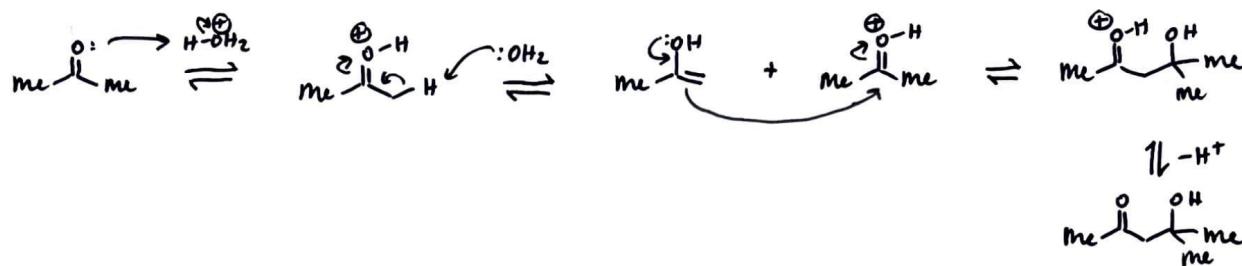


Figure 5.23: Aldol reaction mechanism (acid-catalyzed).

- 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 deprotonate 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.

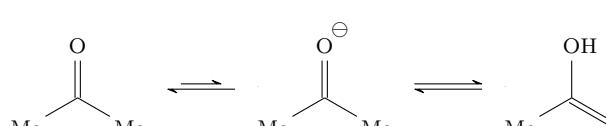


Figure 5.24: Forms of a ketone in basic media.

- 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.

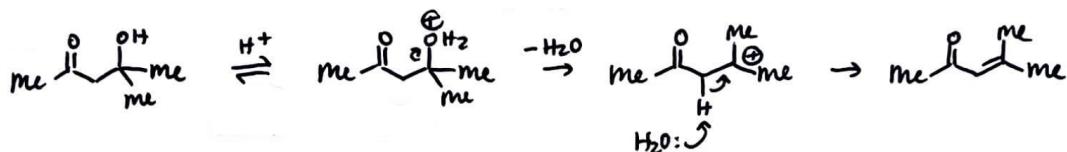
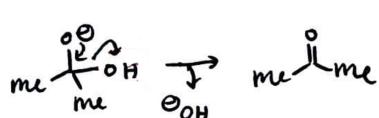
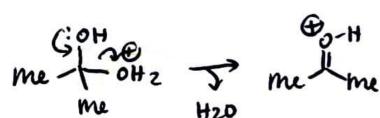


Figure 5.26: Incorrect acid-catalyzed aldol dehydration mechanism.

- 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.”

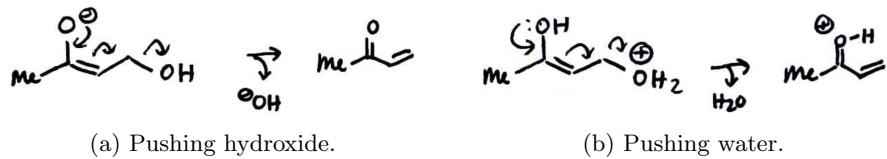


Figure 5.28: Push groups can act from distant positions through electron conduits.

- 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.

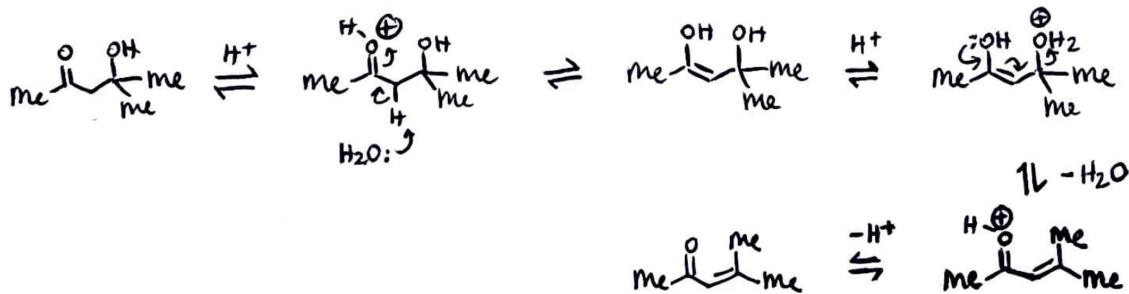


Figure 5.29: Aldol dehydration mechanism (acid-catalyzed).

- 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.

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

- Complication #1: Mixed aldols.

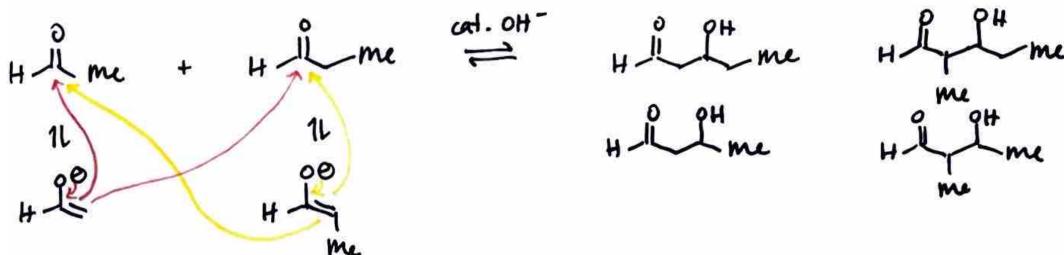


Figure 5.30: Mixed aldol reaction product distribution.

- 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?

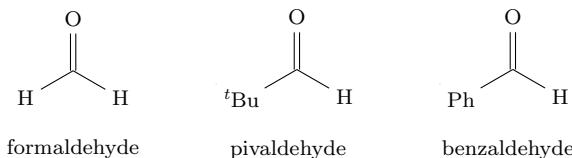


Figure 5.31: Non-enolizable carbonyl compound examples.

- 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!

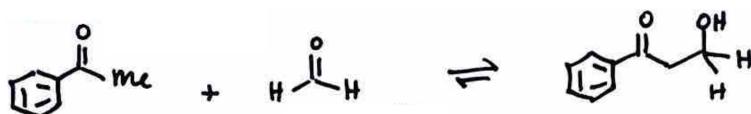


Figure 5.32: Cross-aldol reaction with only one enolizable species.

- 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.

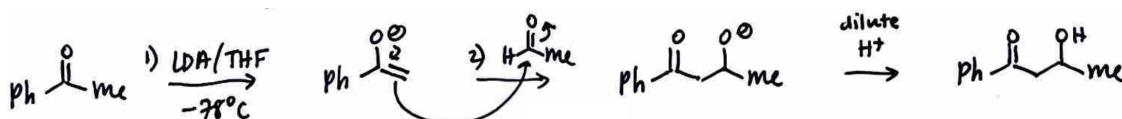


Figure 5.34: Modern cross-aldol reaction.

- Deprotonate with cold LDA to form the kinetic enolate selectively.
- Then add the other coupling partner for quick reactivity.
- Note that  $p\text{-TsOH}$  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.