Week 5

Alpha-Carbon Reactions

5.1 Reactions at the α-Carbon of Carbonyl Compounds 2

4/26:

- Announcements.
  - Professor Tang starts next Tuesday.
  - Midterm 2 will be written by Levin.
  - PSet 4-6 and the final will be written by Tang (she will release practice exams).
- Midterm 1 stats.
  - Range: 0-91.
  - Mean/st. dev: 34 ± 20 recurved to 70 ± 10.
  - Median: 33.
  - Nobody got 3a, the first mechanism.
  - Such recurving will be done for all exams.
- Midterm 1 comments.
  - This is Levin's first time teaching undergrads. As an undergrad, he had a professor for whom it was their first time and it was brutal for him, so he said he wouldn't do that but accidentally did it regardless.
  - Levin also says that for all the people who feel like they don't know what's going on, that's on him.
  - If you wanna judge how good you're doing, see how you did on the cyanohydrin formation and the amine cyclization. If those felt ok, you're doing fine; you can consider the others to have been challenge problems.
- Reversible formation of enols and enolates.
  - As discussed in the previous lecture, a ketone in the presence of a hydroxide base will equilibriate with its enolate.
  - Since $\mathrm{p}K_\mathrm{a} = 25$ for the ketone and $\mathrm{p}K_\mathrm{a} = 15$ for the enolate, 10^{10} times more of the ketone is present in solution.
  - Note that the amount of enolate present is still sufficient to do some chemistry (like that which we discussed last time). It does beg the question, however, of how stoichiometric deprotonation can be accomplished.
  - Stoichiometric deprotonation is useful (and necessary) for the reaction of enolates with relatively weaker electrophiles.

- Stoichiometric deprotonation.
- In theory, we could just use a stronger base.
  - We might assume that nBuLi[1] will deprotontate ketones to form butane and the enolate (with a lithium countercation).
  - Since butane is so basic, this would work very well ($K \approx 10^{25}$). However, nBuLi has competitive reactivity as a nucleophile attacking the carbonyl, and this is what it will do (as we discussed last unit).
  - Thus, we need an **innocent base**.
- **Innocent base**: A base that does not have reactivity competing with its ability to do deprotonations.
- **LDA**: Lithium diisopropyl amide, a sterically hindered, very strong, innocent base. *Structure*

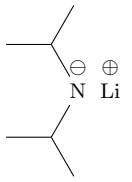


Figure 5.1: Lithium diisopropyl amide (LDA).

  - One implication of the name of this compound is that the term "amide" refers to both the carboxylic acid derivatives of nitrogen (see Figure 2.8e) and deprotonated amines (such as LDA).
  - Some chemists proclaim that there is a difference in pronunciation, i.e., that one is pronounced "AM-id" and the other "AE-mide."
- Synthesis of LDA.

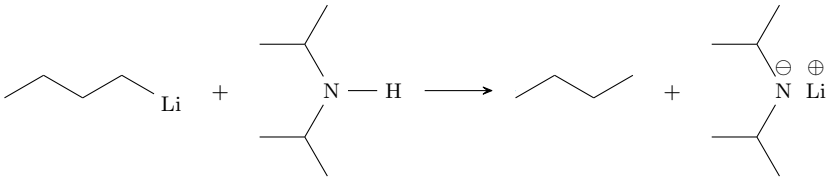


Figure 5.2: Synthesizing LDA.

  - The reactants are n-butyl lithium and diisopropyl amine.
- Consider what would happen if LDA tried to act as a nucleophile.
  - The product would be sterically disfavored.
  - Additionally, there is an easy reversible mechanism because while we an alkoxide can't kick out carbon, the amide is a good leaving group.
  - Thus, this is a reversible reaction that favors the starting material.
- Since LDA has no competitive reactivity, it will stoichiometrically deprotonate ketones.
  - Consider the reaciton of methyl phenyl ketone and LDA.
  - Since the ketone has p$K_a \approx 25$ and diisopropylamine has p$K_a \approx 36$, the equilibrium constant is approximately 10^{11}.

[1] Also pronounced "BYOO-lee".

- Orbital effects for deprotonation.

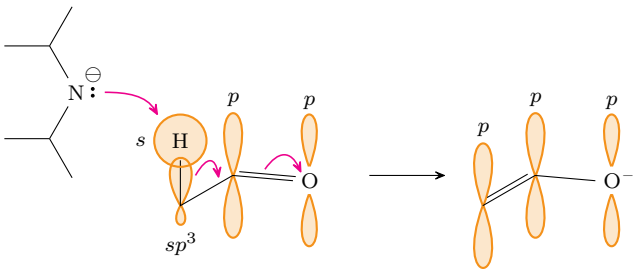
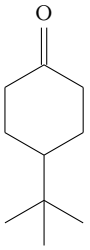


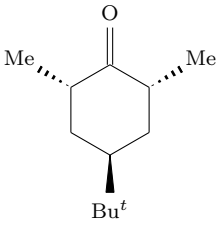
Figure 5.3: Orbital effects for LDA deprotonation.

  - In the fully formed enolate, conjugation of the oxygen anion into the π-system is stabilizing because of resonance.
  - However, for the reaction to proceed, there must be resonance stabilization from the moment the anion begins forming.
  - Thus, we need the sp^3 and the two p-orbitals to be aligned, as above. Notice how the C–H bond is parallel to the p-orbitals of the C=O π-system.
  - As we deprotonate, we continuously transform the sp^3 orbital into a third p orbital that will be in conjugation with the other two preexisting ones.

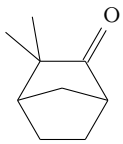
- Consequences of orbital effects.



(a) Axial vs. equatorial acidity.



(b) Blocked α-hydrogens.



(c) Locked α-hydrogen.

Figure 5.4: Molecules with deprotonation reactivity affected by orbital effects.

  - Cyclohexane conformations affect the acidity of equatorial and axial α-hydrogens.
  - Consider the molecule in Figure 5.4a.
    - Recall that *tert*-butyl groups are always equatorial.
    - It follows that the carbonyl is equatorial, too, and therefore that its π-system is axial.
    - Thus, the axial α-protons are more acidic because of their alignment with the C=O π-system.
    - Consequently, LDA selectively deprotonates these.
    - We can confirm this via selective deuteration of some cyclohexane hydrogens.
  - Now consider the molecule in Figure 5.4b.
    - Once again, conformations force the Bu^t group to be equatorial.
    - Thus, this compound cannot be deprotonated by LDA because it has no acidic protons.
  - Lastly, consider the molecule in Figure 5.4c.
    - A bicyclic hydrocarbon can be locked in the unreactive conformation.
  - Drawing the relevant chair conformations here is an important skill.

- Selectivity.
- Some compounds will not be selectively deprotonated.
  - For example, treating 1-phenylheptan-4-one with LDA will yield products that have been deprotonated at every α-hydrogen in equal amounts.
- LDA prefers to deprotonate at less substituted positions due to its sterics.
- Comparing LDA- and hydroxide-based deprotonations.
  - LDA is a lot more basic than hydroxide.
  - Thus, hydroxide deprotonations are reversible while LDA deprotonations are irreversible.
  - It follows that hydride deprotonations are under thermodynamic control (stability is important) while LDA deprotonations are under kinetic control (rate is important).
- Rate is controlled by the transition state energy.
  - Levin draws a 1D energy diagram for an exothermic reaction with a large $\Delta G^{\ddagger}$, noting that this large $\Delta G^{\ddagger}$ will make the reaction slower.
- Selectivity in terms of kinetic and thermodynamic control.

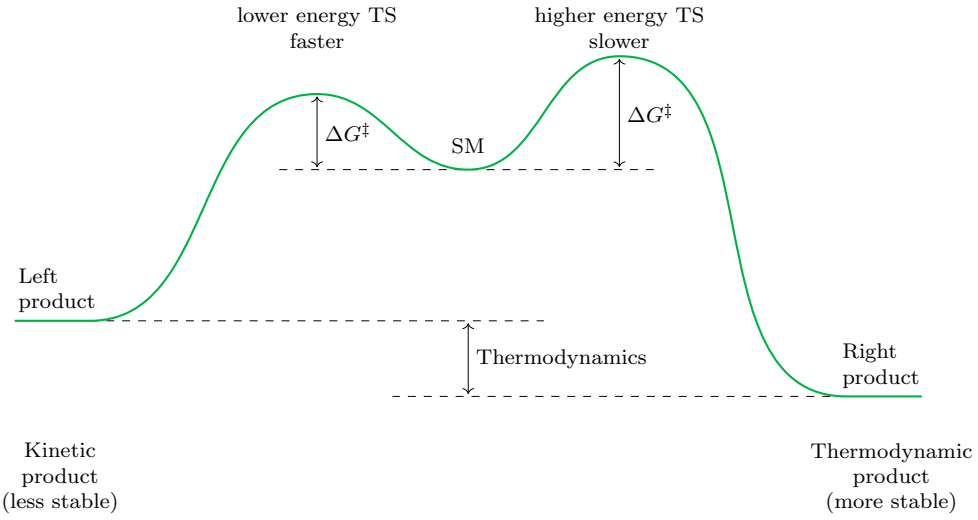
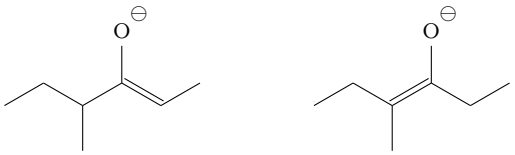


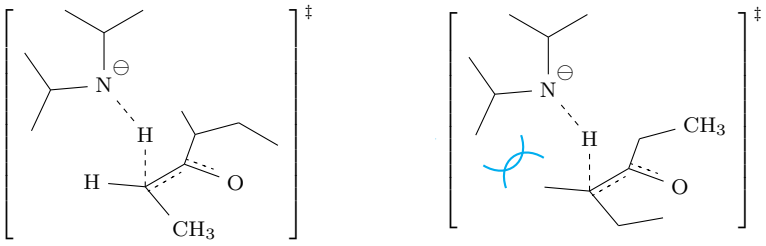
Figure 5.5: Thermodynamic vs. kinetic control.

  - A reaction that is reversible will form the thermodynamic product.
  - A reaction that is irreversible will form the kinetic product.
  - Note that there are paradigms in which one product is both the kinetic and thermodynamic one.
  - To determine the kinetic product, we compare transition states.
  - To determine the thermodynamic product, we compare the products, themselves.
- Application.



Less stable More stable

(a) Thermodynamic stability.



(b) Kinetic favorability.

Figure 5.6: Thermodynamic and kinetic stability in enolates.

  - The tetrasubstituted enolate is the more stable product by Zaitsev's rule.
  - The trisubstituted enolate has a more stable transition state.

- "An analogy may assist in understanding kinetically and thermodynamically controlled reactions. Imagine a very inebriated gentleman stumbling randomly around a pasture. Near each other in the paster are a shallow watering hole and a deep well with a high fence around it. Our drunken friend is likely to fall in the hole several times, but because it is shallow, he can climb out of it and continue staggering around the pasture. After a very long while, however, he makes it over the fence and falls into the well; once in the well, he is there to stay. If we now imagine Avogadro's number of people staggering around a (very large) pasture, we get a reasonably good picture of kinetic and thermodynamic control. Initially, a large number of people fall into the shallow hole. If we wait long enough, however, most of the will end up in the deep well. The frequent occurrence — falling in the shallow hole — is reversible, but the rare occurrence — climbing the fence and falling in the well — is irreversible" (Loudon, 1988).

  - The Avogadro's number correction is to bring an element of statistics and probability into the example.
  - In the new edition, the drunken gentleman has been changed to "disoriented steers," maybe to be PC.

- In general, we cannot guess how long it will take the thermodynamic enolate to accumulate (though it will likely be a long time), so we need an alternate method of generating them.

- Generating thermodynamic enolates.

  1. Use OH^-, which catalyzes *reversible* enolate formation.
  2. Use a sub-stoichiometric equivalent (≈ 0.95) of LDA.

- Sub-stoichiometric LDA addition.

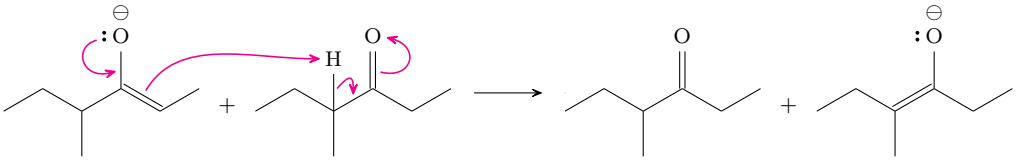


Figure 5.7: Sub-stoichiometric LDA addition.

  - Using a sub-stoichiometric amount leaves some ketone behind to react with the kinetic enolate as in the above picture, generating the thermodynamic enolate and regenerating the ketone to react again.
  - The wait time for this process to occur is usually a few hours at room temperature.

- Note that if you want to form solely the kinetic product, you will need to do it quickly and with more than one equivalent (we can just say one equivalent for the purposes of this class; we use a little excess to account for any mismeasurement/human error in real live), and you will need to keep the mixture at $-78\,^\circ\mathrm{C}$ (using a dry ice/acetone bath).
- Kinetic enolate formation.

$$\text{Ketone} \xrightarrow[-78\,^\circ\text{C}]{\text{LDA (}>\text{ 1 equiv)}} \text{Enolate}$$

- Thermodynamic enolate formation.

$$\text{Ketone} \xrightarrow[\text{time}]{\text{LDA (0.95 equiv)}} \text{Enolate}$$

- Uses for enolates.
  1. Halogenation.
  2. C–C bond formation.
  3. Selenium electrophile reactions.
- **N-bromosuccinimide**: A source of electrophilic bromine. *Also known as* **NBS**. *Structure*

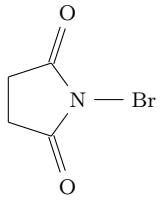
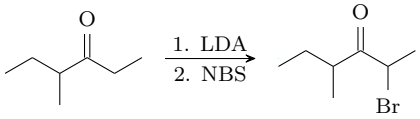
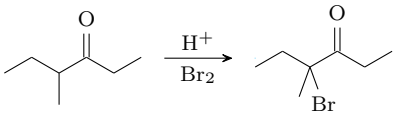


Figure 5.8: N-bromosuccinimide.

- Halogenation.
- General form.

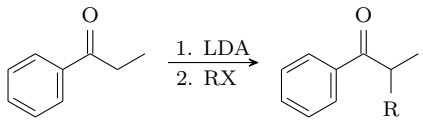


  - We get bromination of the kinetic enolate assuming we perform keep this reaction cold and perform it fast.
- Mechanism.
  - The enolate attacks the bromine of NBS, and the N–Br electrons retreat onto the nitrogen.
- Reacting the thermodynamic enolate.
  - Although we might think to use OH^- / Br_2, this would from an α, β unsaturated compound as per Figure 4.9.
  - Thus, we turn to acidic conditions.
- Acidic conditions form thermodynamic enols.



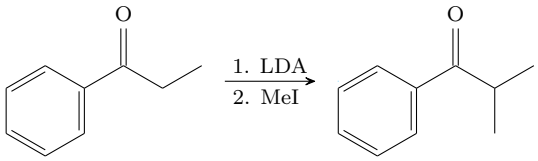
  - These enols are formed reversibly (see Figure 4.7), so they have an opportunity to equilibriate and favor the thermodynamic product.
  - Once the thermodynamic enol has been built up, it reacts selectively with Br_2.

- C–C bond formation with enolates.
- General form.

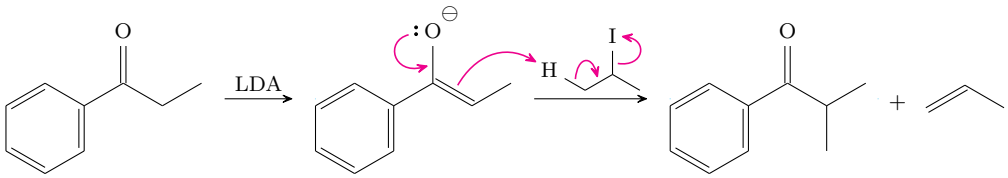


  - Note that phenyl alkyl ketones have no selectivity problems because they only have α-hydrogens on one side.
  - X is bromine or iodine.
  - Works great if R is a methyl group.
  - Works ok if R is a primary alkyl.
  - E2 of the alkyl halide starts to dominate if R is secondary or tertiary.

- Examples.



(a) Methyl R group.

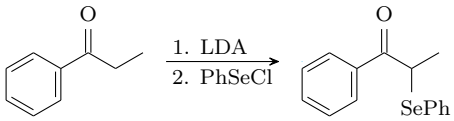


(b) Isopropyl R group.

Figure 5.9: Examples of C–C bond-forming reactions with enolates.

  - We'll fix the issue that arises in Figure 5.9b next time.

- A new electrophile (selenium).
- General form.

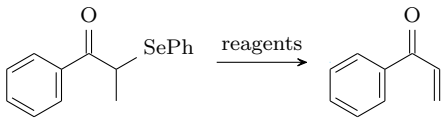


  - We can use either the phenyl selenyl chloride or phenyl selenyl bromide.

- Mechanism.
  - The enolate attacks the selenium atom and kicks out chlorine in one concerted step.
- The purpose of adding selenium to compounds.

  - We put selenium in just to take it back out again.
  - We typically don't want to build molecules with it because it's quite toxic and not commonly used in biochemistry.

- Eliminating phenyl selenide.
- General form.



  - The reagents are either mCPBA or H_2O_2.
  - We use this method over hydroxide and bromine because it is compatible with LDA, which means that we can get selectivity for elimination now in addition to bromination.

- Mechanism.

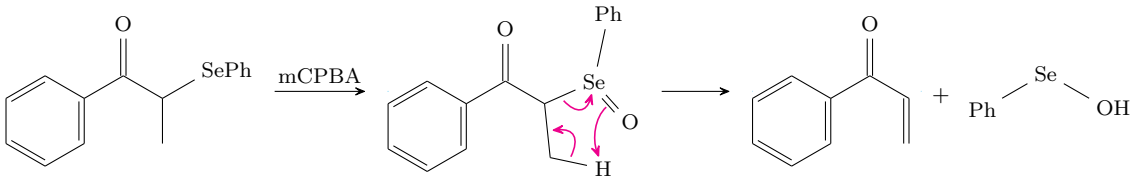


Figure 5.10: Phenyl selenide elimination mechanism.

  - The first intermediate is a **selenoxide**.

- Selectivity.

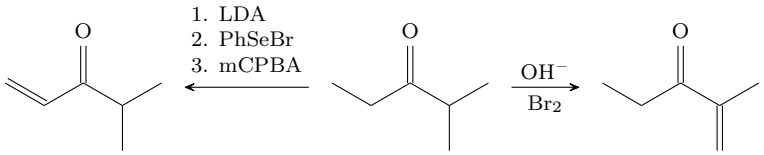
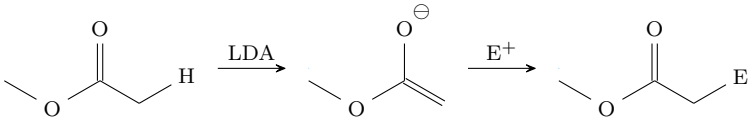


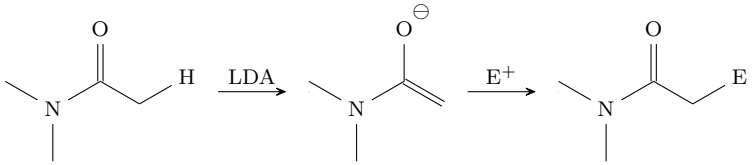
Figure 5.11: Selectivity in the formation of α, β unsaturated compounds.

  - We use the thermodynamic enolate (accessible via reversible hydroxide) for the right side and the kinetic enolate (accessible via irreversible LDA) for the left side.

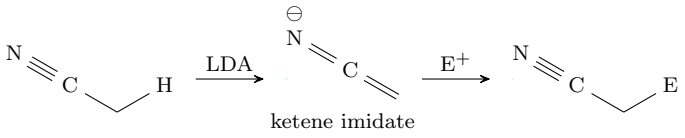
- Applications to carboxylic acid derivatives.



(a) Esters.



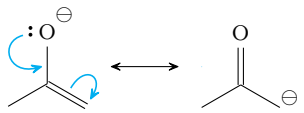
(b) Amides.



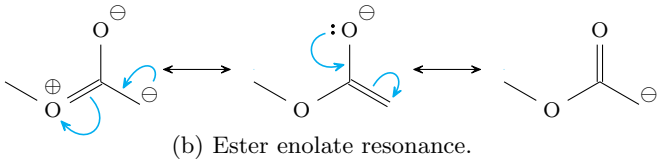
(c) Nitriles.

Figure 5.12: Carboxylic acid derivatives as enolates.

- Comparing the nucleophilicity of ketone enolates, ester enolates, and amide enolates.



(a) Ketone enolate resonance.



(b) Ester enolate resonance.

Figure 5.13: An extra resonance form for carboxylic acid derivative enolates.

  - Nucleophilicity depends on how electron-rich the π system is.
  - Oxygen and nitrogen both donate their lone pairs to the π system.
  - The additional resonance form makes the carboxylic acid derivative enolates more nucleophilic.
  - Nitrogen is the most nucleophilic (because of its lower electronegativity relative to oxygen), then oxygen, then carbon (of these three).

- We will not be asked to compare the nucleophilicity of ketene imidates to ketone, ester, or amide enolates.

- Selectivity is nice for all carboxylic acid derivatives; there's at most one set of α-hydrogens for all of them.

- Compounds whose enolates are less useful.

  - Carboxylic acids: These will become carboxylates upon the first deprotonation. The second deprotonation takes a much stronger base, forms a dianion, and doesn't work too well.
  - Amides with hydrogens: These deprotonate first as well and then run into the same dianion problem.
  - Acid chlorides: These kick out the chloride along with deprotonation, forming a **ketene**. There are things we can do with ketenes, but we won't talk about them since they aren't useful as enolates.
  - Aldehydes: These will dimerize. In particular, one deprotonated aldehyde will engage in a nucleophilic attack on another.
    - This will form most of the rest of the class.