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

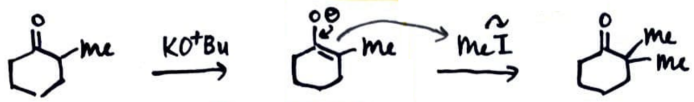


Figure 5.14: Thermodynamic enolate formation.

  - Treating this with MeI then generates the α-dimethylated form of cyclohexanone.
- You can add in Me_3SiCl to trap enolates the silyl enol ether.

Figure 5.15: Trapping enolates as silyl enol ethers.

  - This silyl protecting group could then be removed with MeLi, regenerating the enolate and yielding tetramethylsilane ($SiMe_4$) 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 diisopropylamine), so this conjugate acid cannot react backwards.
  - Use of a somewhat strong, somewhat bulky base (like KO^tBu in ^{t}BuOH).
    - This process is highly reversible, so we'll abstract the unhindered proton first. But then the enolate can react backwards with ^{t}BuOH to reform the ketone!
    - This process is highly reversible because $pK_a \approx 19$ for ^{t}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 MeI into the corresponding α-alkylation product.

- Lecture outline.

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

- We return to Topic C: α-alkylation.

- Let's consider the properties of several strong bases.

Base	Conjugate Acid (of Base)	pKa of Conjugate Acid
NaOEt/EtOH	EtOH	~16
KO^{t}Bu/^{t}BuOH	^{t}BuOH	~19
LDA/THF	iPr$_2$NH	~35

Table 5.1: pK_a'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 it's conjugate acid!
  - It follows from the table that NaOEt and KO^{t}Bu are reversible bases, and LDA is an irreversible base.
  - The difference between the first two is that KO^{t}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_1H has p$K_a > 22$.
    - Then the reaction is irreversible.
    - Example: LDA!
  - Suppose that the conjugate acid B_2H has $16 <$ p$K_a < 22$.
    - This reaction is reversible.
    - Examples: NaOEt and KO^{t}Bu!
  - Suppose that the conjugate acid B_3H has p$K_a < 16$.
    - Nothing happens! The base isn't strong enough.
  - Note: We'll read in Clayden et al. (2012) that we can use bases with p$K_a < 16$ *if* we pair it with a Lewis acid.
    - Example: Trimethylsilyl chloride (TMSCl) and NEt_3.
  - Generalizing this.
    - Consider the pK_a of our α-proton.
    - If the base is 3 pK_a units weaker or stronger, we get reversible enolate formation.
    - If the base is more than 3 pK_a units stronger, we get irreversible enolate formation.
    - If the base is more than 3 pK_a 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 KO^{t}Bu in ^{t}BuOH to form the thermodynamic enolate.
- How about forming enolates from esters?
  - We need LDA because p$K_a \approx 25$ for the ester's α-proton.
  - Indeed, esters have significantly less acidic α-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 S_N2 reactivity here.
  - Enolates are more hindered than, for example, cyanide nucleophiles (CN^-), azide nucleophiles (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 α-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 α-substituted malonate esters.

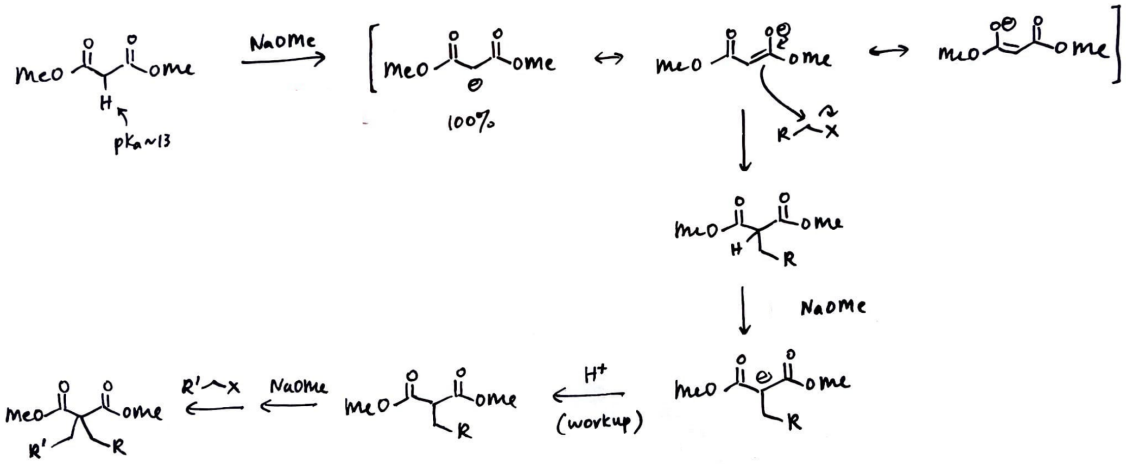
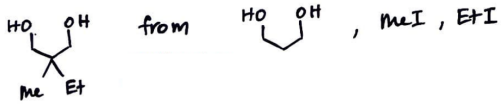


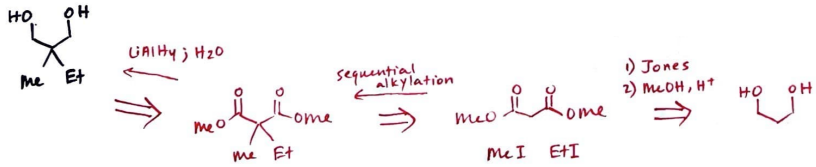
Figure 5.16: Malonate ester synthesis.

- Recall malonate esters from last class (see Figure 5.12a).
- Since these compounds have p$K_a \approx 13$ at their α-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 α-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.



(a) The desired molecule and starting materials.



(b) Retrosynthetic pathway.

Figure 5.17: TTQ: Synthesis of an α-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**.

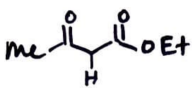


Figure 5.18: Ethyl acetoacetate.

- 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.
- p$K_a \approx 11$ for ethyl acetoacetate.

- Let's now begin the synthesis.

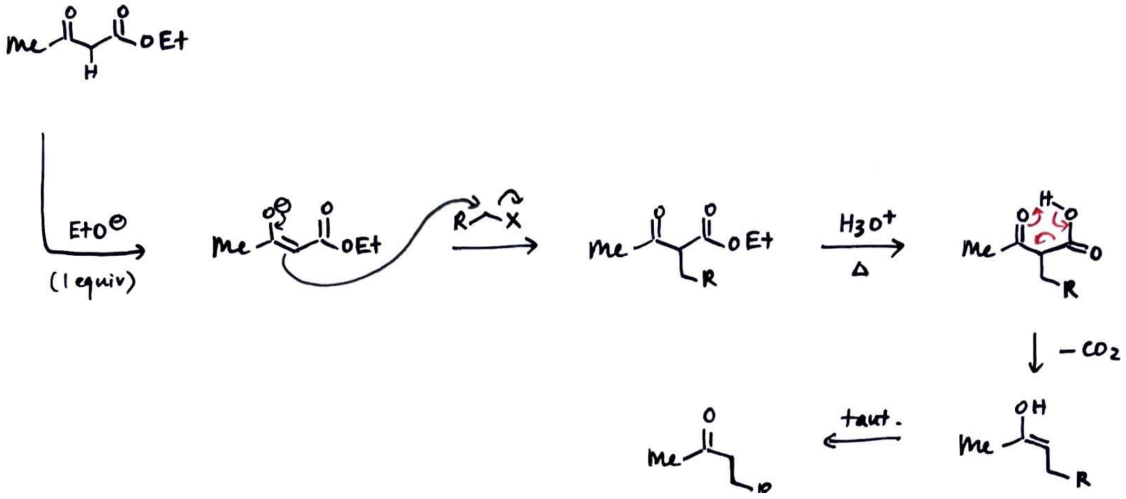
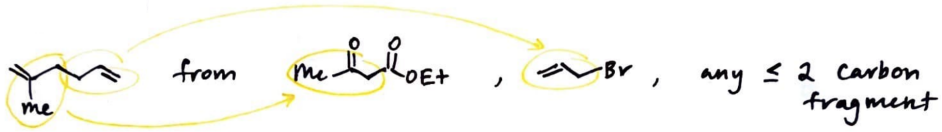


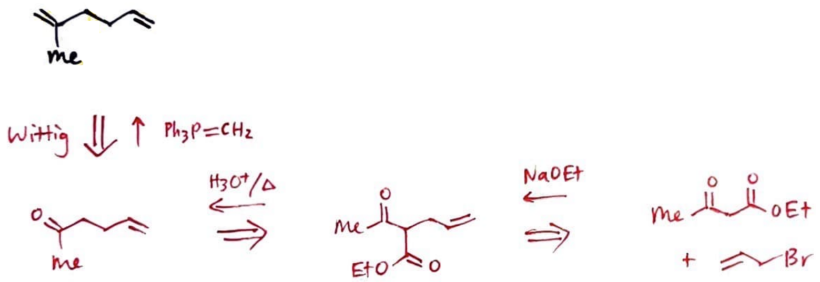
Figure 5.19: Acetoacetate synthesis.

  - Adding 1 equivalent of 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 **β-ketoacid**.
    - β-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.



(a) The desired molecule and starting materials.



(b) Retrosynthetic pathway.

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.