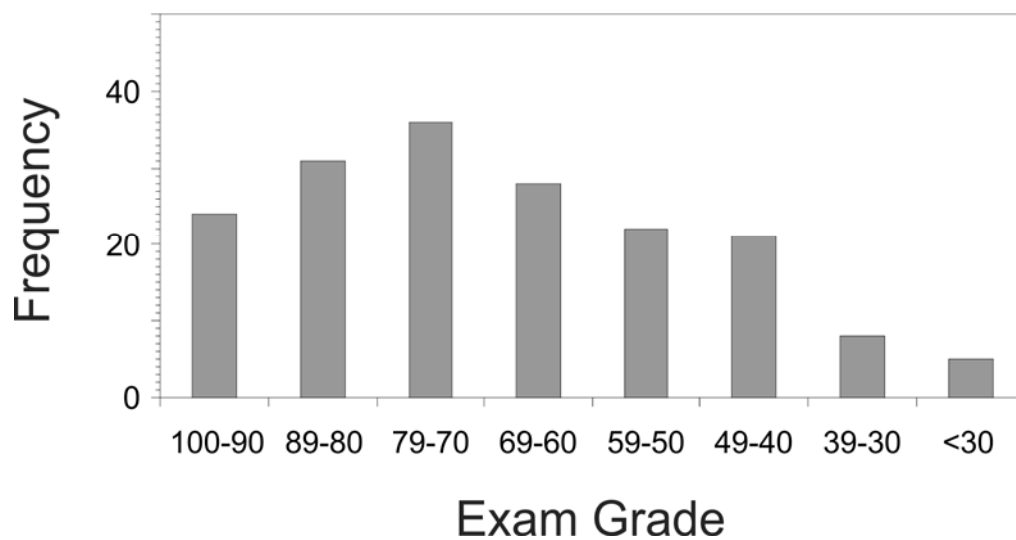
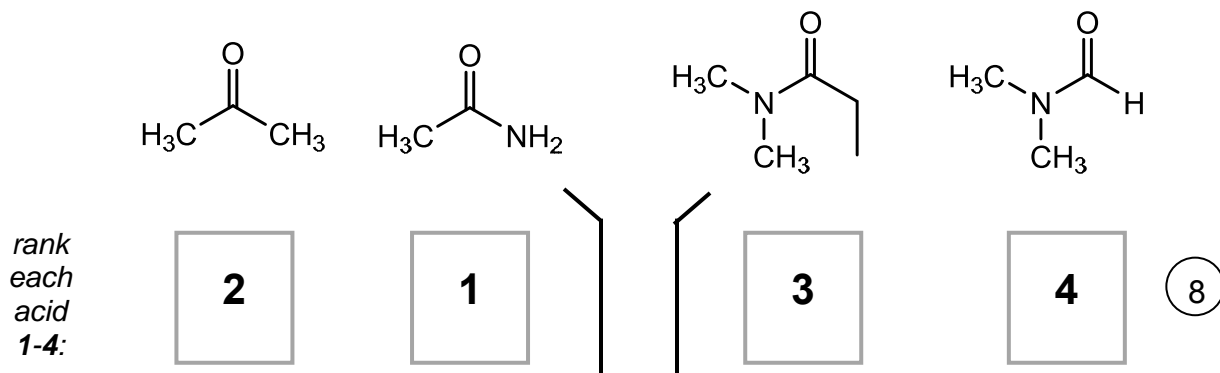


**Exam 3
Answer Key**

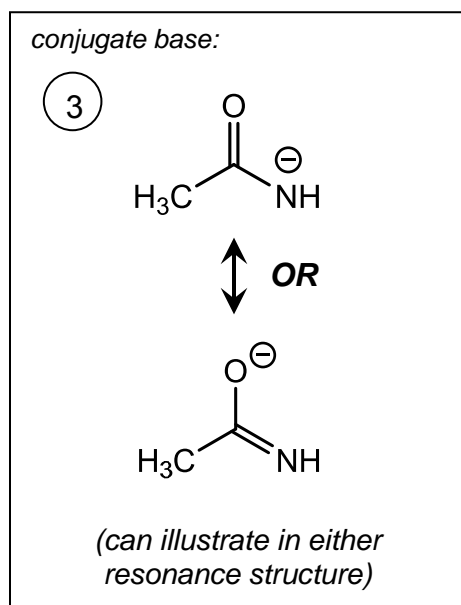
Exam 3 Mean: 68
Exam 3 Median: 70
Exam 3 St. Dev.: 19



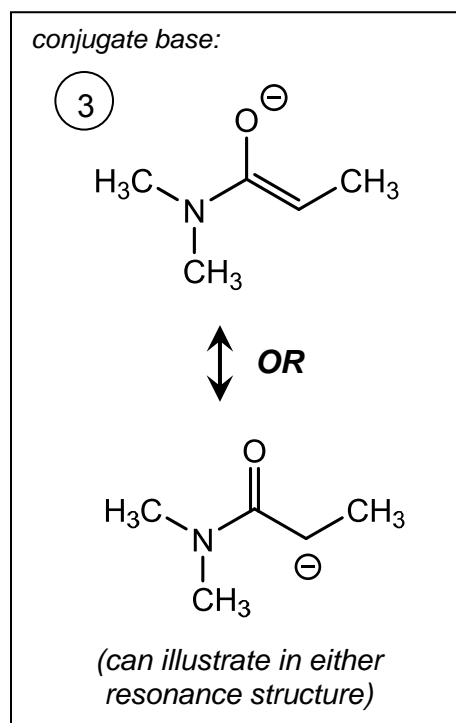
1. (14 pts) Each of the four carbonyl-containing compounds below is acidic, and would be deprotonated by a strong base like amide anion (NH_2^-). Rank each molecule **1** through **4** in terms of its acidity, from most acidic (**1**) to least acidic (**4**). Then, for the two acids in the middle, draw the preferred conjugate base structure that would be generated by deprotonation with sodium amide (NaNH_2).



NaNH_2 deprotonates these to:



Out of all of the carbonyl-containing starting materials, the unsubstituted amide is the only one that has a proton that is more acidic than an α -proton. The proton at nitrogen is removed preferentially.



The product, in this case, should have (*Z*)-stereochemistry at the double bond, because steric interactions make this the most stable enolate configuration. You could also illustrate this as the carbanion resonance form, but if you did, the central C-C bond still needs to have its $-\text{CH}_3$ pointed across from the amide *N* to be fully correct.

The ketone is less acidic than the unsubstituted amide, but more acidic than the other amides (because the π -donating amide nitrogen destabilizes their enolates). The amide on the far right has no α -protons, so it is not acidic at all.

Rubric:

8 points for the correct acidity sequence.

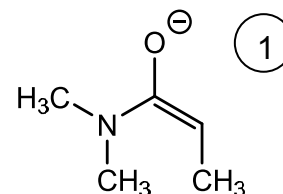
4 points partial if two numbers are switched (but the other two are correct).

4 points partial for a transposed endpoint. This is true for 1-4-2-3, or 3-2-4-1.

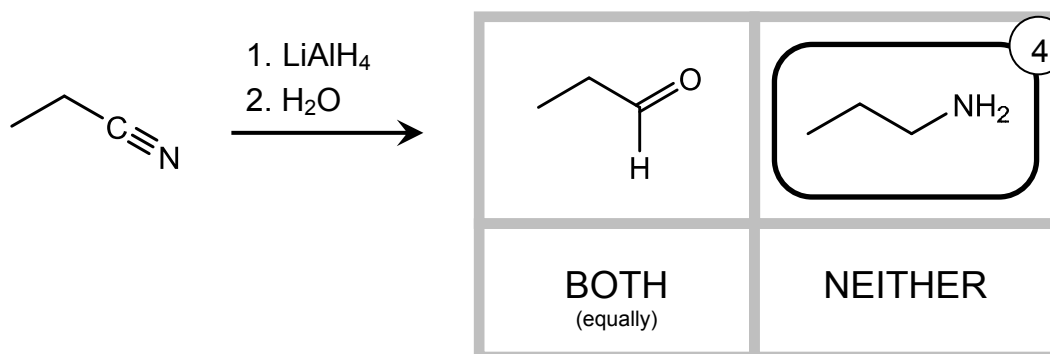
2 points partial for just one number correct.

3 points for each correct conjugate base.

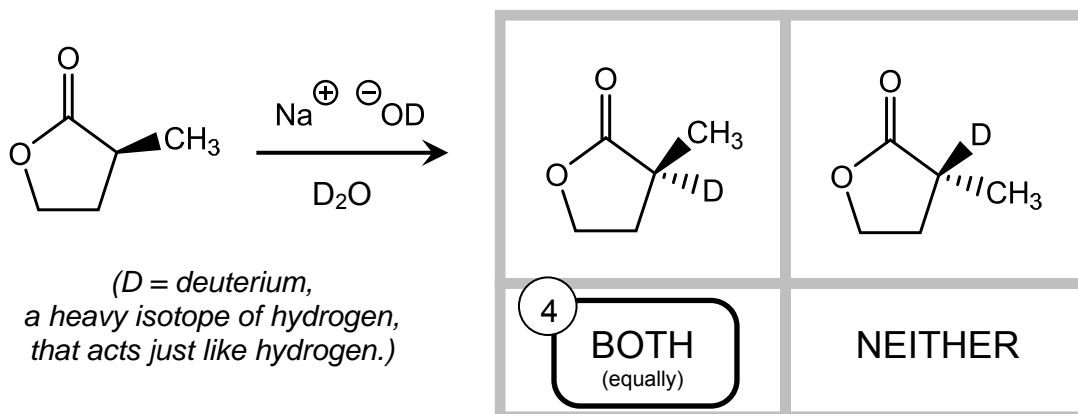
1 points partial for (Z)-enolate of ester rather than (E).



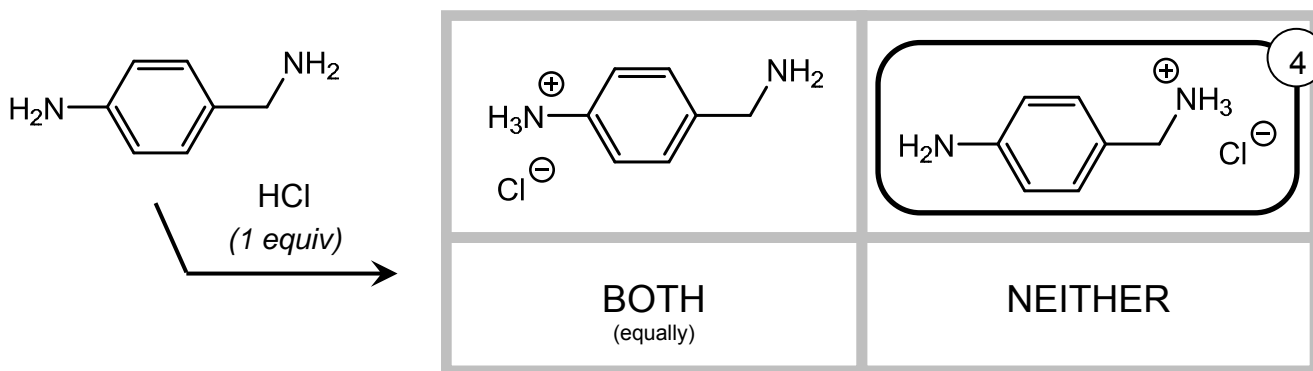
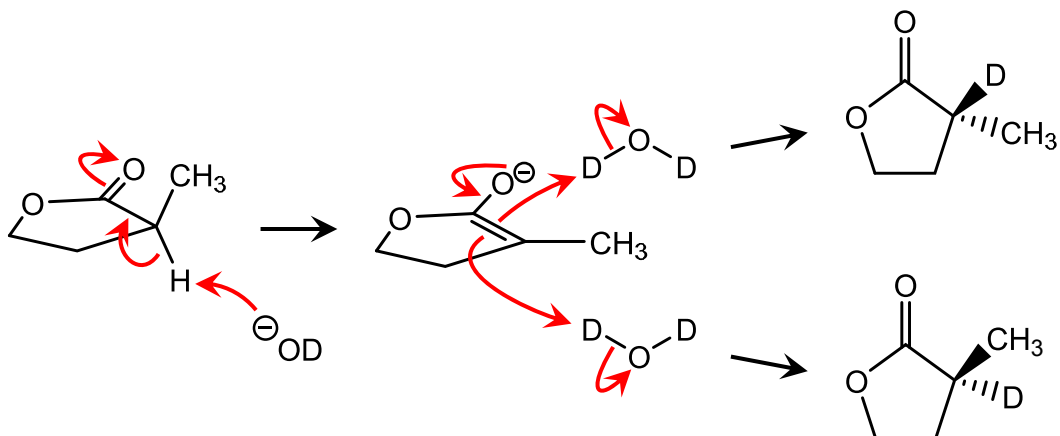
2. (20 pts) Each of the reactions on the following pages is drawn with two possible products. If one of the two products predominates, circle that preferred product. If the two products are produced equally, circle "BOTH". If neither product would result from the reaction, circle "NEITHER". **Circle one answer only.**



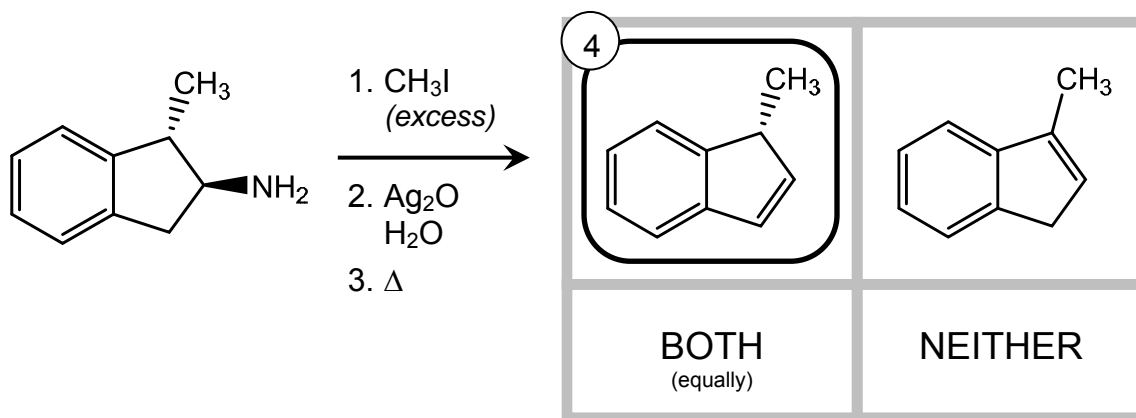
LiAlH_4 reduces nitriles to amines.



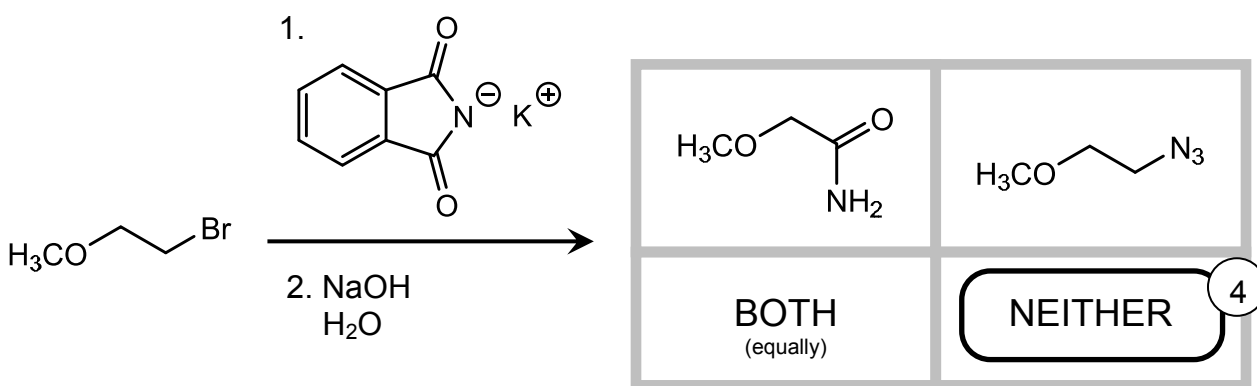
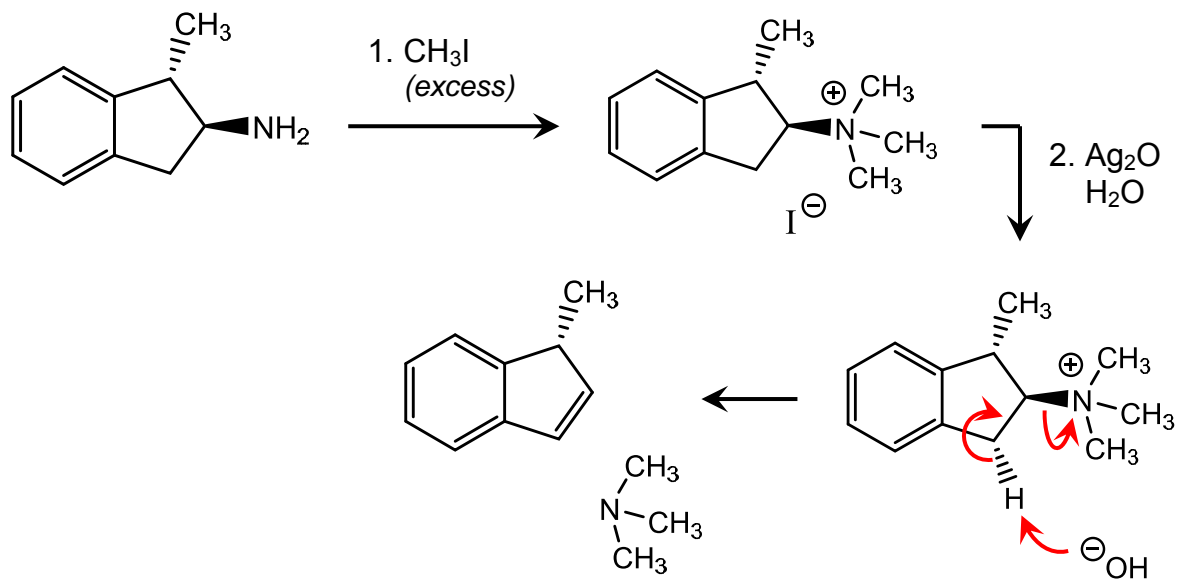
The starting ester deprotonates at the α -carbon to form a planar enolate, that can add a deuterium atom to either face:



Protonation on the left would end the conjugation between the benzene ring and the nitrogen lone pair; this is why aniline (aminobenzene) is a weaker base than other, non-conjugated amines.



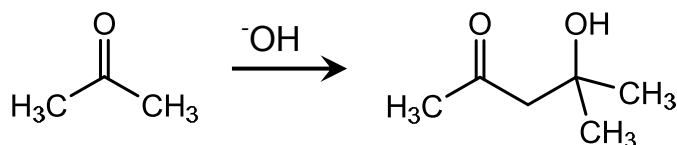
This is the reaction scheme for Hoffman elimination, in which an amine is converted to the less substituted alkene via elimination:



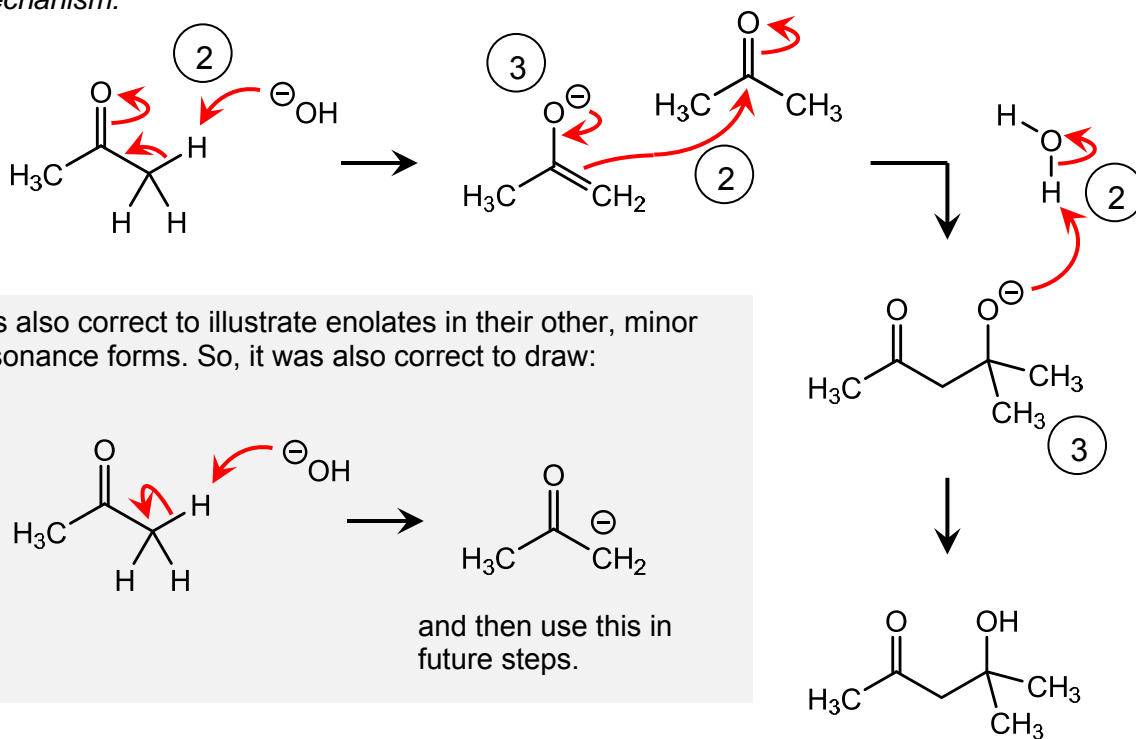
This is the scheme for the Gabriel synthesis of primary amines; the intended product is amine, not either of the products shown.

3. (30 pts) For each reaction shown below, draw a mechanism that explains how the product is generated from the starting material. In your answer, make sure that you:

- Draw each step of the mechanism separately;
- Use “electron pushing” to show where the electrons in each step go;
- Use only the molecules that you are given; do not invoke reactants or solvents that aren't in the problem.



Mechanism:



Rubric: (12 points for this part.)

2 points for each electron-pushing step.

3 points for each intermediate.

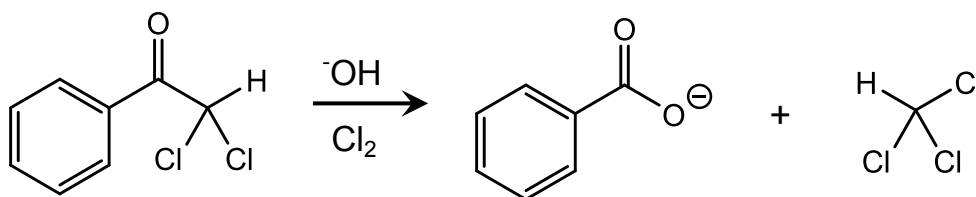
Overall notes:

Overall, the minimum score for each step is zero; errors in a step cannot earn you negative points that count against another, correct step.

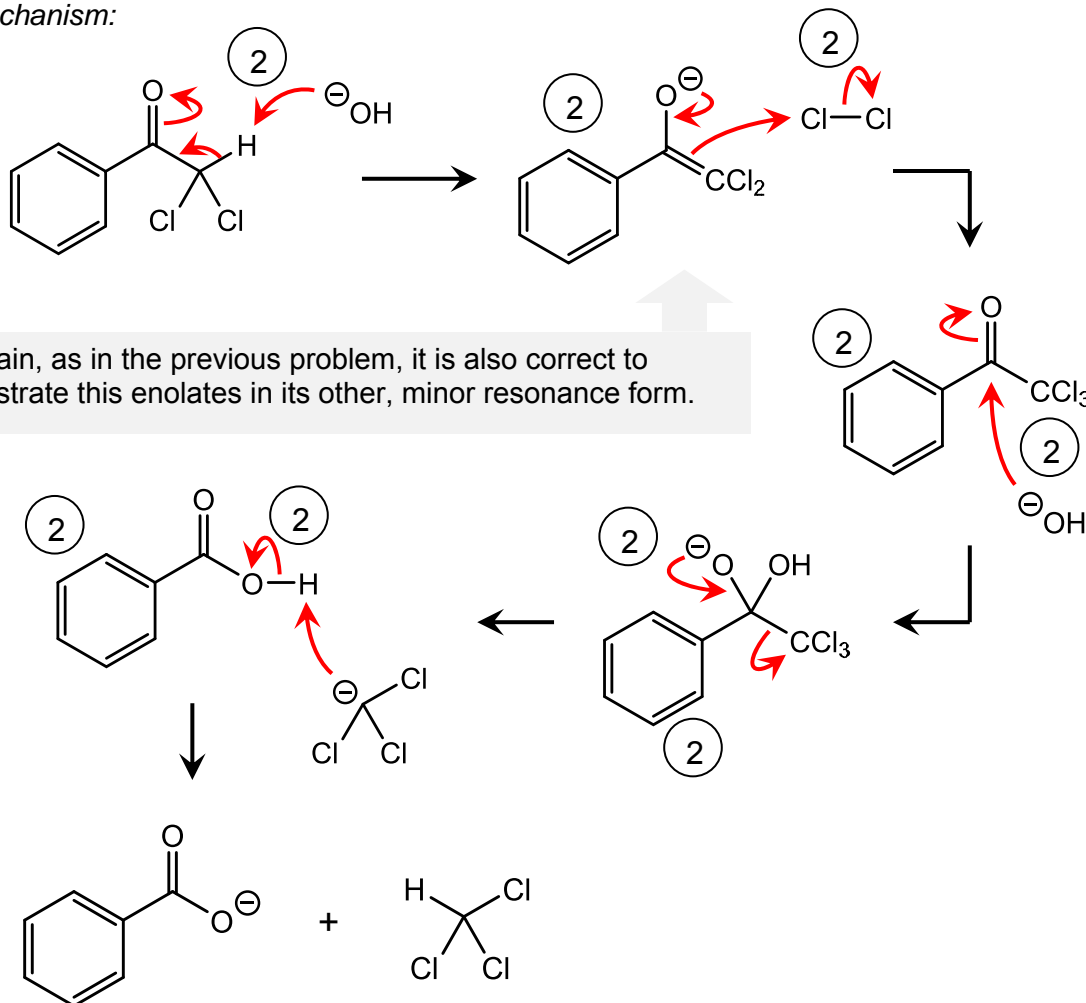
Things that have left for good and spectators may be omitted.

Resonance is NOT a mechanistic step; it is just multiple ways of drawing the same intermediate. As a result, we did not evaluate electron-pushing that showed resonance—you can push electrons for resonance, or not, your

- choice. In addition, resonance does not have to be shown as an explicit “step”—it can be combined with adjacent steps, for full credit. Any molecule in your mechanism can be illustrated in any resonance form, for full credit.
- 1 point, for each arrow in each step, for errors in drawing arrows. Arrow must start at an electron pair, and end at nucleus where electrons will newly interact. Can only lose points if you get them.
 - 1 point for each minor error in charge, valency, structure, etc.; if error propagates, points are taken off only for initial error.
 - 2 points for each use of a generic or incorrect acid/nucleophile/base.
- If you combine steps that can't be combined, you can get points for arrows that are in the rubric, but not for the intermediate you skipped.

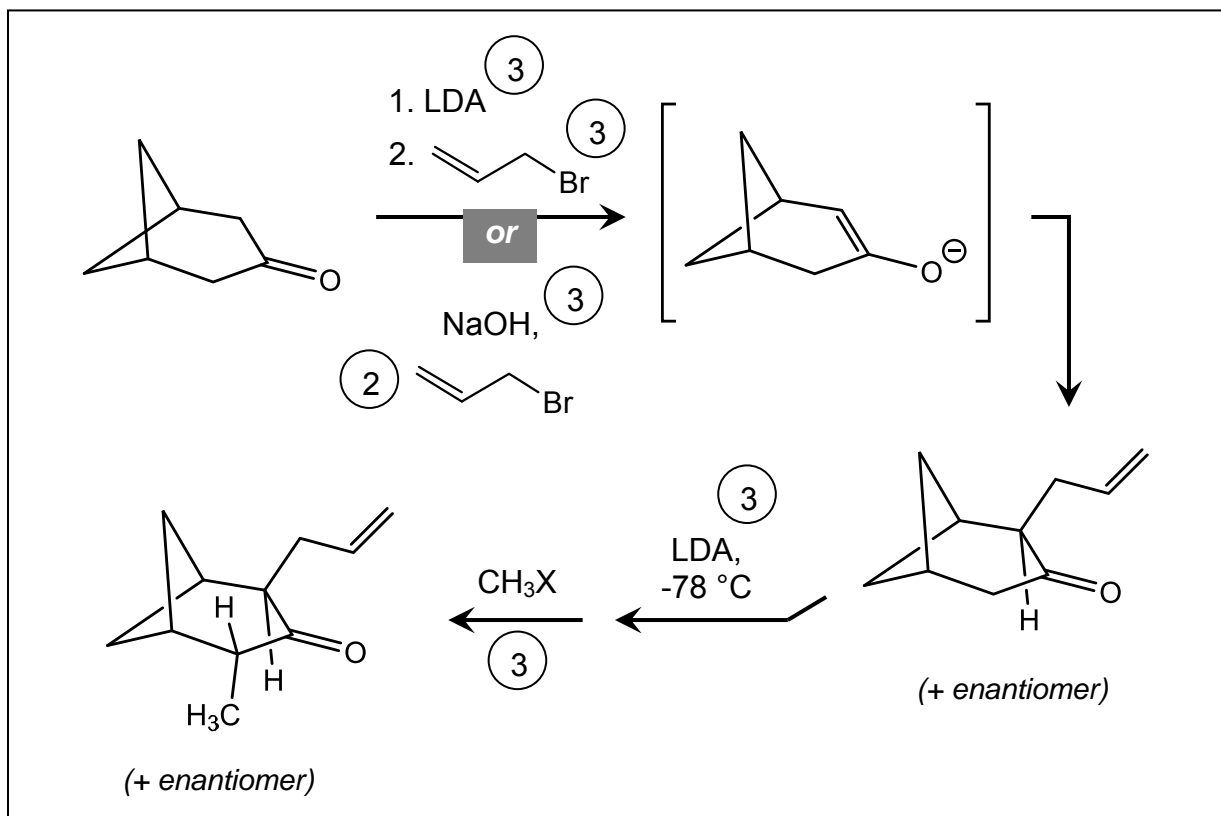
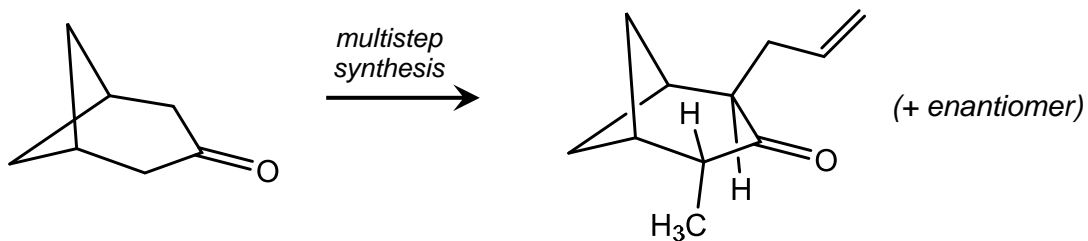


Mechanism:



Rubric: (18 points for this part.)
 2 points for each electron-pushing step.
 2 points for each intermediate.
 Same rubric elements as above problem.

4. (12 pts) In the box on the next page, propose a multistep synthesis of the product below, beginning with the starting material given. In addition to this organic starting material, you can use any reagents and reactions we've learned about in class. You might discover multiple answers to this problem; draw only your best (one) synthetic route. Feel free to draw an incomplete route—we will give you partial credit where we can.



Rubric:

General notes:

Each task is judged separately, and does not require that the synthesis makes sense, or that other tasks are correct.

-1 point for each minor, trivial error in structures or reagents; if error propagates, points are taken off only for initial error.

-2 points if step reagents are incorrect, but reaction could otherwise be accomplished with correct reagents.

-2 points if reagents are correct, but product is wrong. If this happened, and you were led down an incorrect synthetic path by your mistake, you can also lose later points.

We only gave points for reagents if they connected a starting material and a product in an understandable way. So, for example, just writing a change in the starting material, by itself, isn't worth any points.

1. Initial deprotonation (3 points).

Virtually any deprotonation will work here. A strong base (like LDA) will yield the enolate quantitatively, so it can subsequently be alkylated; a weak base will give the enolate transiently, so it can be alkylated in the presence of electrophile.

2. First alkylation (3 points).

I have drawn the first alkylation as an allylation, but you could also do methylation first. Either order receives full credit.

2 points partial for alkylation in a weak base like NaOH. Oligo-alkylation will occur.

3. Second deprotonation to form kinetic enolate (3 points).

This deprotonation must be performed with LDA at -78 °C, in order to remove the proton at the less substituted carbon.

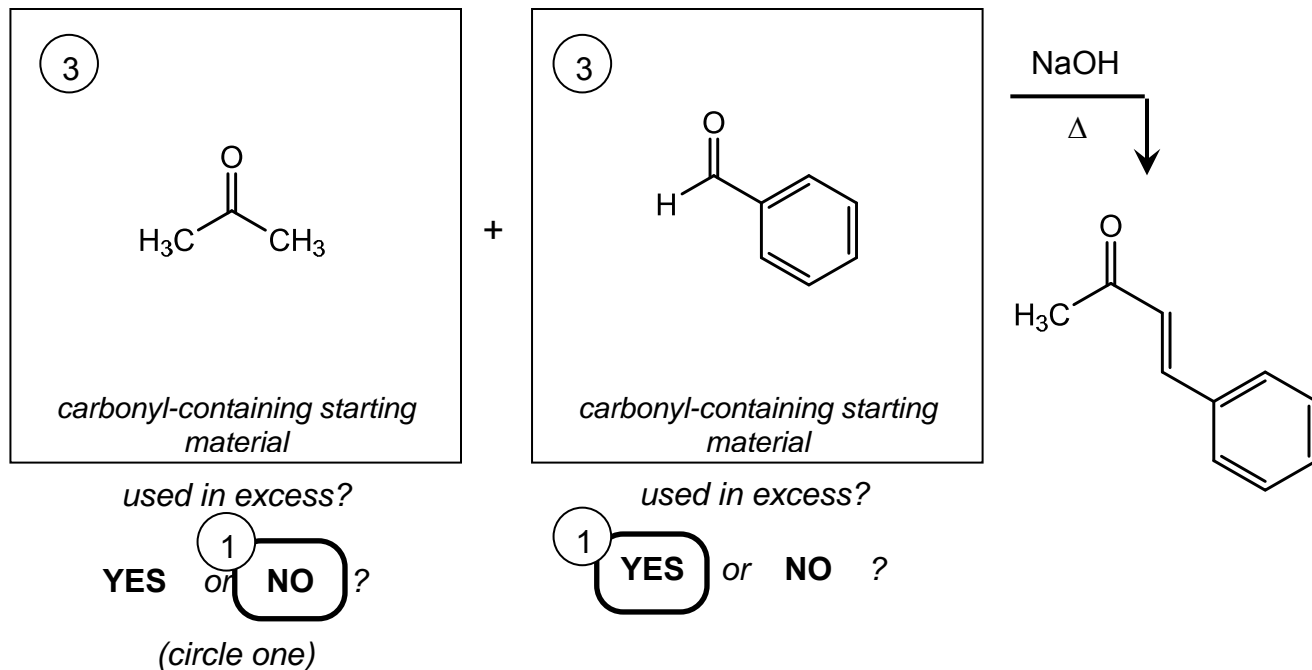
1 point partial for any other deprotonation method.

4. Second alkylation (3 points).

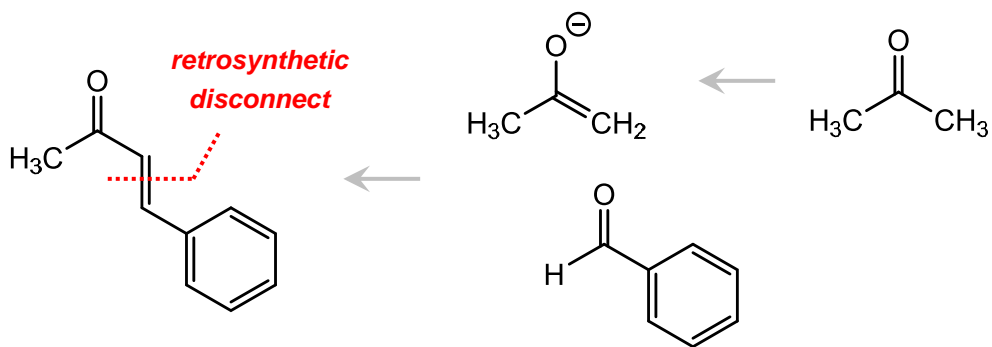
Again, any order is fine—could do allylation second.

Why do I have the two alkyl groups trans in the product? Because I think the first alkyl group will block the second one from coming in on the same face, and because I think the trans-product will be more stable than the cis-product, so I expect it to be favored in the second addition.

5. (24 pts) For each of the reactions below, fill in the empty box corresponding to reactants, reagents, or products. Give only one answer in each box. For reactions that you expect to yield multiple products, draw one major product. For reactions that yield multiple enantiomers, draw only one enantiomer in the box, and include the note "+ enantiomer".



Our product is an α,β -unsaturated ketone, which is a synthon for the aldol reaction. We can go backwards, from product to reactants, by applying the retrosynthetic disconnect for the aldol reaction, which cuts through the double bond and replaces it with a C=O:



Out of these two carbonyl-containing starting materials, the top one *must* be the enolate, and the bottom one *must* serve as the electrophile. We said in class that there were two ways to accomplish this specificity: (1) the expensive way, by using a strong base (like LDA) to make the enolate quantitatively, followed by addition of the electrophile; or (2) the cheap way, by mixing a weak base and our two reactants in a way that makes the desired reaction happen. Here, the bottom aldehyde can't make

an enolate, so we can use the cheap way; all we need to do is use excess aldehyde, to make sure that the acetone enolate can't add to another molecule of acetone.

Rubric:

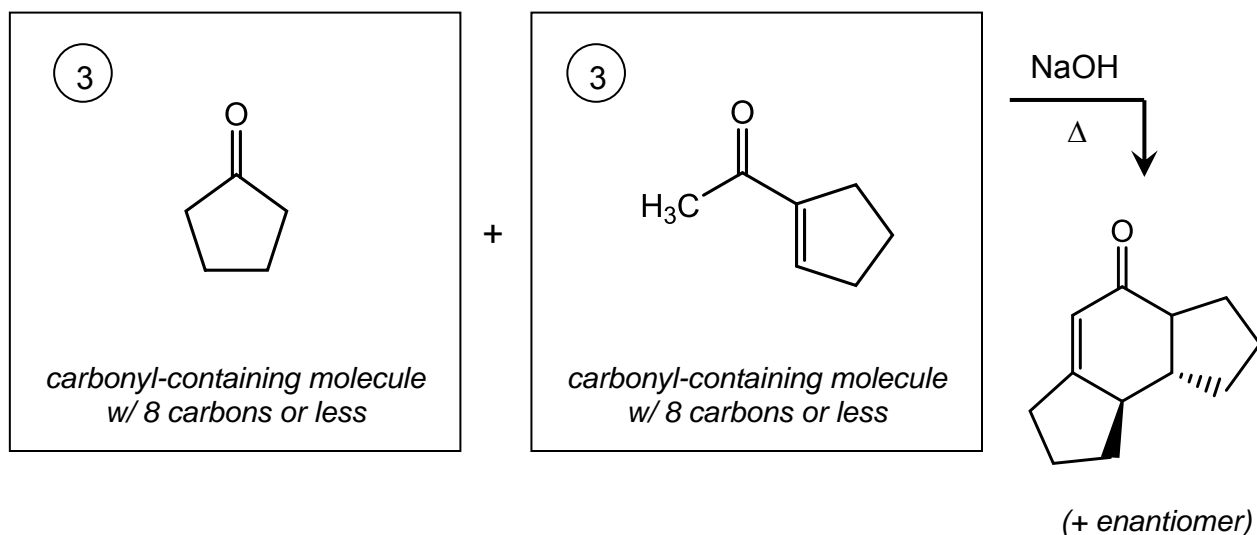
Either answer can be in either box.

3 points for acetone.

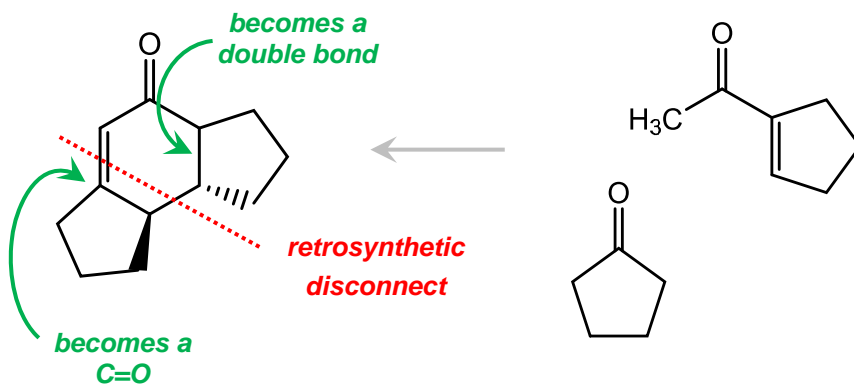
2 points partial for acetone enolate. The NaOH base will form this for you—you don't need to start with it.

3 points for benzaldehyde

-2 points for minor errors.



Our product is a cyclohexanone, which is a synthon for the Robinson annulation. We can use the retrosynthetic disconnect for the Robinson annulation as a way of visualizing the two starting materials required:



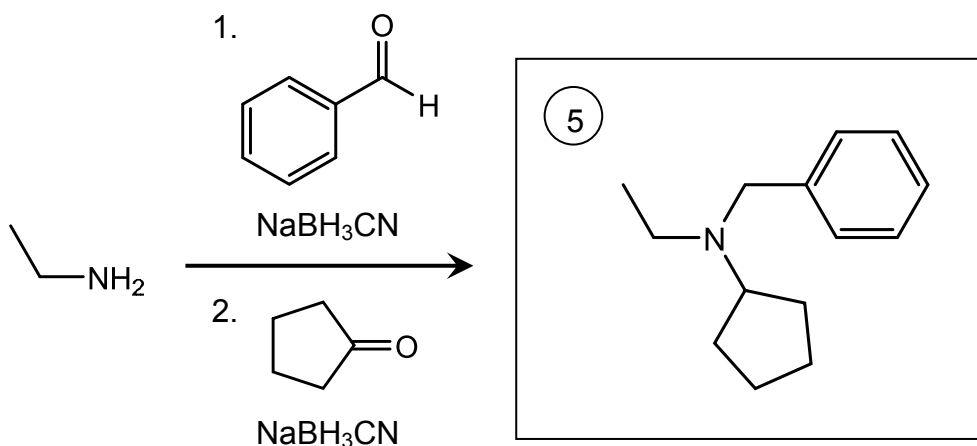
I've proposed a *trans*-disubstituted product, working under the assumption that the reaction will generate the most stable product.

Rubric:

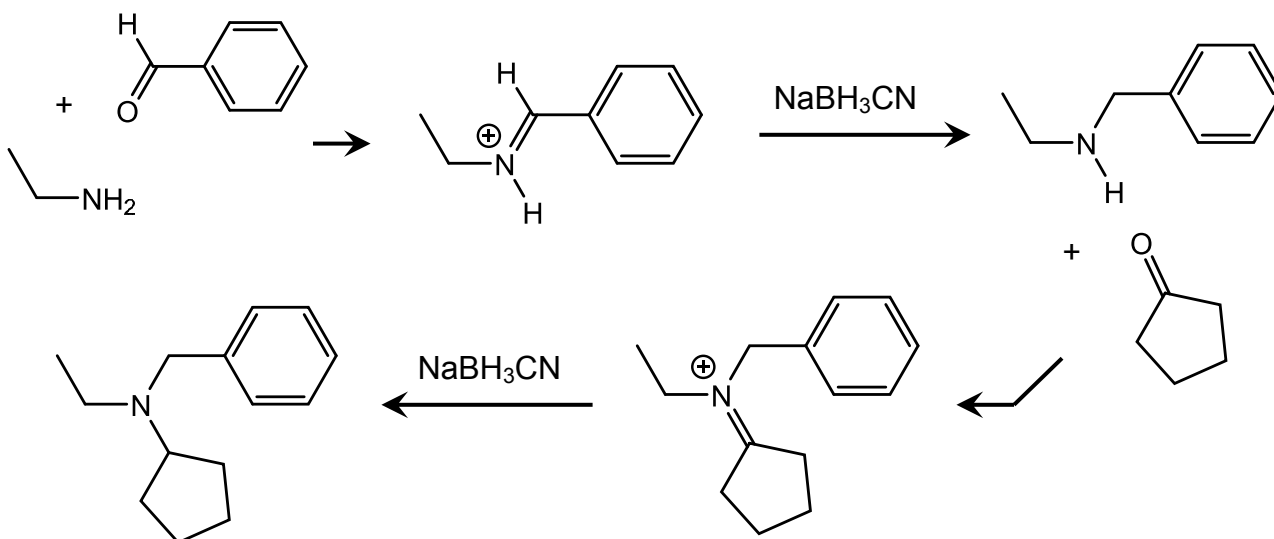
Either answer can be in either box.

3 points each answer.

-2 points for a minor error, such as omitting the double bond, or omitting a ring or -CH₃ carbon.



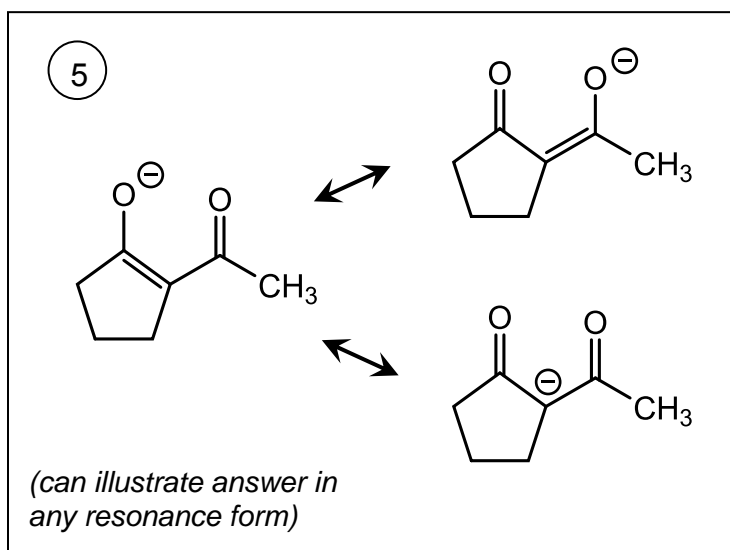
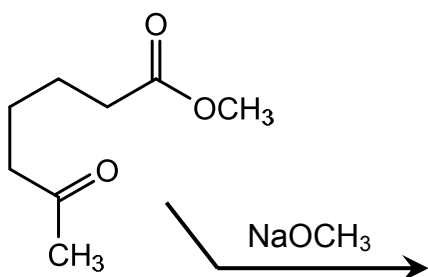
This set of reaction conditions shows two, sequential reductive amination reactions:



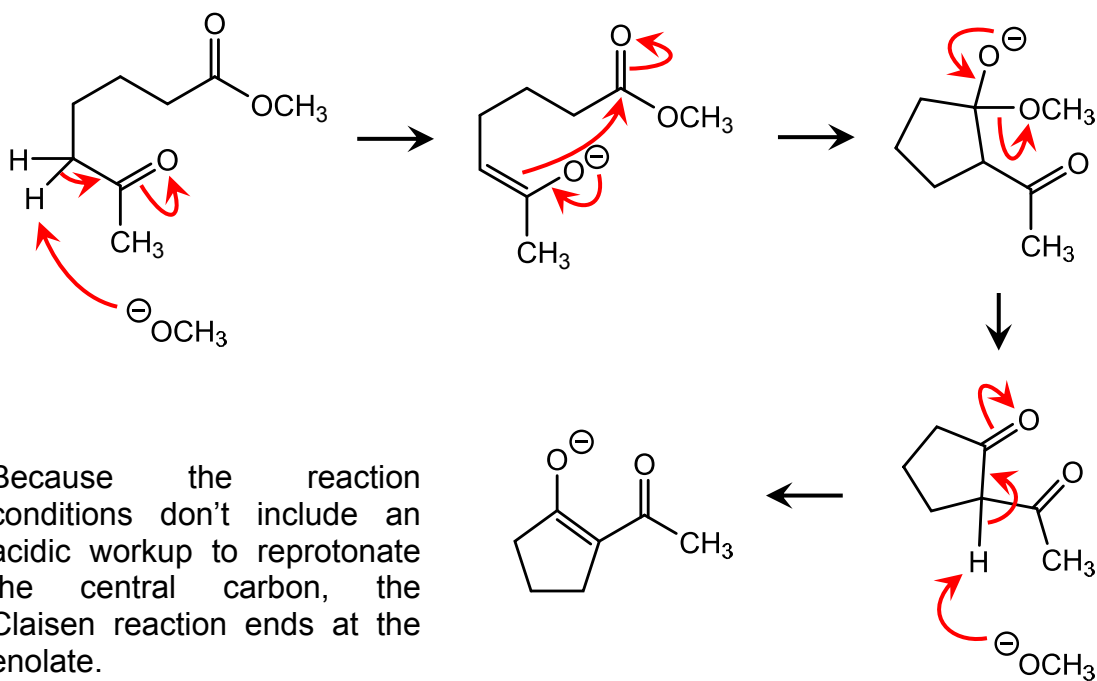
Rubric:

5 points for correct amine.

-2 points for each error (e.g., one too many or too few carbons) in each side chain.



This problem illustrates an intramolecular crossed-Claisen reaction, in which an enolate from the ketone side reacts as a nucleophile in a nucleophilic acyl substitution on the ester side:



Our reaction happens specifically in this way--ketone enolate reacting with ester electrophile--because the ketone is more acidic than the ester. In addition, the more substituted side of the ketone reacts because the 5-membered ring product is stable; in class, we talked about situations that choose not to form a smaller, strained ring, but that doesn't apply here.

Rubric:

5 points for correct product.

4 points partial for re-protonated diketone.

3 points partial for enolate made by reacting at less substituted side of ketone.

2 points partial for re-protonated diketone from this less-substituted side reaction.

2 points partial for product of ester enolate reacting with ketone electrophile.

-2 points for a trivial error (e.g., one too many or too few carbons). Intent needs to be clear.

