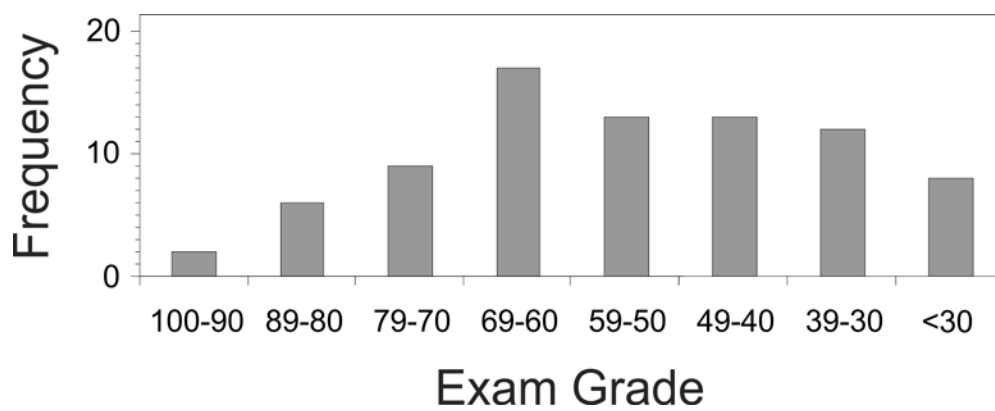
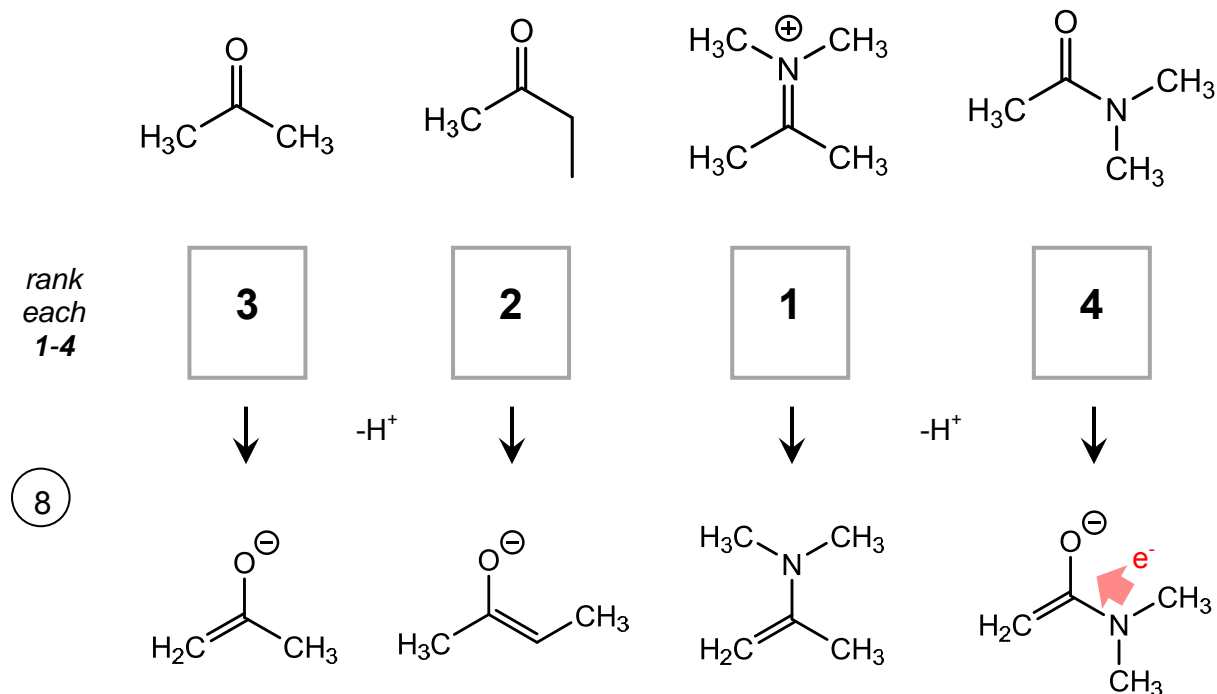


**Exam 3
Answer Key**

Exam 3 Mean: 54
Exam 3 Median: 56
Exam 3 St. Dev.: 19



1. (12 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).



Relative acidity and basicity are determined by the stabilities of ions in acid-base equilibria, because the small atoms in organic molecules don't like charge. The third acid goes from charged to uncharged as a result of deprotonation, and this is very favorable--this will be the strongest acid. But to compare the other three, we need to evaluate the relative stability of the conjugate enolate bases of our three neutral carbonyl-containing acids. The amide enolate on the right is destabilized by electron donation from the nitrogen lone pair, so I'd expect the amide would be the worst base (because it doesn't want to make that unstable anion). Of the two enolates on the left, the second one has the more substituted double bond, and that makes it more stable than the first enolate. So the second ketone must be more acidic than the first.

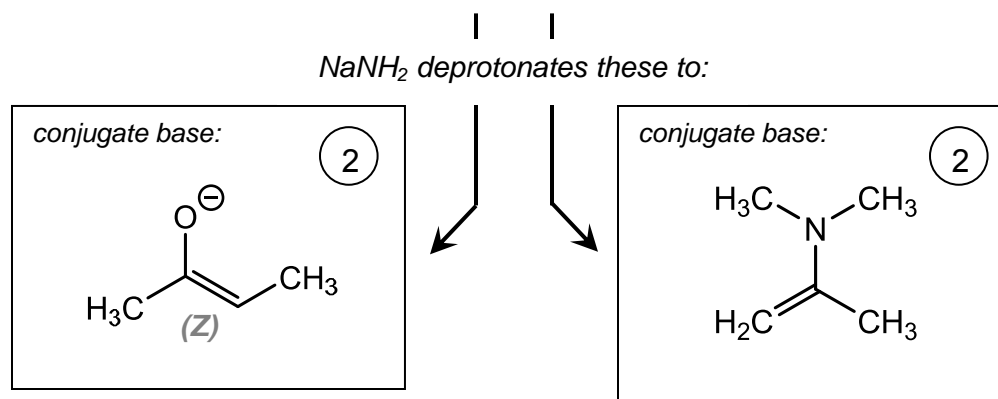
Rubric for this part:

8 points for the correct 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 2-1-4-3, or 4-3-2-1.

2 points partial for just one number correct.



Rubric for this part:

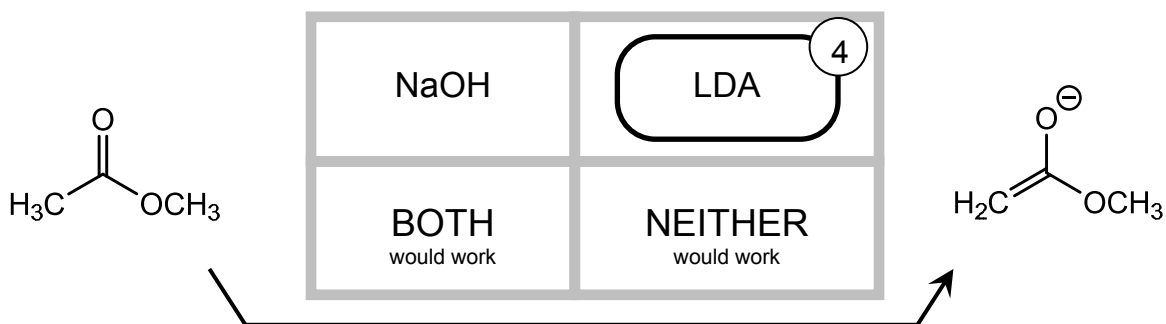
2 points for each correct structure.

Full credit for a resonance structure of either, as long as conformation and deprotonation site are correct.

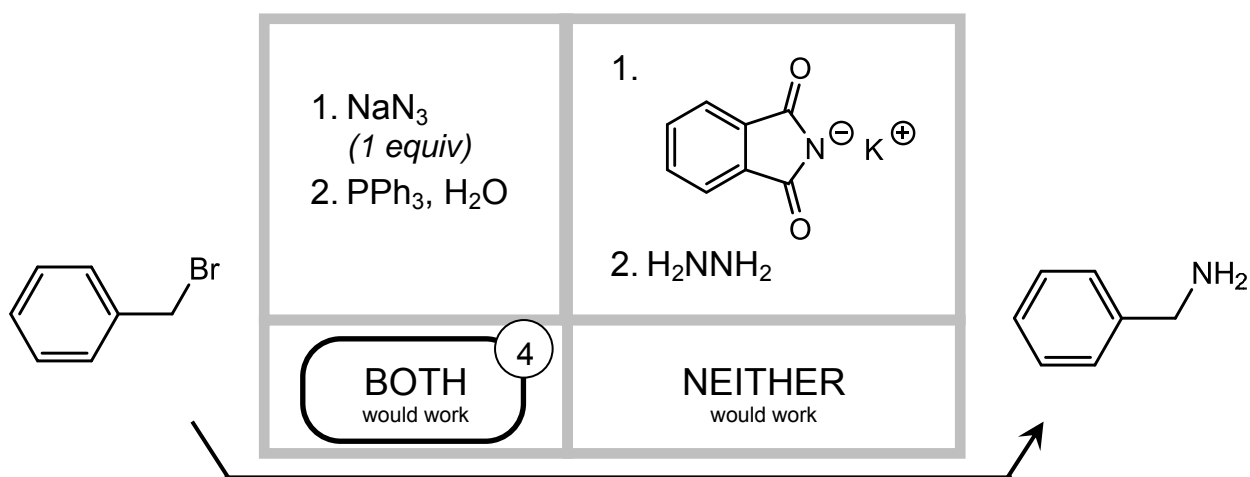
Left: 1 point partial for (E)-enolate, or deprotonation at less substituted carbon.

No partial credit for incorrect charges or deprotonation site.

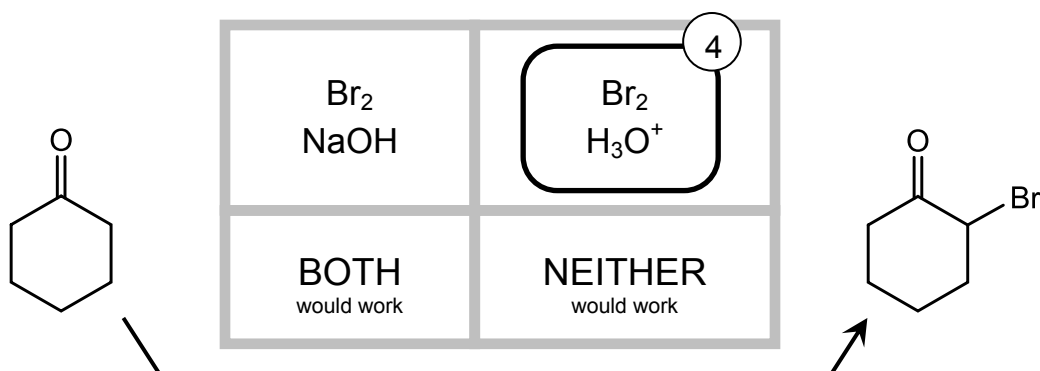
2. (12 pts) Each of the reactions on the next page is drawn with two possible reaction conditions. If only one of the two reaction conditions would generate the given molecule as the major product, circle those conditions. If both sets of conditions would accomplish the reaction, circle "BOTH". If neither set of reaction conditions would succeed, circle "NEITHER". **Circle one answer only.**



This reaction shows an ester being deprotonated at the α -position to yield an ester enolate. Esters aren't very acidic; in class, we said they have pK_a values ~ 25 . NaOH isn't basic enough to generate the enolate quantitatively, but LDA is.

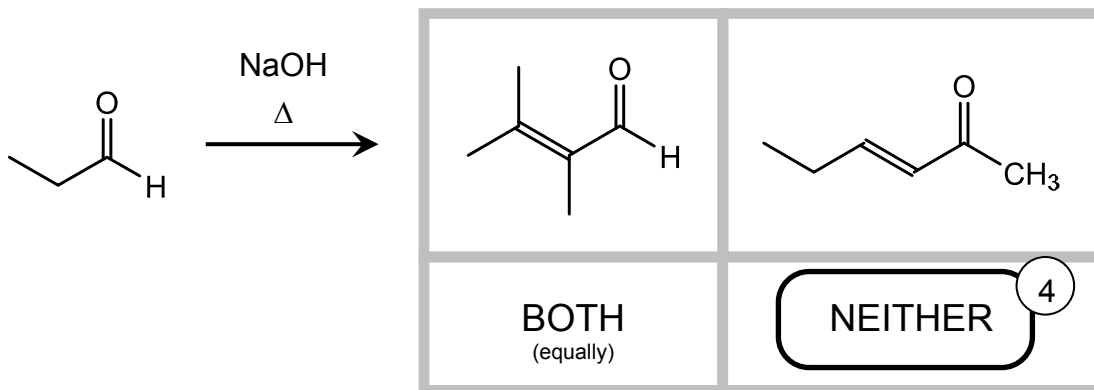


Both of these methods—the azide substitution on the left, and the Gabriel synthesis on the right—convert a halide into a primary amine.

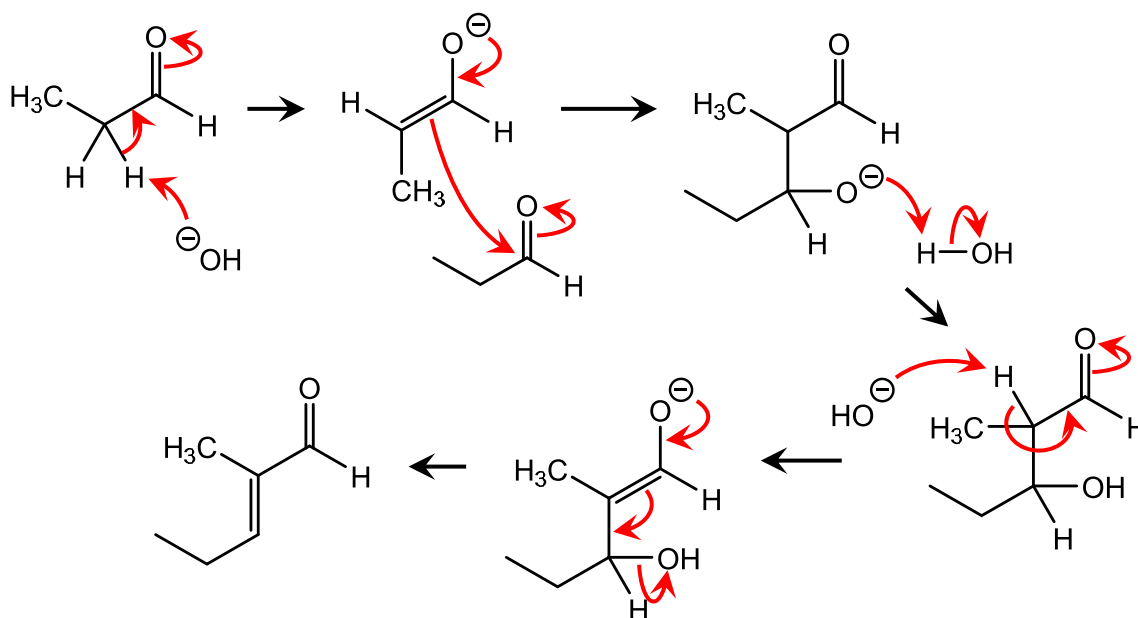


Both of these conditions perform α -halogenation of the carbonyl-containing starting material, but basic conditions (on the left) will do so repeatedly, while acidic conditions will cause the bromination to stop at one addition.

3. (20 pts) Each of the reactions on the next page 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.**

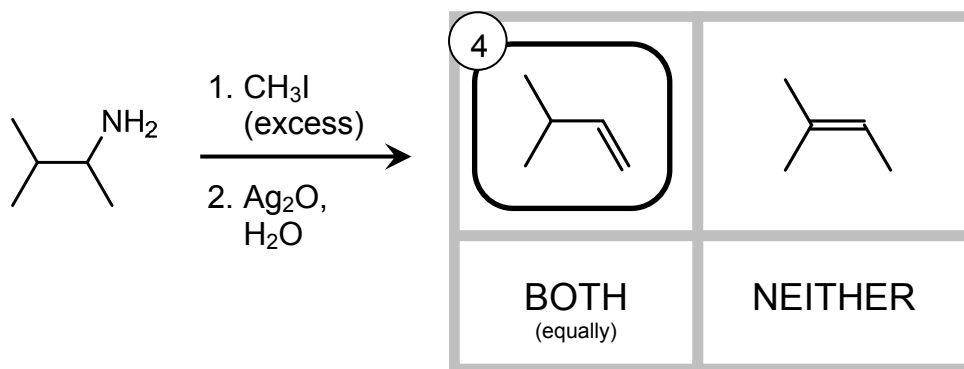


Both of our products are α,β -unsaturated carbonyl compounds, which can be made by aldol condensation. Sure enough, the reaction conditions shown would result in aldol condensation of our aldehyde starting material. But would it make either of these products? I think there were two different ways to answer this problem—retrosynthetically, or by thinking through the mechanism in the forward direction. I think backwards was easier, but here I'll do it forwards, the hard way:

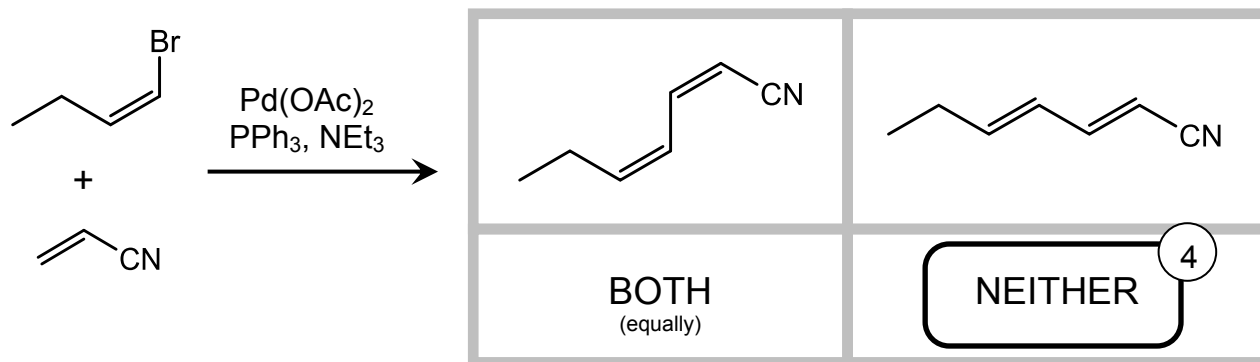
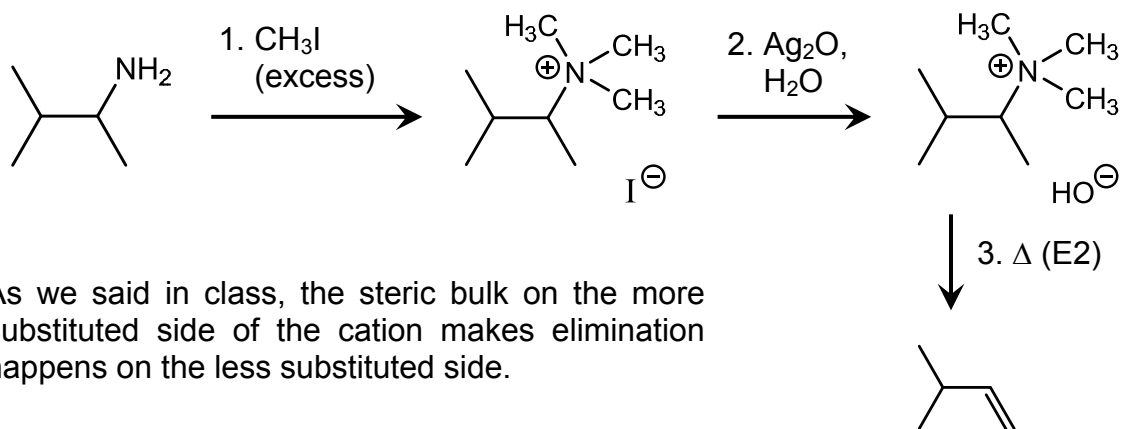


The product above isn't either of the products in the boxes.

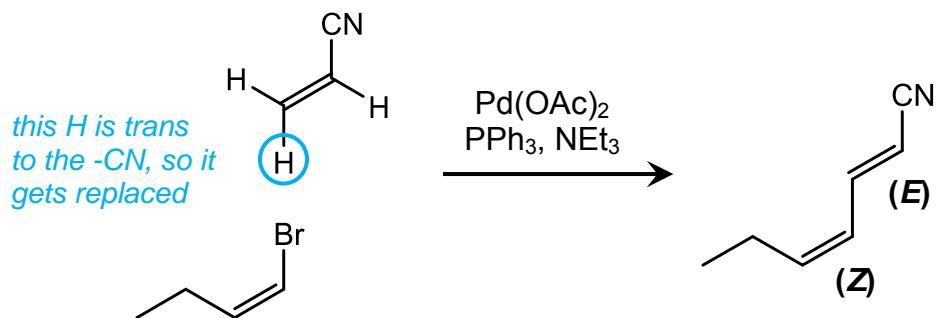
Alternately, we could solve this problem retrosynthetically. If we disconnect each of the products shown at the α - β C=C bond—which is the location of the aldol condensation disconnect—do we get the expected starting material? In each case, we do, but we also get another starting material, acetone, that is not in the problem. (So, each of the products shown is from a crossed aldol, and one of the two starting materials isn't available.)



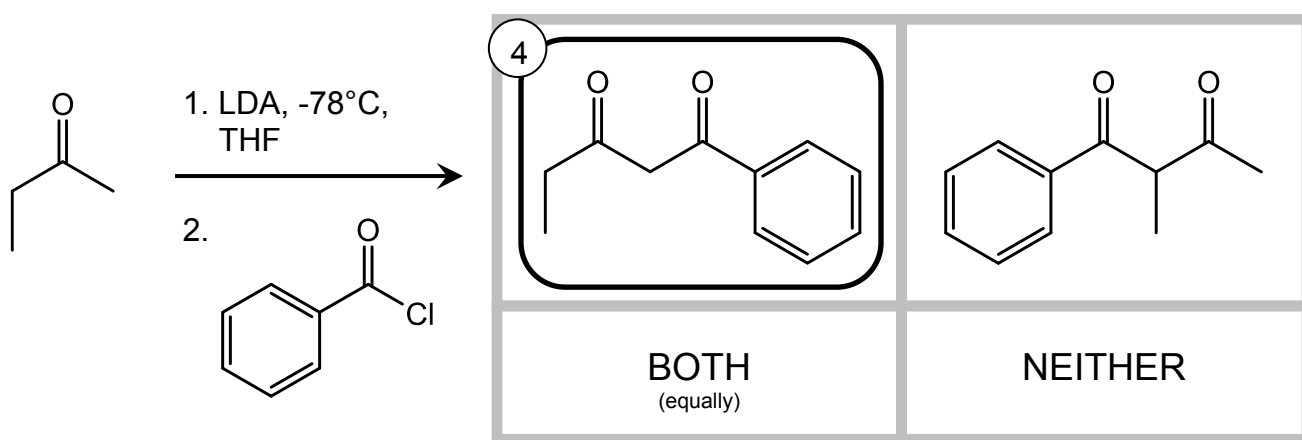
This reaction illustrates a Hoffman elimination, whereby the starting material is first alkylated, and then elimination occurs at the less substituted side of the leaving group:



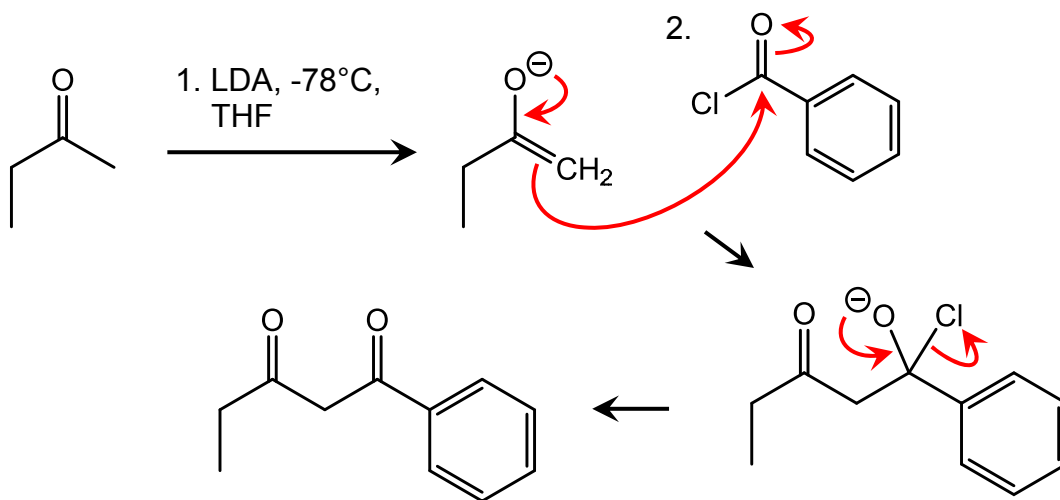
This illustrates a Heck reaction. The Heck reaction forms a C-C bond between an sp^2 -hybridized C-X halide and an alkene. If the alkene is functionalized with an electron-withdrawing group (like the bottom starting material above is), the new bond replaces the C-H that is *trans* to the electron withdrawing group. So, in this case:

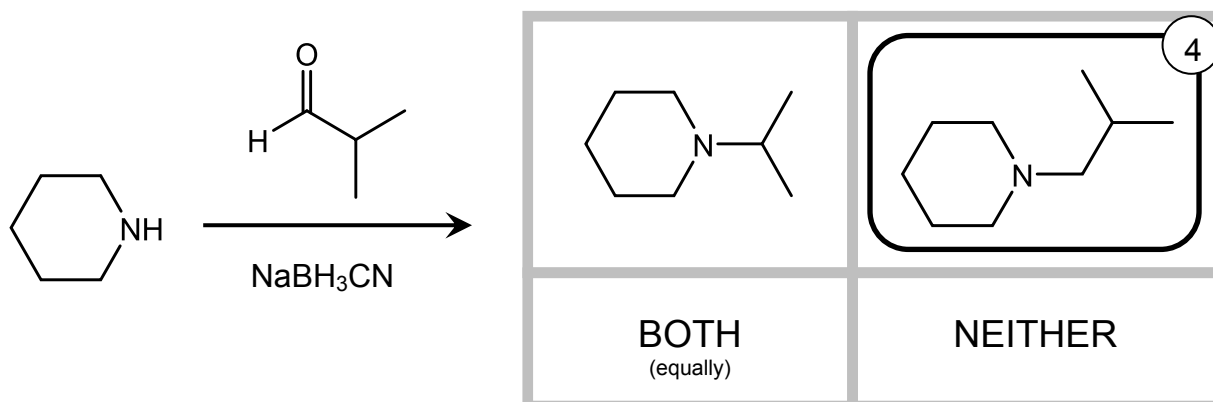


This (Z,E)-diene isn't the same as either of the answers given in the problem; the first answer is (Z,Z) and the second is (E,E).

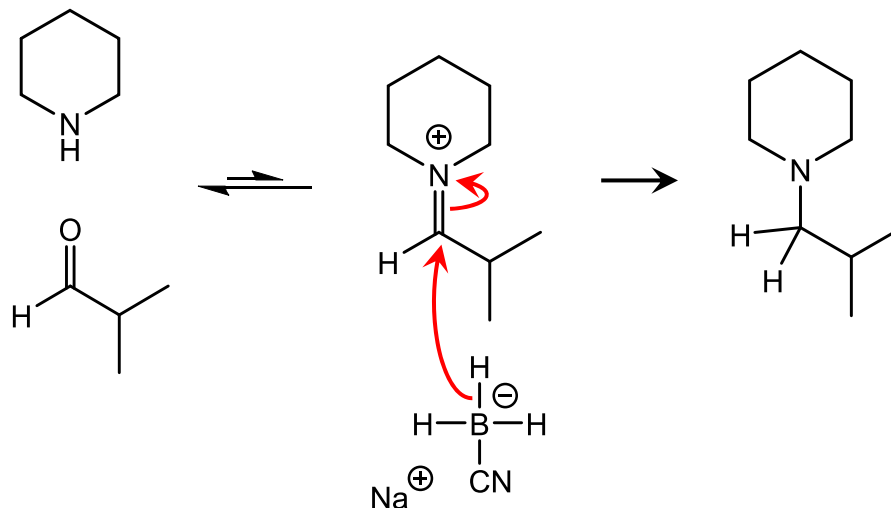


The conditions of the first step—LDA, cold, polar aprotic solvent—generate the kinetic, less-substituted enolate from our starting material. This enolate is then acylated at the less-substituted carbon:



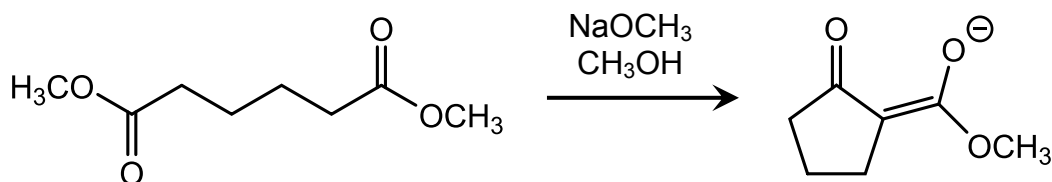


This reaction is a reductive amination--a reaction in which a $\text{C}=\text{O}$ bond swaps its O for an N , and then undergoes hydride addition:

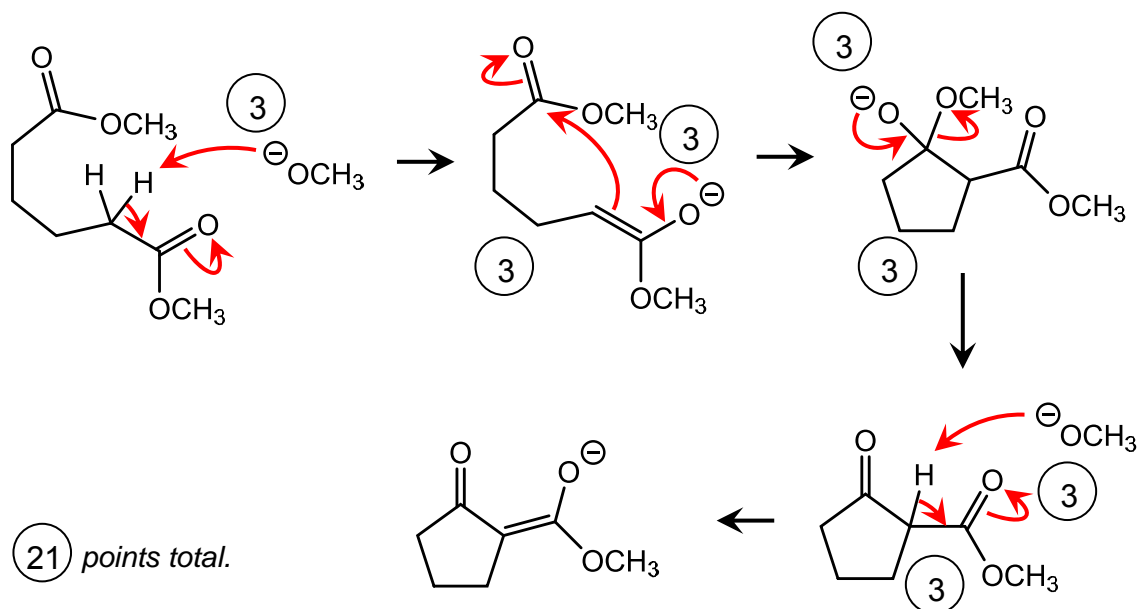


4. (21 pts) For the reaction shown below, draw a mechanism that explains how the product is generated from the starting material. In your answer, make sure that you:

- 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: (21 points total.)

3 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. Species may be drawn as any resonance structure, major or minor, for full credit. For example, I have drawn enolates as oxy-anions, but they could also be drawn in their carbanion resonance structure forms for full credit. This may affect electron pushing arrows.

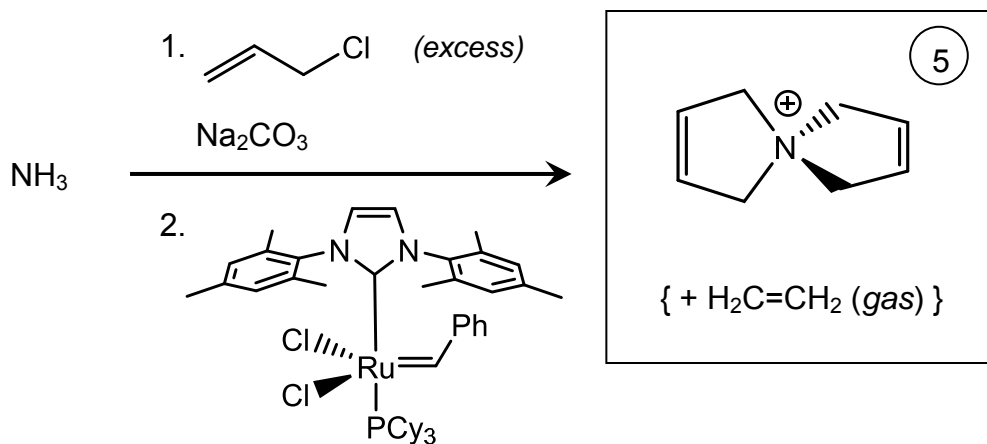
-2 points, for each arrow in each step, for errors in drawing arrows. Arrow must start at an electron pair, and end at nucleus where electrons will newly interact. Can only lose points if you get them.

-1 point for each minor error in charge, valency, structure, etc.; if error propagates, points are taken off only for initial error.

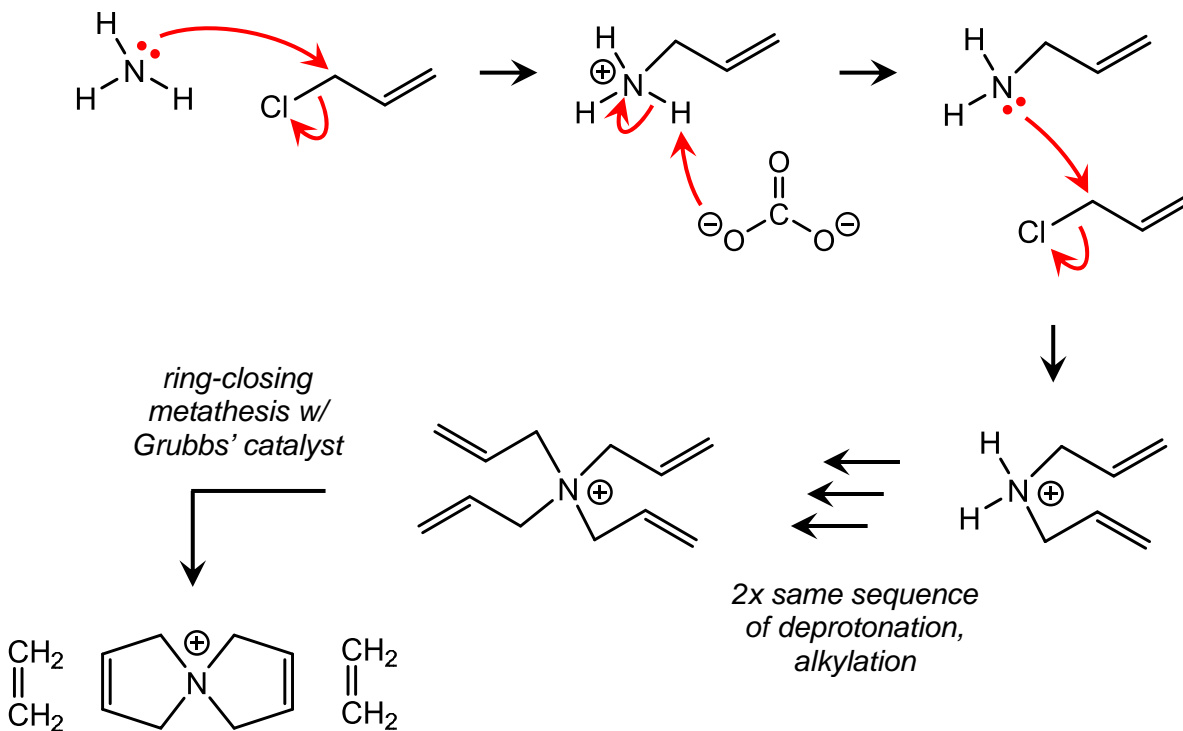
-2 points for each use of a generic or incorrect acid/nucleophile/base. For example, in the first step you couldn't invoke any base other than OCH_3^- that you may have used in other problems.

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.

5. (23 pts) For each of the reactions on the following pages, 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”.



Ammonia will alkylate four times, without stopping, because each alkylation makes it a better nucleophile. The resulting tetraalkylammonium salt will then undergo ring-closing metathesis, twice:



Rubric for this part:

5 points for correct structure.

Product structure can include a counterion, or not; we didn't grade counterion.

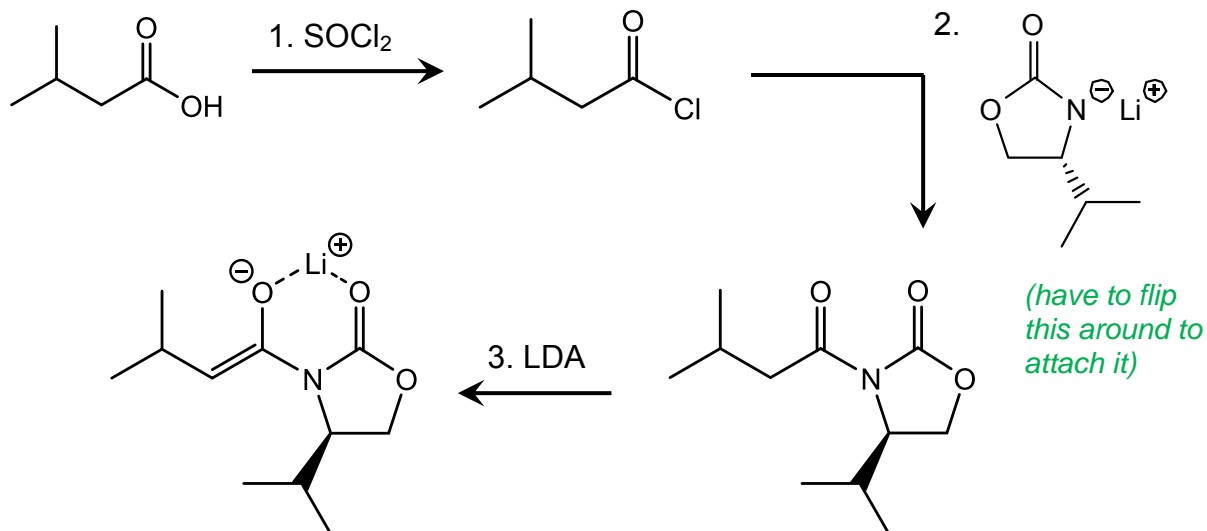
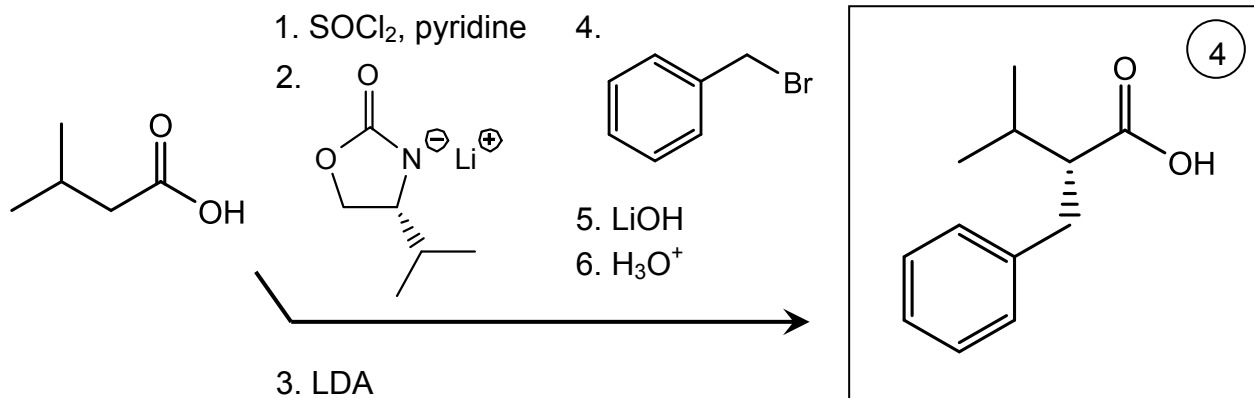
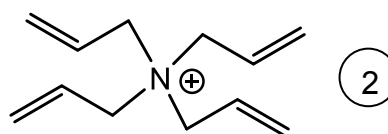
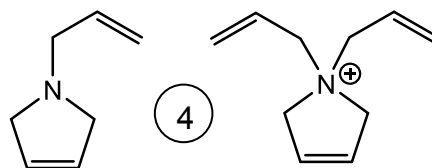
I have drawn the product above with wedges and hashes, but you didn't need to.

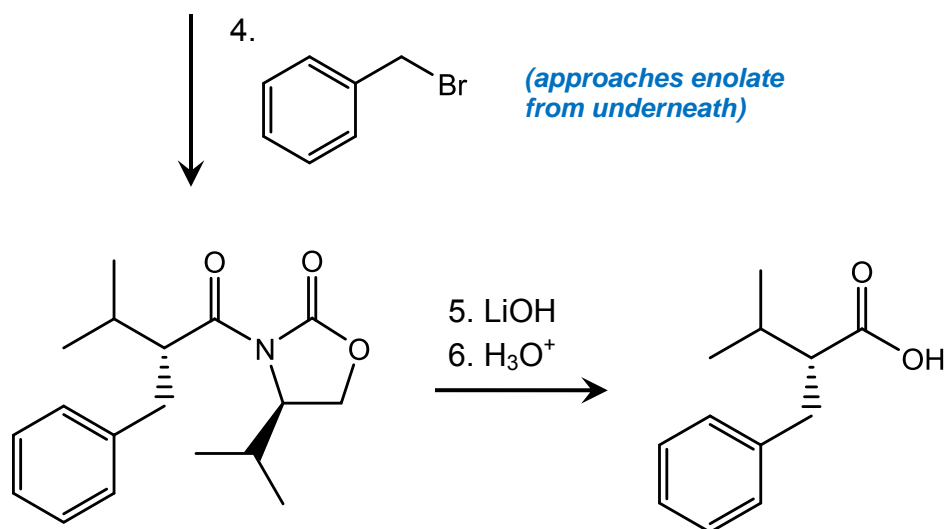
4 points partial for tertiary amine or quaternary ammonium ion with just one correct 5-membered ring.

3 points partial for any other structure with one correct five-membered ring.

2 points partial for tetraallylammonium ion.

-2 points for each trivial error (like incorrect number of carbons in the ring, or omitting double bond).



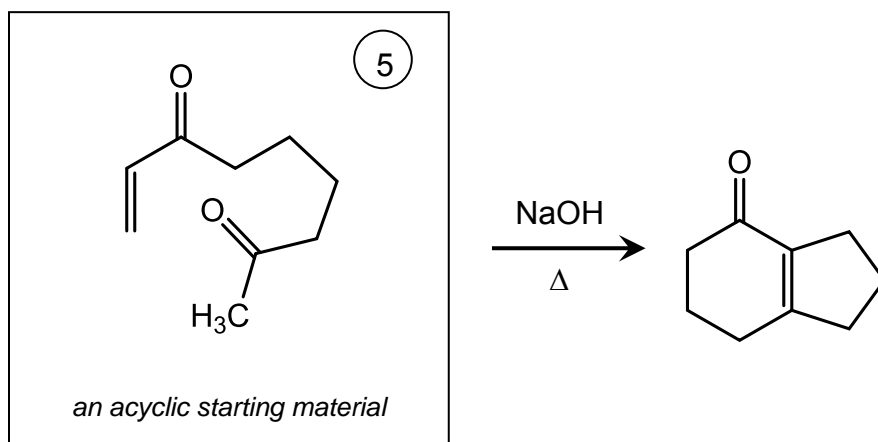


Rubric for this part:

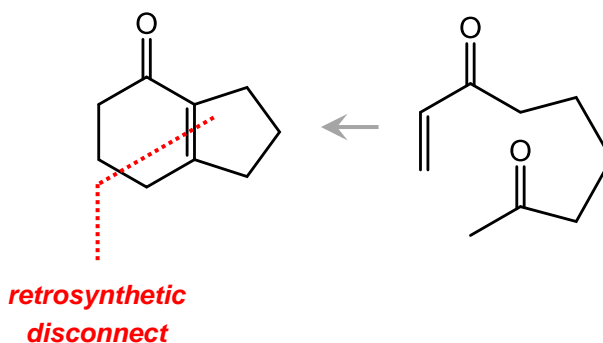
4 points for correct structure.

2 points partial for incorrect stereochemistry (wedge instead of hash), unclear stereochemistry, or for writing "+ enantiomer".

-2 points for a trivial error (like leaving a carbon out of the structure, but stereochemistry and product functionality is correct).

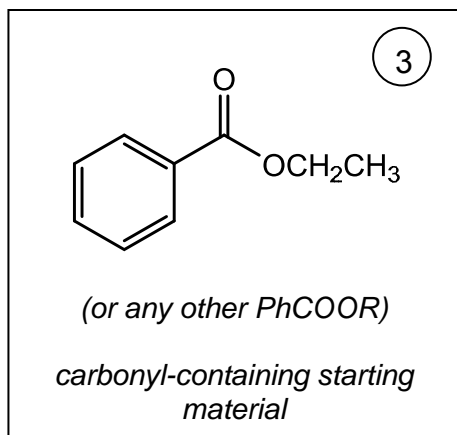


The cyclohexenone is a synthon for the Robinson annulation. The Robinson disconnect passes through two bonds of the cycle to yield an α,β -unsaturated carbonyl and a ketone; in this case, the two pieces are still part of the same molecule.



5 points for correct structure.

-2 points for each trivial error (like leaving a carbon out of the structure, or omitting double bond).

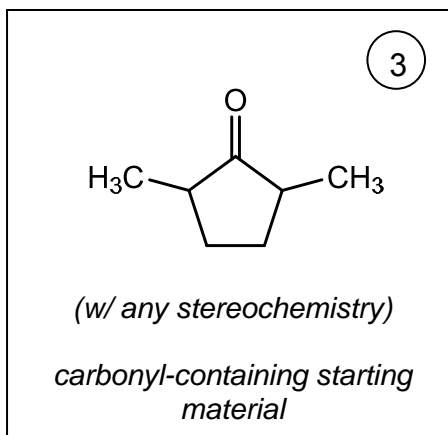


used in excess?

YES or **NO** ?

(circle one)

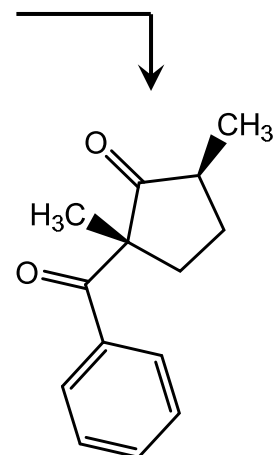
(3)



used in excess?

YES or **NO** ?

1. $NaOCH_2CH_3$
 $HOCH_2CH_3$
2. H_3O^+

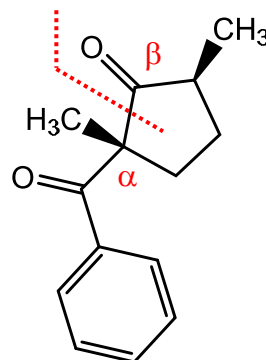


Here, the product is a 1,3-diketone, and this is the synthon for the Claisen condensation--a reaction between an aldehyde/ketone enolate and an ester. 1,3-Diketones are unique synthons, in that they can be retrosynthetically disconnected in two different places to point to two different sets of starting materials:

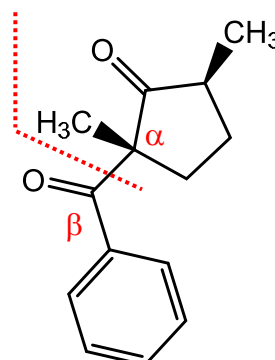
This problem specifically asks for two carbonyl-containing starting materials, not one. Only the disconnect on the right breaks our molecule into two pieces, so this is the correct one.

As we discussed in class, aldol and Claisen condensations can be conducted one of two ways: (i) using a very strong base (like LDA) on one starting material, to make the preferred enolate, followed by addition of the second starting material; or (ii) using a weak base (like ^-OH or ^-OR), and manipulating starting material concentrations to ensure that the right reaction pairing takes place. Here, the reaction conditions use a weak base. Out of our two starting molecules, only the ketone can make an enolate; to make

retrosynthetic
disconnect



retrosynthetic
disconnect



sure that the ketone enolate doesn't add to another molecule of ketone, and instead adds to the ester, we use an excess of the ester.

Rubric for this part:

3 points for each correct structure.

Either answer could be written in either box.

Any ester is fine. Typically, the base is chosen to match the ester (so, I have drawn an ethyl ester to match the ethoxide base). But any one will work.

Answer could also be an acyl halide or anhydride; reaction conditions will just turn this into an ester anyways.

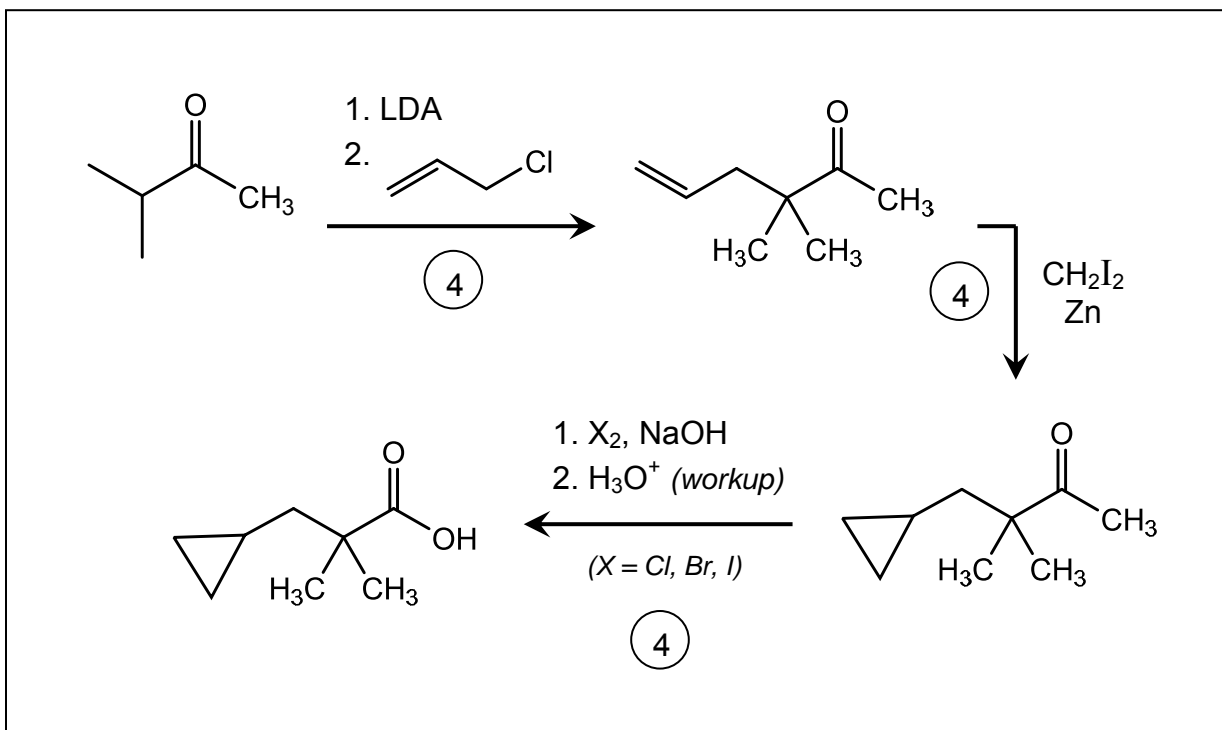
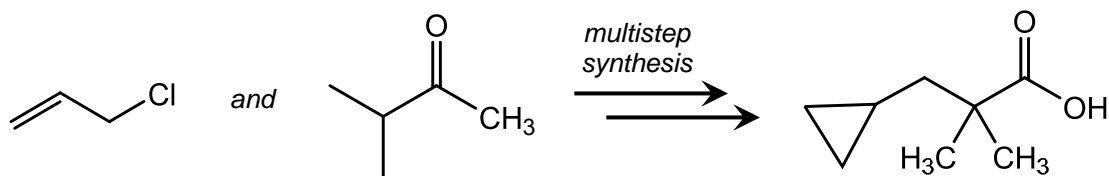
3 points (out of 6 total) for single-molecule aldehyde ester that comes from disconnect on the left.

3 points for combination of circles.

"YES" must go with an ester and "NO" with an aldehyde/ketone for credit.

No partial credit for circling both "YES" or both "NO".

6. (12 pts) Propose a multistep synthesis of the product below, beginning with the starting materials given. In addition to those organic starting materials, 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. Your intent needs to be clear for the error to be considered trivial.

-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.

Tasks:

1. Allylate more substituted carbon. (4 points.)

You could do this either by sequential deprotonation (using LDA or NaNH₂) followed by addition of allyl chloride, or by simultaneous addition of base (like NaOH) and allyl chloride. (This second combination would make a lot of allyl alcohol by-product, but it would still work.)

This reaction fails if haloform reaction has been used first. Under that circumstance, deprotonation won't occur at carbon, but at -COOH instead. No points for this step, but other steps will still succeed.

2. Cyclopropanate double bond. (4 points.)

Full credit for Simmons-Smith at any point in the synthesis.

2 points partial for K₂OtBu/CHCl₃, as long as there are no acidic protons available.

This reaction would place 2 Cl atoms on the cyclopropane.

3. Haloform reaction. (4 points.)

Full credit at any point in the synthesis.