Fall 2025 **Chemistry 4000 Final Exam** ____/82 marks

Confidentiality Agreement:
I agree not to discuss (or in any other way divulge) the contents of this exam with (or in the presence of) any CHEM 4000 student who has yet to write it. I understand that breaking this agreement would constitute academic misconduct. The minimum penalty would be a mark of 0/82 on this exam.

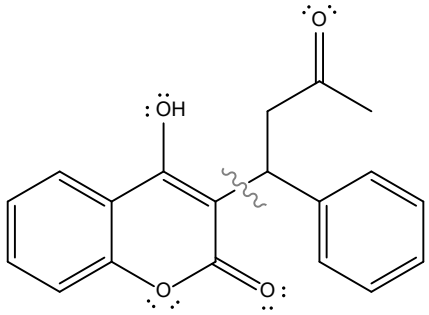
Signature: _____ Date: _____

1) Please read the test carefully before starting. It has eleven pages of questions.
2) You have been given a data sheet with a periodic table. This page does not have a QR code, so nothing written on this sheet of paper will be graded. If you wish to do rough work that you might want a grader to be able to see, use the back of any page of the test.
3) You are allowed to bring one index card (maximum size 3"x5") into the exam with you as a "cheat sheet". This card must be submitted with your exam.
4) You **may** use a molecular model kit. You may not have written materials in your model kit.
5) You may **not** use a calculator or any other electronic device.
6) **DO NOT WRITE ON ANY QR CODE!!!** Work on pages without a QR code will not be graded.
7) If your work is not legible, it will be given a mark of zero. For full credit, explanations must be complete. In many cases, complete explanations include drawing relevant structures. If delocalization of electrons is invoked, the relevant resonance structures must be drawn.
8) Marks will be deducted for incorrect information added to an otherwise correct answer.
9) You have 3 hours to complete this test.

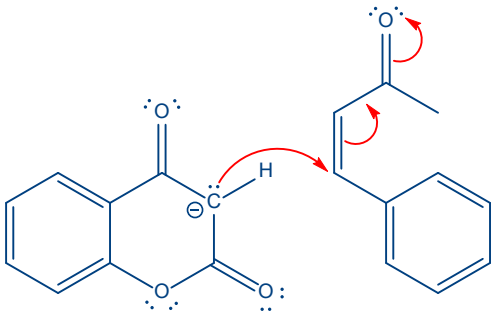
Question Breakdown

Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8								Total
/ 8	/ 5	/ 9	/ 12	/ 22	/ 20	/ 5	/ 1								/ 82

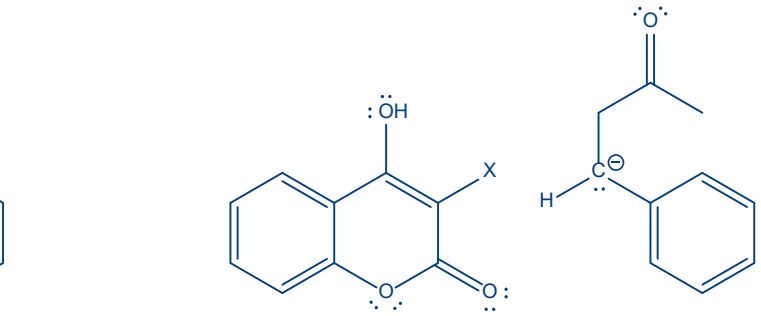
1. Warfarin was first marketed as a rat poison. Several years later, it received FDA approval as a medication for the treatment of blood clots. The structure of warfarin is shown below with one of the bonds marked for disconnection. **[8 marks]**



(a) Disconnection at the marked bond can lead to two different pairs of synthons. Draw each pair of synthons and label each synthon as a^1, d^1, a^2, d^2, etc. *[4 marks]*



d2



a3 a2 d3

The d^2 synthon shown is the most practical option but, given that this is a retrosynthetic proposal, other d^2 synthons were accepted as long as the correct nucleophilic carbon atom was identified.

Please note that the a^3 synthon is natural because the conjugated pi system includes the electrophilic site. As such, just attaching a leaving group (X) to the desired electrophilic site doesn't make it a true a^3.

(b) Which pair of synthons is expected to be easier to use to design a synthesis of Warfarin? Why? *[2 marks]*

$d^2 + a^3$ In this pairing, both synthons are natural.

(c) Give two additional reasons why the disconnection shown is a good choice. (In other words, don't repeat reasons discussed in either part (a) or (b) of this question.) *[2 marks]*

Reasonable answers include:

- Both synthons are similar in size.
- The disconnection is next to a ring and gives two relatively simple synthons from a skeletal perspective.

2. Within the past couple of weeks, I have attended two different seminars that included discussion of "mechanochemistry". This is the use of mechanical force to provide the energy necessary for reactions. Both talks described the use of milling balls which are small metal balls added to the reagents in a reaction container. Rotation of the container makes the balls move (as they respond to gravity), creating 'hot spots' of localized high temperature and pressure that promote reaction. **[5 marks]**

(a) One of the mechanochemical reactions discussed was a solvent-free Suzuki coupling in which the milling balls would not only perform the role described above but would also serve as the catalyst for the reaction. What metal would the milling balls need to be made from for them to be able to catalyze a Suzuki cross-coupling reaction? *[1 mark]*

palladium (Pd)

(b) With reference to at least three principles of green chemistry, explain why the reaction described in part (a) would qualify as "green". *[3 marks]*

Reasonable answers include:

- "Hot spots" are attained without heating the whole mixture so that saves energy.
- No solvent is used.
- The reaction is catalytic.

(c) Identify one drawback of the reaction described in part (a). *[1 mark]*

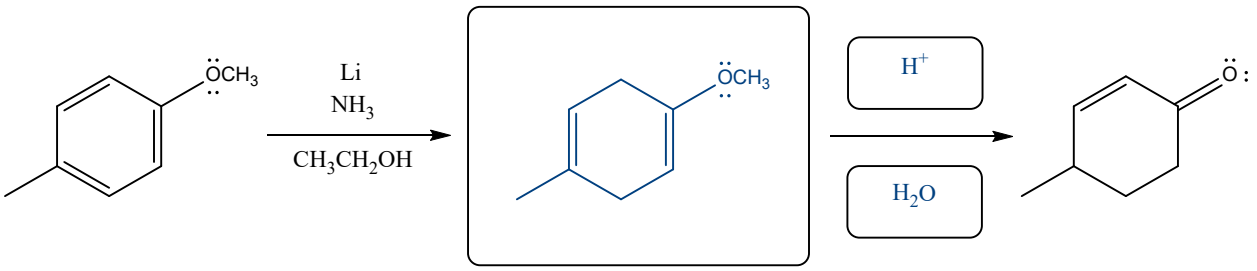
Assume that the chemistry will work. I'm looking for either a practical concern or a green-related concern.

The milling balls are made from an expensive transition metal but only the surface reacts. As such, a lot of money is spent on material that is not involved in the reaction, and this may not be the most efficient use of a valuable natural resource.

Other reasonable answers were accepted

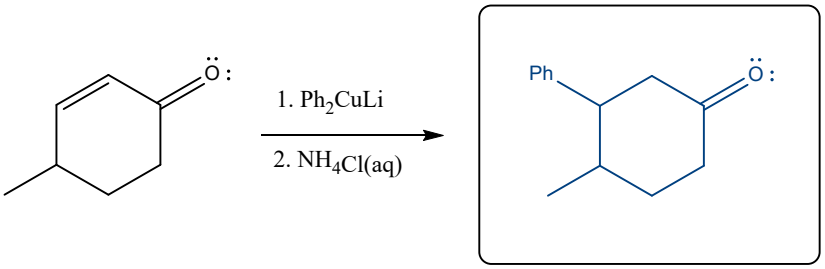
3. α,β-unsaturated ketones are very useful starting materials and/or intermediates in organic synthesis. The following questions address how to make them and some of their many uses. **[9 marks]**

(a) Fill in the boxes to show the missing reactants and intermediate in the following synthesis of an α,β-unsaturated ketone via a Birch reduction. *[3 marks]*

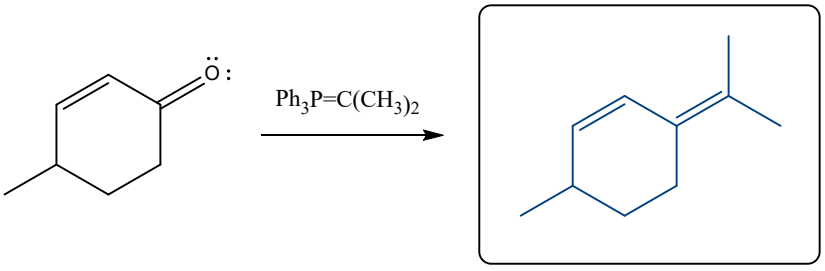


(b) Fill in the boxes to show the products of each of the following reactions. *[6 marks]*

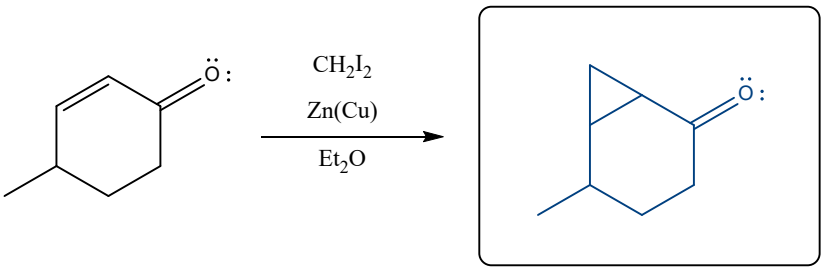
i.



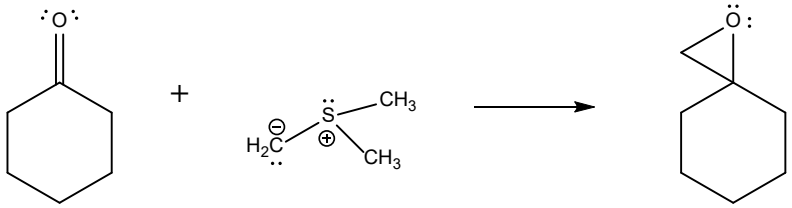
ii.



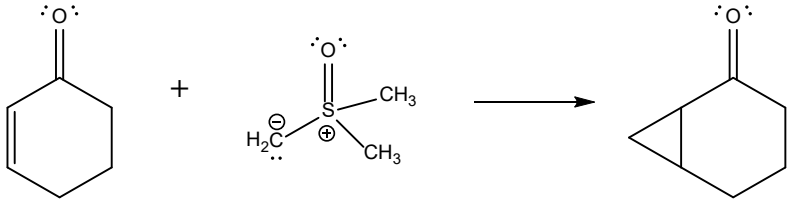
iii.



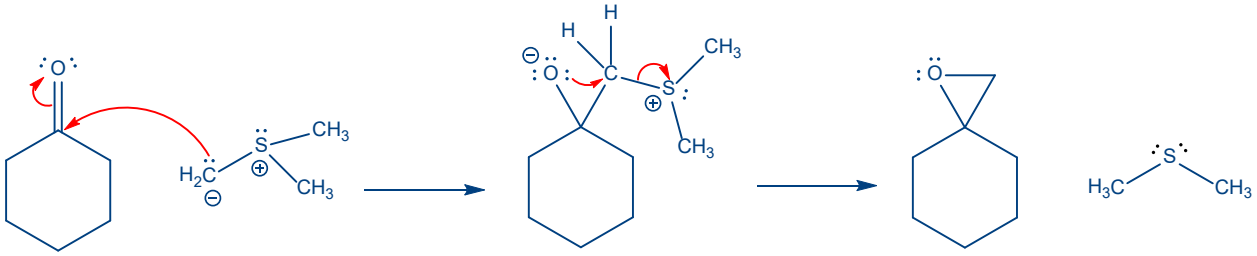
4. When we learned that sulfonium ylides can be used to convert ketones and aldehydes into epoxides, all the examples that we looked at involved isolated carbonyl groups. **[12 marks]**



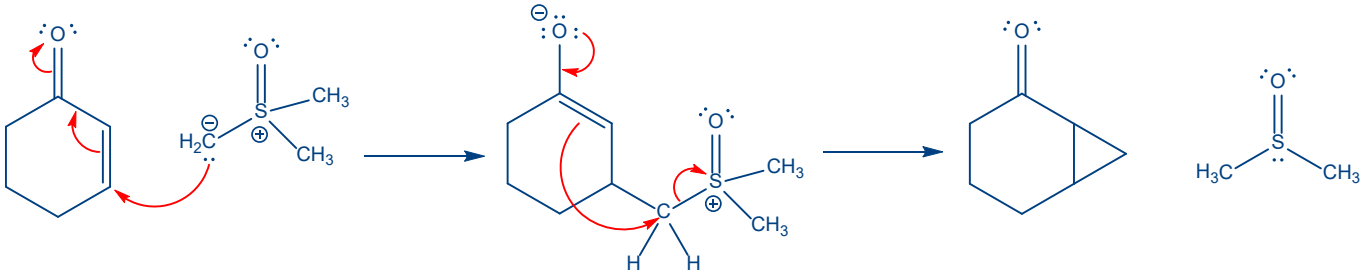
When a sulfonium ylide is reacted with an α,β-unsaturated ketone or aldehyde, we start to see cyclopropane formation instead. If we replace the sulfonium ylide *(see above)* with a sulfoxonium ylide *(see below)*, cyclopropane formation becomes even more favoured:



(a) Propose a reasonable mechanism for the first reaction shown (epoxide formation). *[3 marks]*

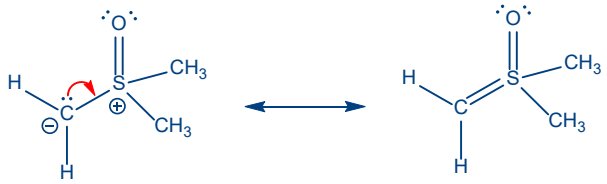


(b) Propose a reasonable mechanism for the second reaction shown (cyclopropane formation). *[3 marks]*

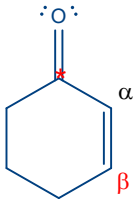


(c) Use an argument based on Hard-Soft Acid-Base theory to explain why a cyclopropane is formed instead of an epoxide in the second reaction. *For full marks, discuss both nucleophile and electrophile.* *[5 marks]*

Ylides are soft nucleophiles. While the question shows the resonance structures with formal charges on carbon and sulfur, there is actually only a fractional negative charge on the nucleophilic carbon atom:



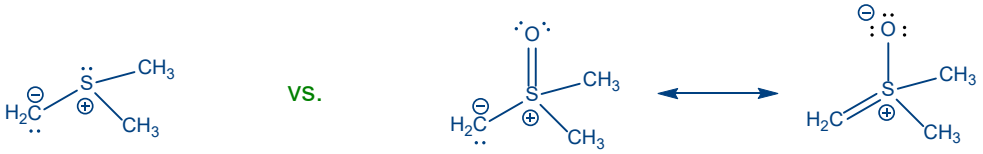
Soft nucleophiles tend to react at softer electrophilic sites. Of the two electrophilic sites in cyclohex-2-enone, the beta carbon (β) has a lower charge density than the carbonyl carbon (*) because it is farther away from the electronegative oxygen atom and therefore feels its inductive electron withdrawing effect less strongly:



Thus, ylides will tend to attack the softer beta carbon, giving rise to the cyclopropane product via the mechanism shown in part (b).

Selectivity for cyclopropane formation over epoxide formation increases with the softness of the nucleophile (see part (d)).

(d) Use an argument based on Hard-Soft Acid-Base theory to explain why it is better to use the sulfoxonium ylide than the sulfonium ylide if you want to make the cyclopropane product. *[1 mark]*



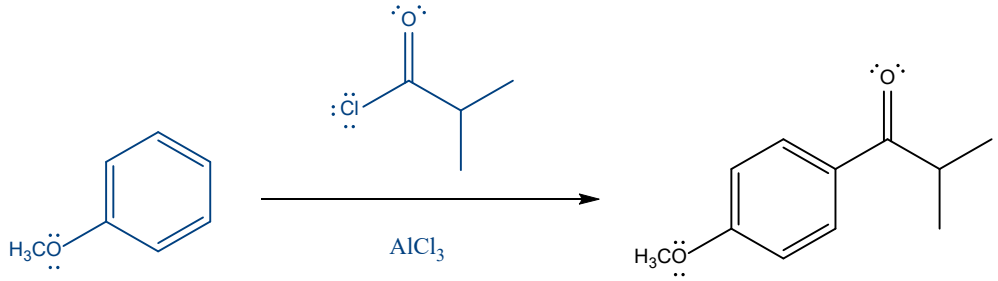
sulfonium ylide vs. sulfoxonium ylide

The electronegative oxygen atom increases the electron withdrawing effect of the electron-poor sulfur atom as shown by the resonance structures above. As such, the charge density of the nucleophilic carbon atom is lower in the sulfoxonium ylide than it is in the sulfonium ylide and the sulfoxonium ylide is therefore the softer nucleophile.

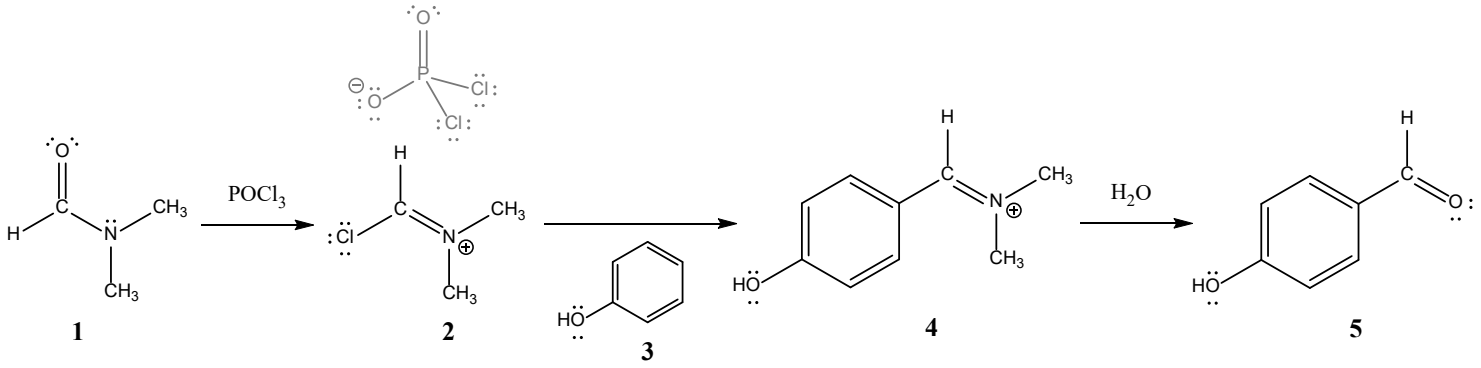
It is also reasonable to use a strictly inductive argument in this case. Oxygen is the more electronegative element in the sulfur-oxygen bond therefore the sulfur atom in the sulfoxonium ylide has a greater positive charge than the sulfur atom in the sulfonium ylide. As such, the sulfur in the sulfoxonium ylide is a stronger electron withdrawing group, leaving less negative charge on the carbon atom.

5. The Friedel-Crafts acylation reaction is useful for preparing phenyl ketones. It is not, however, capable of producing benzaldehydes. To attach an aldehyde group to an aromatic ring, a related reaction called the Vilsmeier-Haack reaction can be used instead. **[22 marks]**

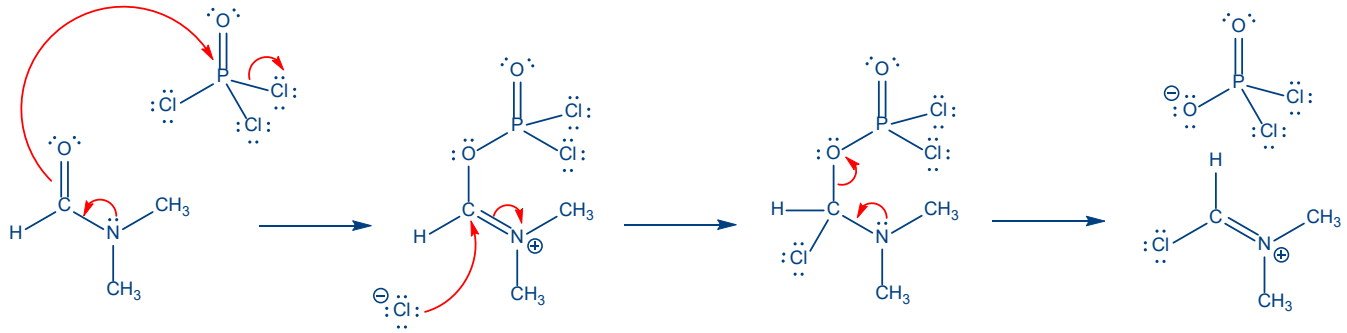
(a) Complete the reaction equation below showing all starting material(s) and reagent(s) required to make the product via a Friedel-Crafts acylation reaction. *[3 marks]*



(b) In the Vilsmeier-Haack reaction, DMF (**1**) is reacted with $POCl_3$ to form the Vilsmeier reagent (**2**). To this, an activated aromatic ring (**3**) is added giving iminium ion **4**, hydrolysis of which gives benzaldehyde **5**.

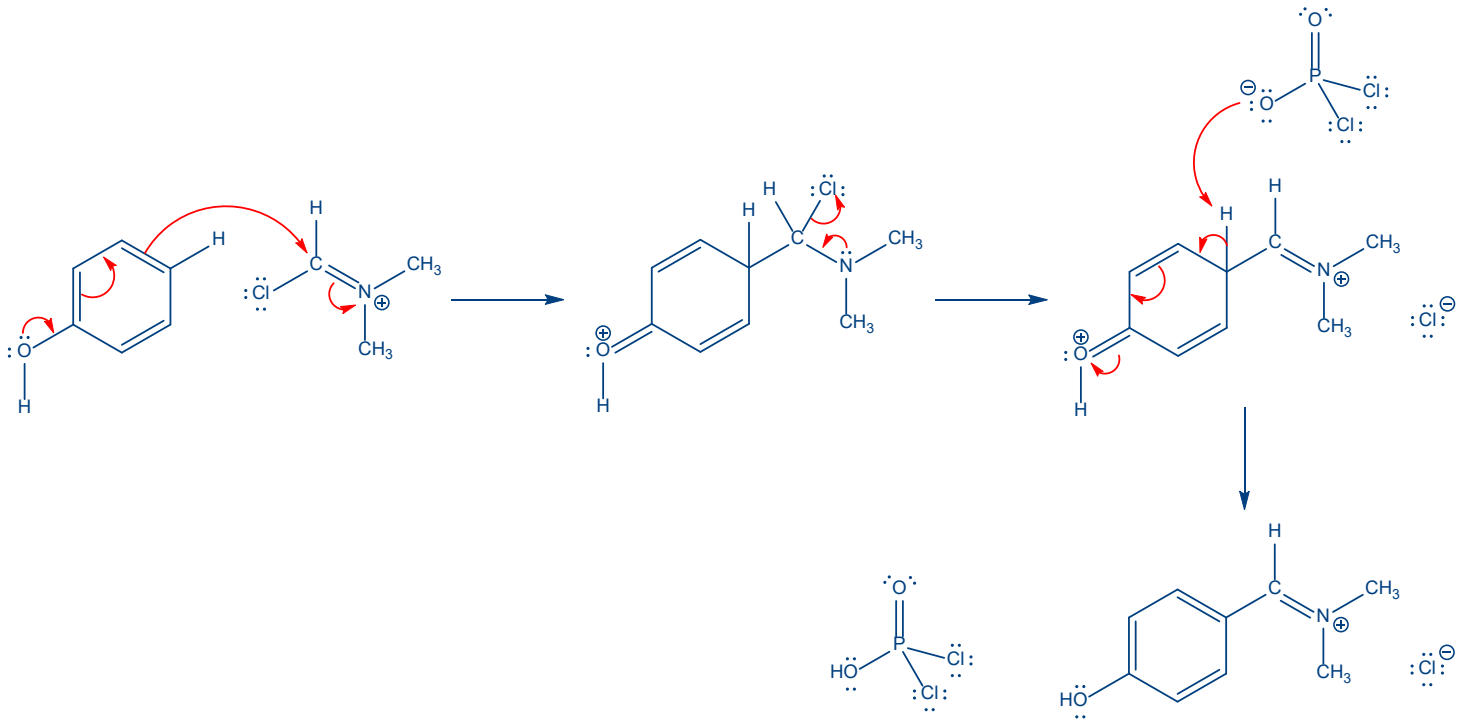


i. Propose a reasonable mechanism for the reaction of **1** and $POCl_3$ to give **2**. *[5 marks]*



Phosphorus is tetrahedral so can act as the electrophilic site in an S_N2 reaction (step 1). On the other hand, trigonal planar atoms cannot undergo S_N2 reactions so, when chloride attacks in step 2, the C-N pi bond must break giving a tetrahedral intermediate that collapses in step 3.

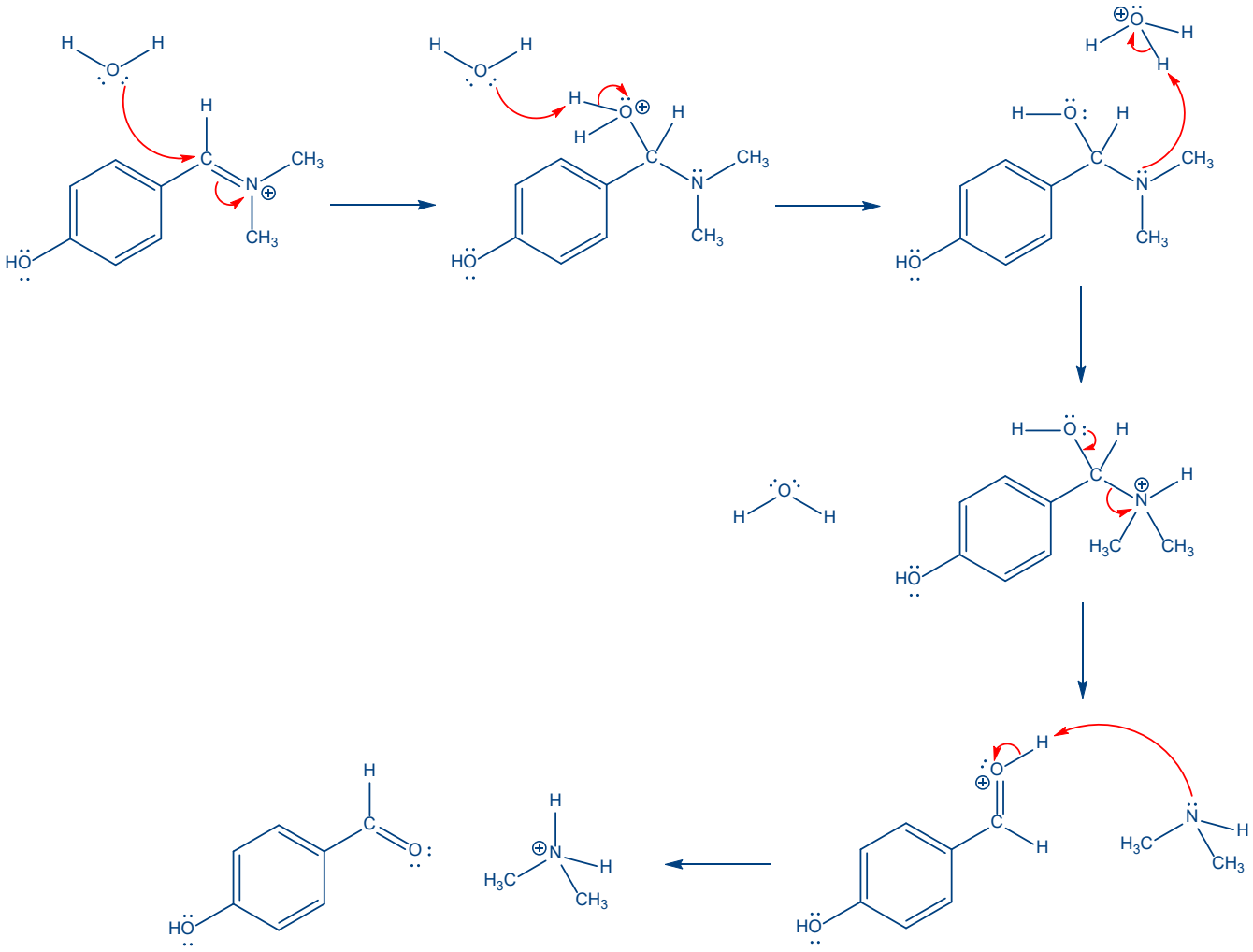
ii. Propose a reasonable mechanism for the reaction of **2** and **3** to give **4**. *[5 marks]*



Again, trigonal planar atoms cannot undergo S_N2 reactions so, when phenol attacks the electrophile, the C-N pi bond must break giving a tetrahedral intermediate that collapses in the next step. (Intramolecular reactions are usually faster than intermolecular reactions.)

Because deprotonation restores aromaticity to the ring and the dication that is deprotonated in the last step is therefore extraordinarily acidic, chloride is also a strong enough base to do the deprotonation. So, while $PCl_2O_2^-$ is the stronger base, it was also acceptable to use Cl^- as the base in this step.

iii. Propose a reasonable mechanism for the hydrolysis of **4** to **5**. *[9 marks]*



Pay attention to the charges. You're working in acid so organic species should either be neutral or positively charged (while avoiding net charges that are greater than +1).

6. Choose **two** of the molecules below and propose a synthetic route to make each. **[20 marks]**

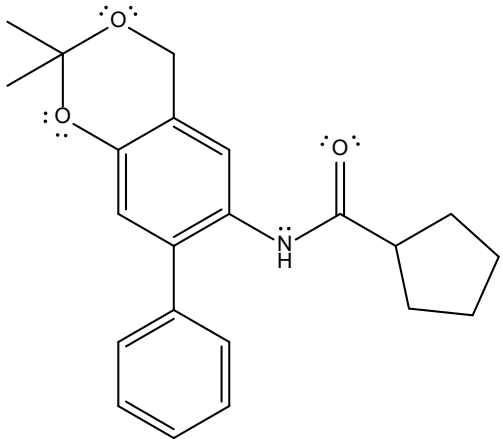
Your answers should take the form of a retrosynthetic analysis followed by chemical equations for the reactions in the synthesis itself. Show all required reagents, and number steps within a reaction if order of addition is important.

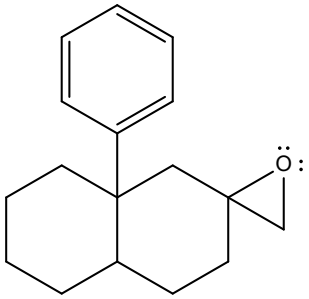
You may use any reagents that you could reasonably expect to be commercially available and that contribute no more than 7 carbon atoms to the final product.

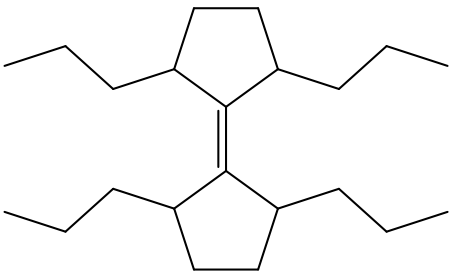
If you are suggesting a multi-step synthesis, write an equation for each step.

There are two pages after this. Use one of those pages for each synthesis and clearly identify the synthetic target at the top of the page. This page is scrap paper.

Options





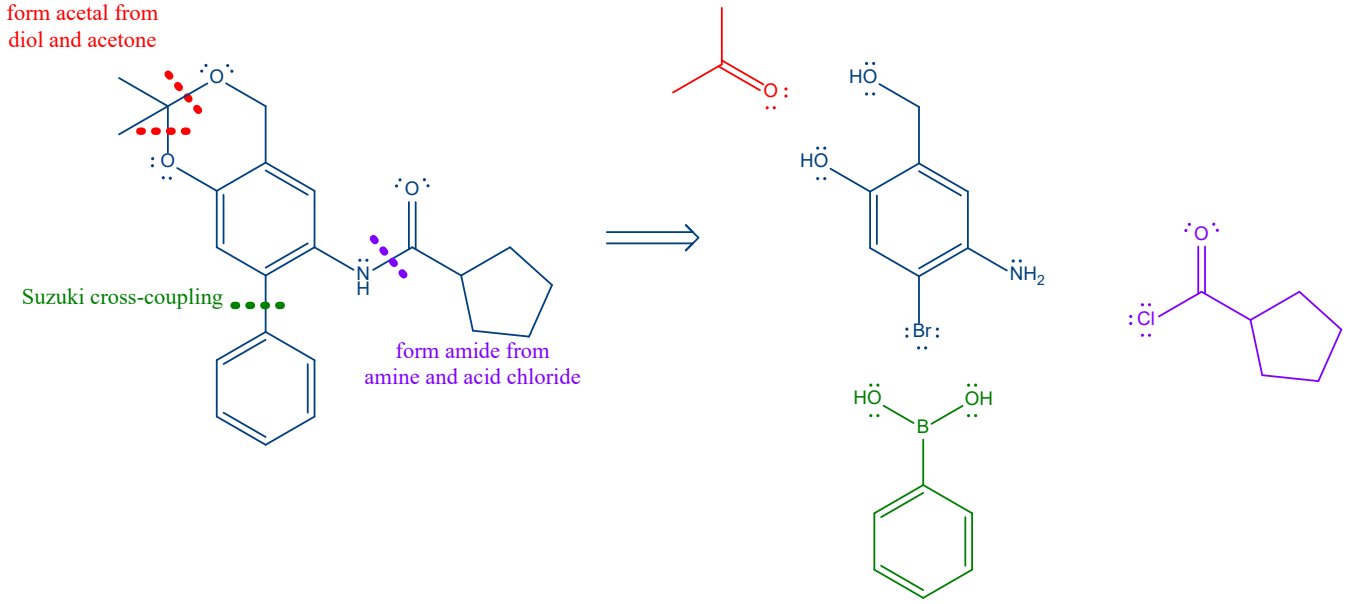


The answers in this answer key are representative. There will be many other valid approaches to synthesis of each molecule.

6. *continued…* *[10 marks]*

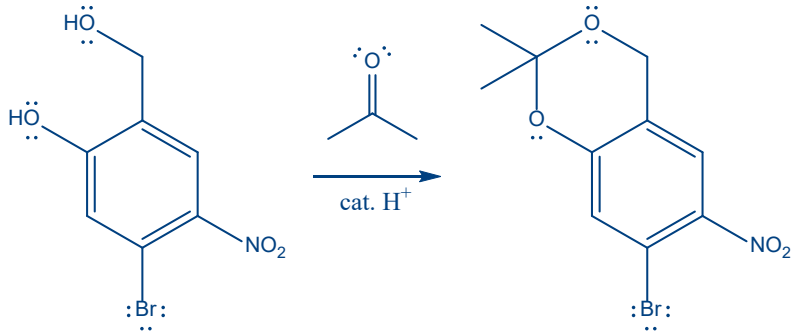
First Retrosynthesis and Synthetic Proposal

Retrosynthetic Analysis

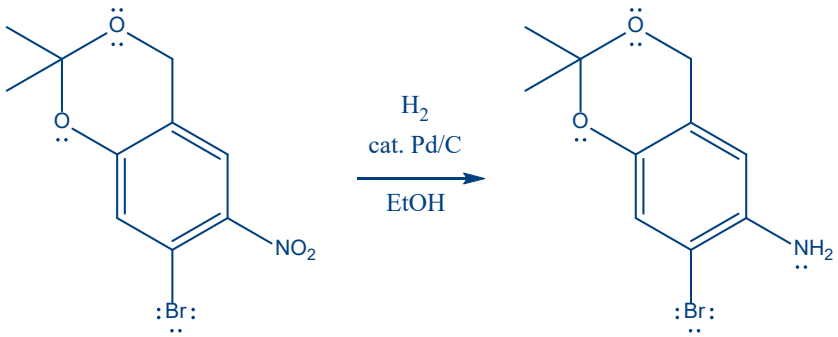


Synthetic Proposal

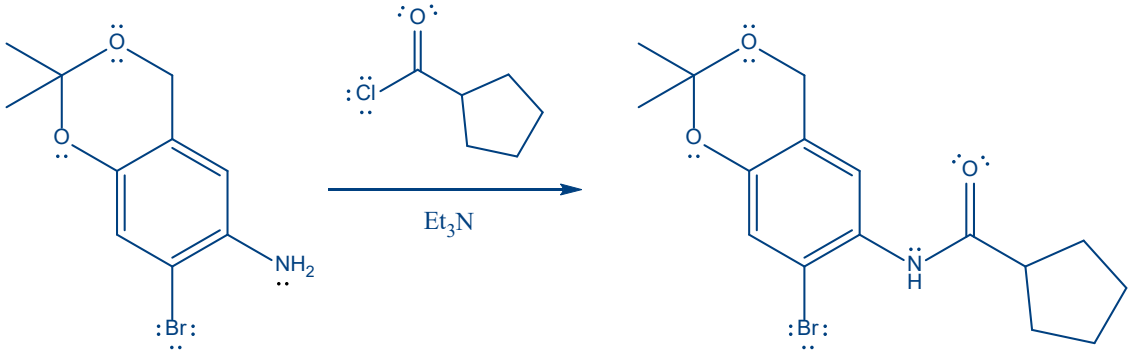
1. Form the acetal by reacting an appropriate diol with acetone in the presence of an acid catalyst. Do this first to avoid potential side reactions involving the phenol OH groups. I've chosen to start with a nitrobenzene (rather than an aniline) to avoid any complications from the NH_2 group attacking acetone (since amines are stronger nucleophiles than alcohols).



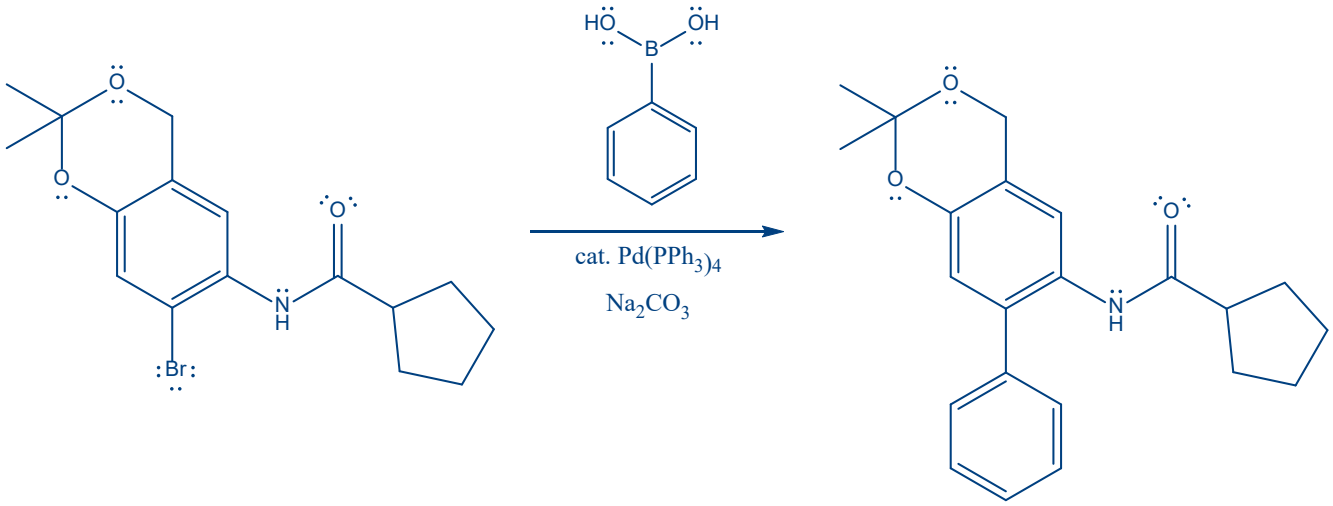
2. Hydrogenate the nitro group to give the aniline.



3. Form the amide by reacting the aniline with the relevant carboxylic acid derivative in the presence of an amine such as triethylamine or pyridine. I have chosen the acid chloride because they're cheaper and easier to work with than acid bromides while also being more reactive than anhydrides. Reacting the aniline with a carboxylic acid in the presence of a coupling agent such as DCC would also be viable.



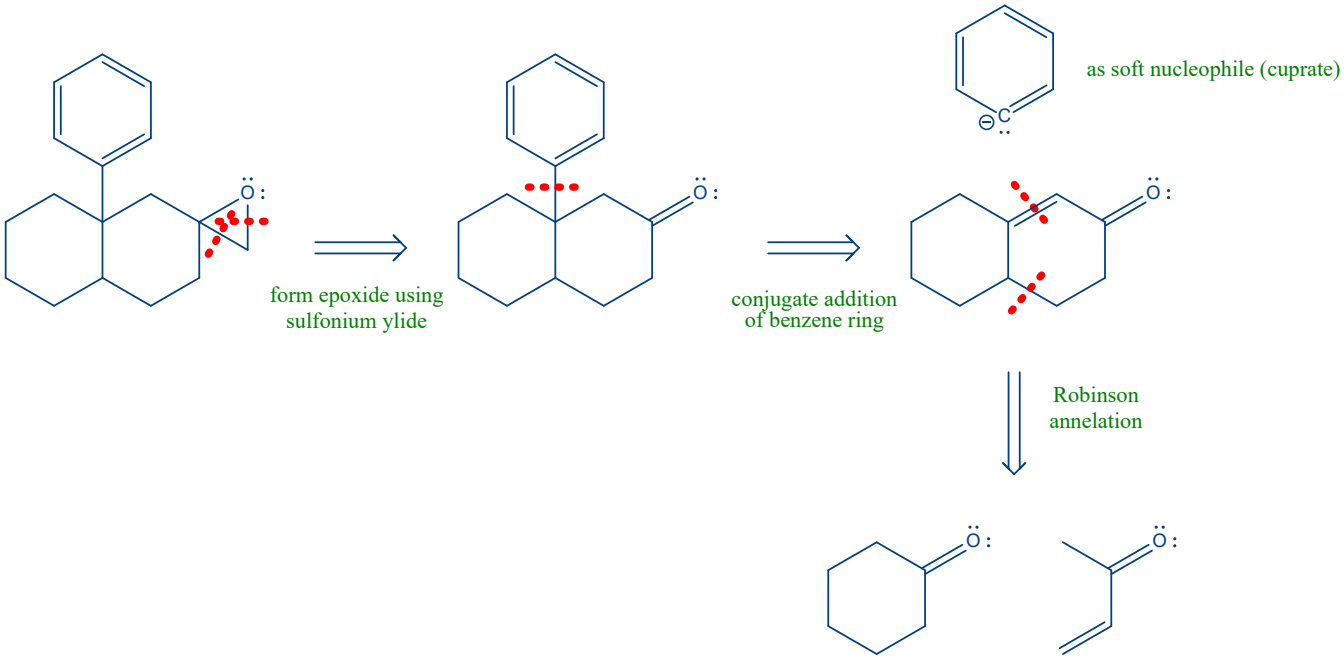
4. Use a Suzuki cross-coupling reaction to replace the bromine atom with a phenyl group. Remember that you need a palladium catalyst and stoichiometric quantities of oxygen-containing base ($NaOH$, $NaOtBu$, Na_2CO_3, etc.) in addition to the aryl bromide and either boronic acid or boronate ester.



6. *continued…* *[10 marks]*

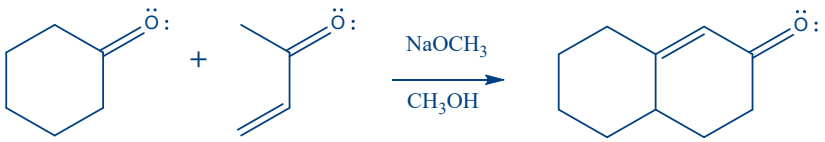
Second Retrosynthesis and Synthetic Proposal

Retrosynthetic Analysis

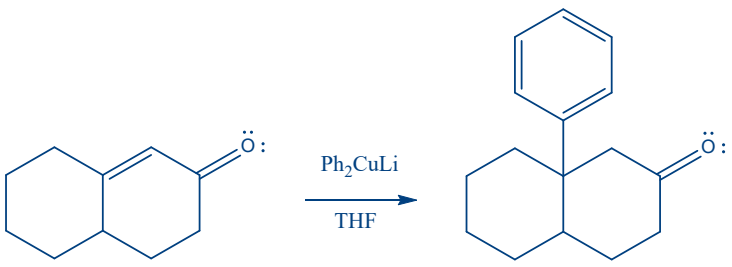


Synthetic Proposal

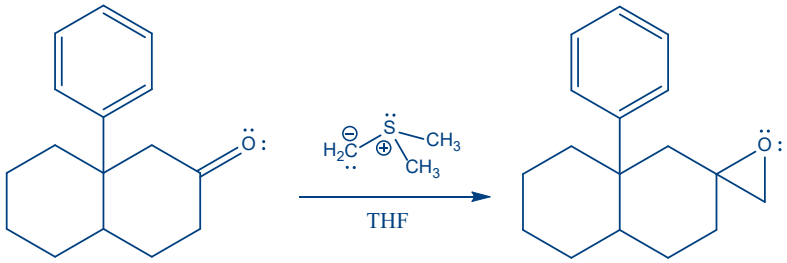
1. Use a Robinson annelation to form the bicyclic core. You will need a base strong enough deprotonate cyclohexanone, giving the corresponding enolate but weak enough that its conjugate acid can be deprotonated by the enolate formed from the initial conjugate addition. We typically use alkoxides for this purpose.



2. Use a cuprate (soft nucleophile) to attach a phenyl group via conjugate addition (1,4-addition)



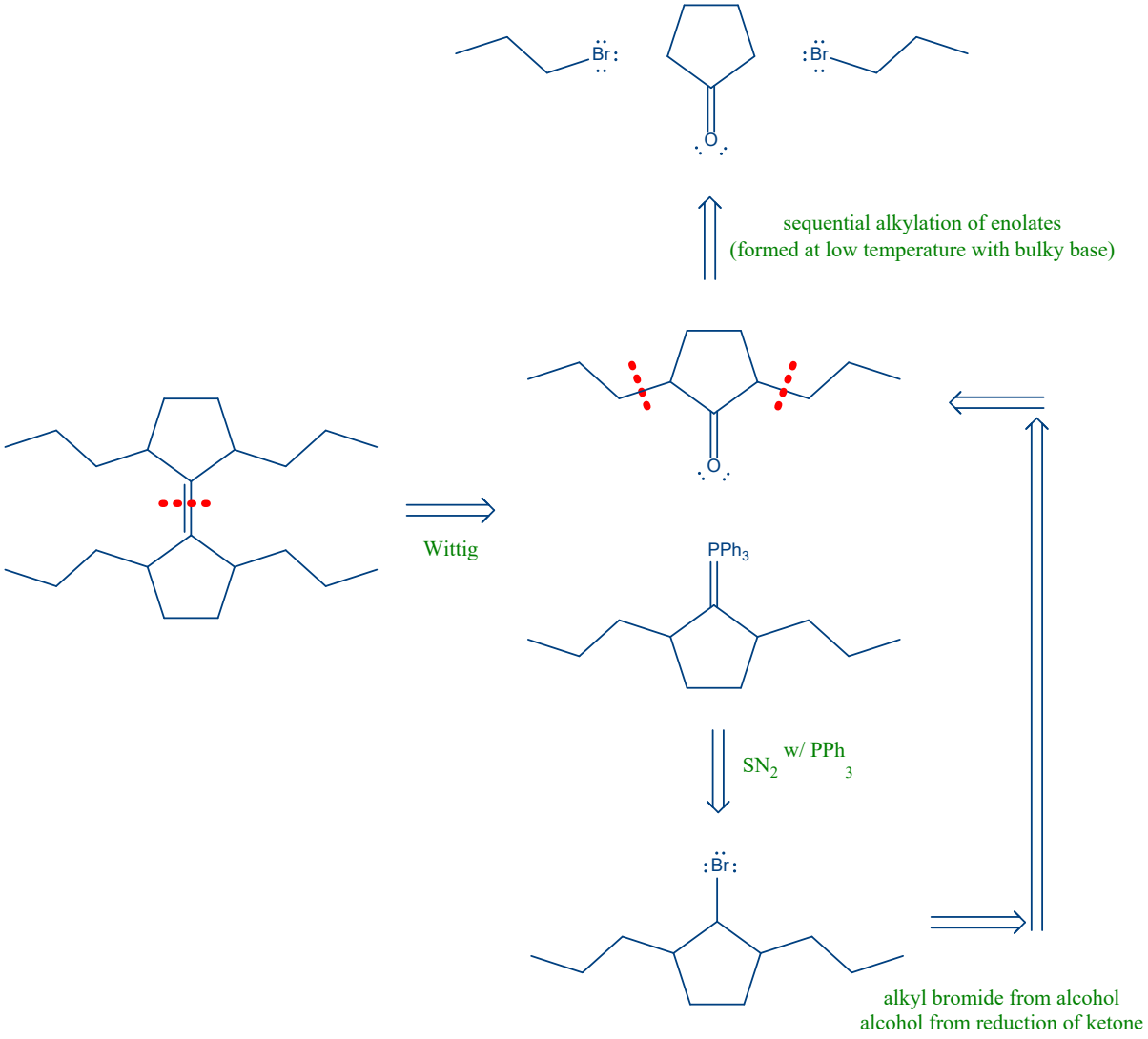
3. Use a sulfonium ylide to convert the ketone into an epoxide.



6. *continued…* *[10 marks]*

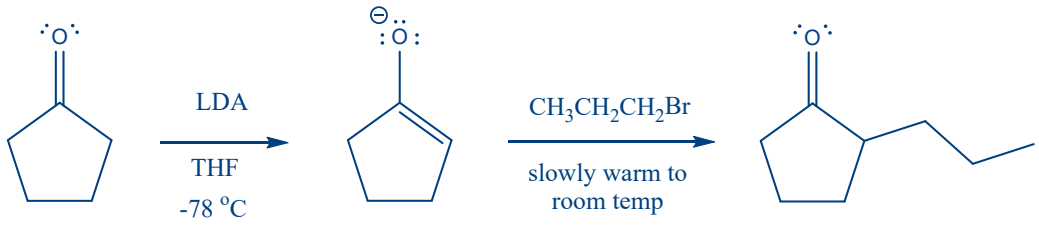
Third Retrosynthesis and Synthetic Proposal

Retrosynthetic Analysis

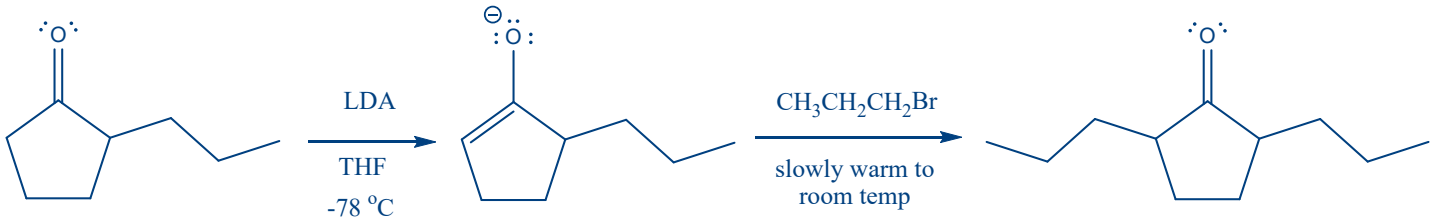


Synthetic Proposal

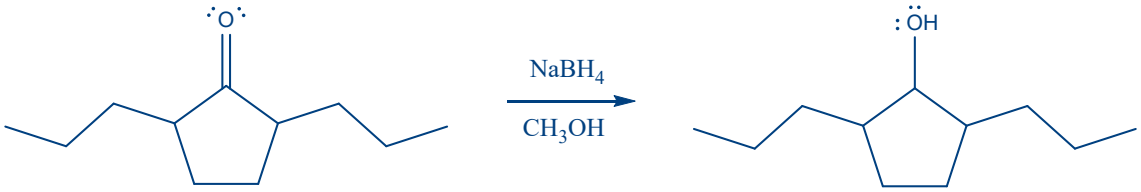
1. Use a strong bulky nonnucleophilic base at low temperature to form enolate from cyclopentanone then quench with 1-bromopropane (or similar) to singly alkylate.



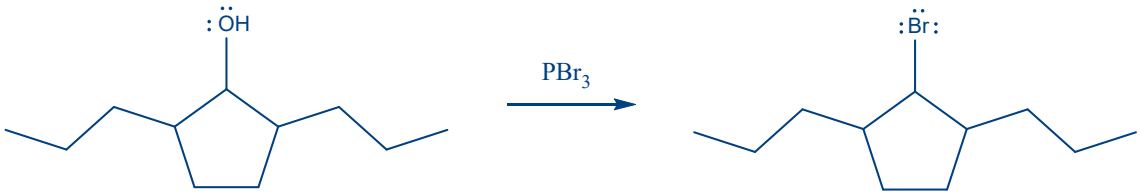
2. Use a strong bulky nonnucleophilic base at low temperature to form kinetic enolate from 2-propylcyclopentanone then quench with 1-bromopropane (or similar) to singly alkylate on the other side of the carbonyl group. Note that this question conveniently ignores where the two propyl groups are *cis*- or *trans*- to each other. You're welcome! 😊 Reserve some of this product for use in the Wittig reaction.



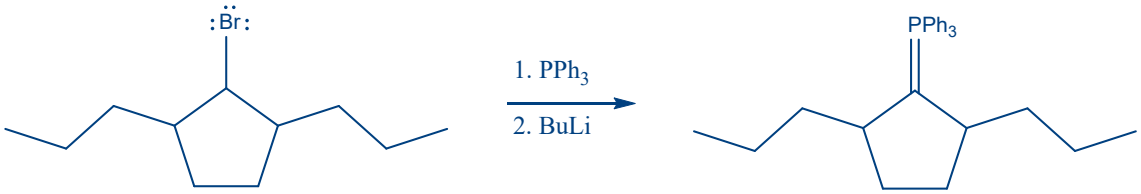
3. Reduce the remainder of the 2,5-dipropylcyclopentanone to the corresponding alcohol using any appropriate reducing agent ($LiAlH_4$, $DIBAL$ and $NaBH_4$ are all suitable choices).



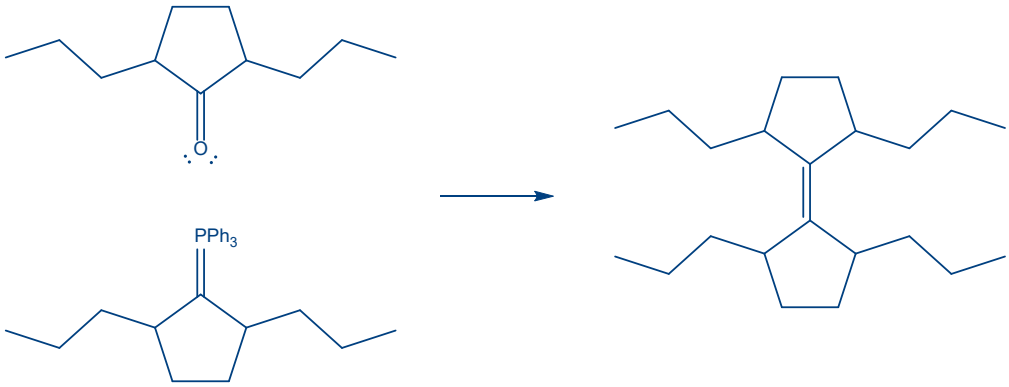
4. Convert the alcohol to the corresponding alkyl bromide using a reagent such as PBr_3.



5. Prepare the phosphonium ylide from the alkyl bromide by first reacting with PPh_3 (to give the phosphonium bromide salt) then adding a strong base such as $BuLi$ (deprotonating alpha to PPh_3, giving the ylide).



6. Finally, react the phosphonium ylide with the reserved ketone to prepare the final product via a Wittig reaction.



7. Four-atom rings are generally considered difficult to make – especially if all four of the atoms in the ring are carbon (a "carbocycle"). **[5 marks]**

(a) Why are four-atom carbocycles difficult to make from a kinetic perspective? *[1 mark]*

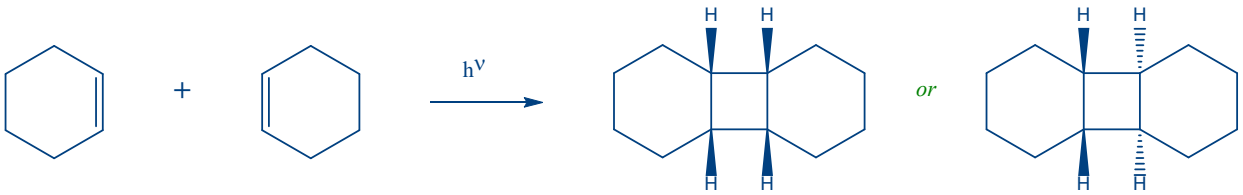
The relative positions of the nucleophilic and electrophilic sites are not conducive to collision/reaction. For the nucleophilic site to attack the electrophilic site, the required transition state would be very high energy due to unfavourable bond angles, eclipsed bonds, etc.

(b) Why are four-atom carbocycles difficult to make from a thermodynamic perspective? *[1 mark]*

Four-atom rings are highly strained due to unfavourable bond angles, eclipsed bonds, etc. As such, these compounds are high energy and their formation is not normally thermodynamically favoured.

(c) If you absolutely had to make a four-atom carbocycle, which of the reactions discussed this semester would be your best chance for success? Give an example that includes starting material, any necessary reaction conditions and product. *[3 marks]*

[2+2] cycloaddition



8. What was the most useful and/or interesting thing you learned in CHEM 4000? **[1 mark]**

…AND THAT'S ALL FOR CHEM 4000.

HAPPY HOLIDAYS!