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.

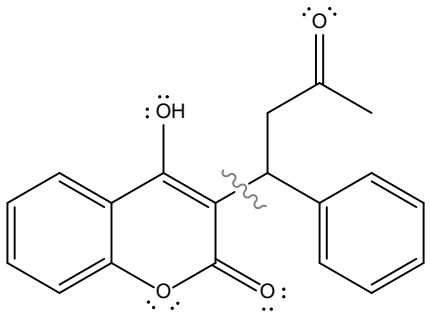
Signature: _____ Date: _____

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]*

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

(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]*

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]*

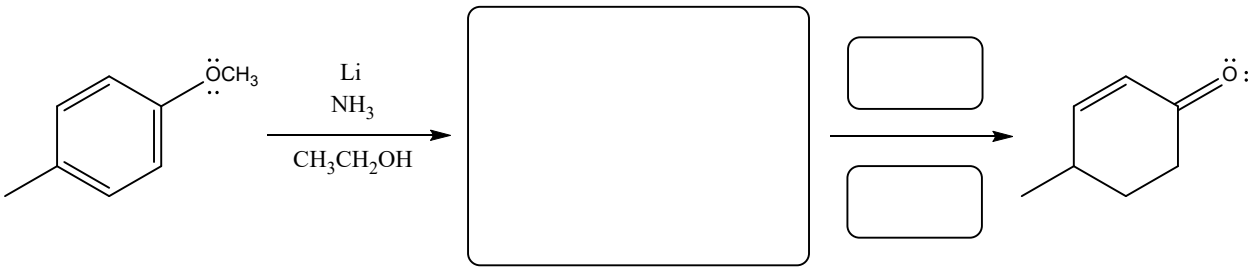
(b) With reference to at least three principles of green chemistry, explain why the reaction described in part (a) would qualify as "green". *[3 marks]*

(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.*

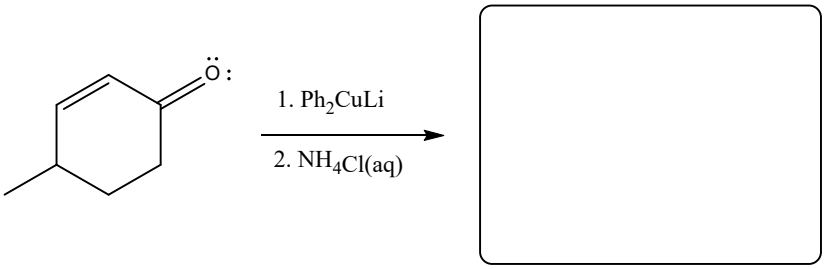
3. α,β-unsaturated ketones are very useful starting materials and/or intermediates in organic synthesis. The following questions address how to make them and some of their many uses. **[9 marks]**

(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]*

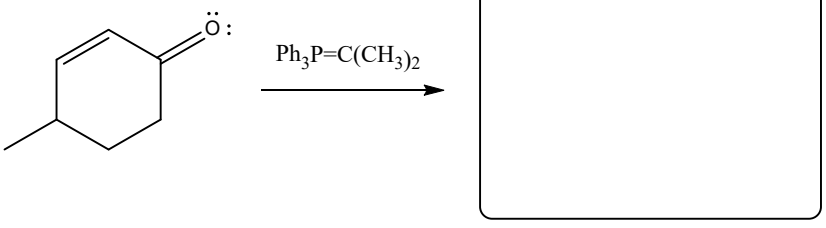



(b) Fill in the boxes to show the products of each of the following reactions. *[6 marks]*

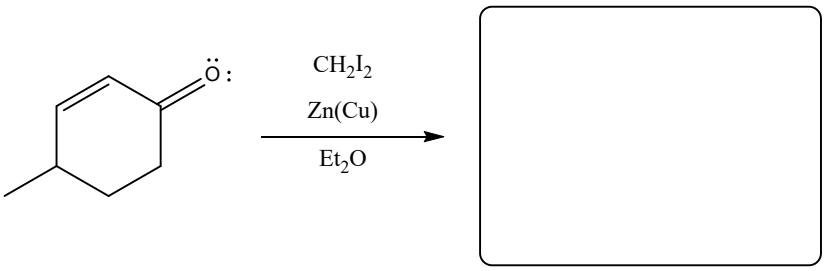
i.



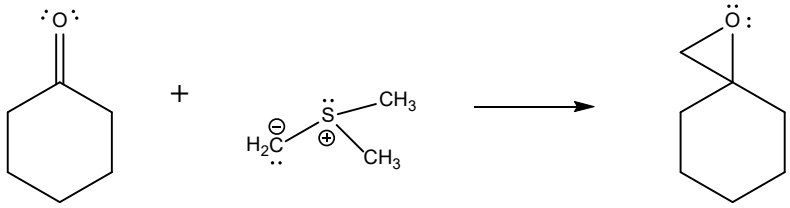

ii.



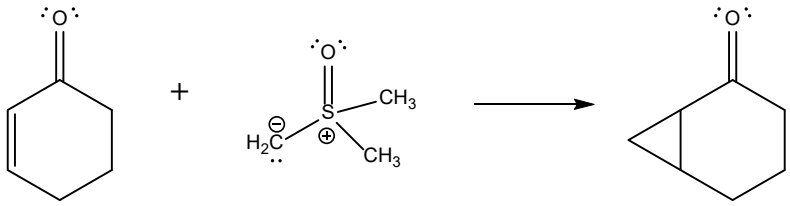

iii.



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]*

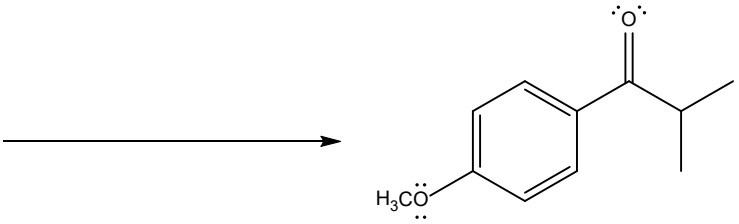
(d) Use an argument based on Hard-Soft Acid-Base theory to explain why it is better to use the sulfoxonium ylide than the sulfonium ylide if you want to make the cyclopropane product. *[1 mark]*

*more space on next page…*

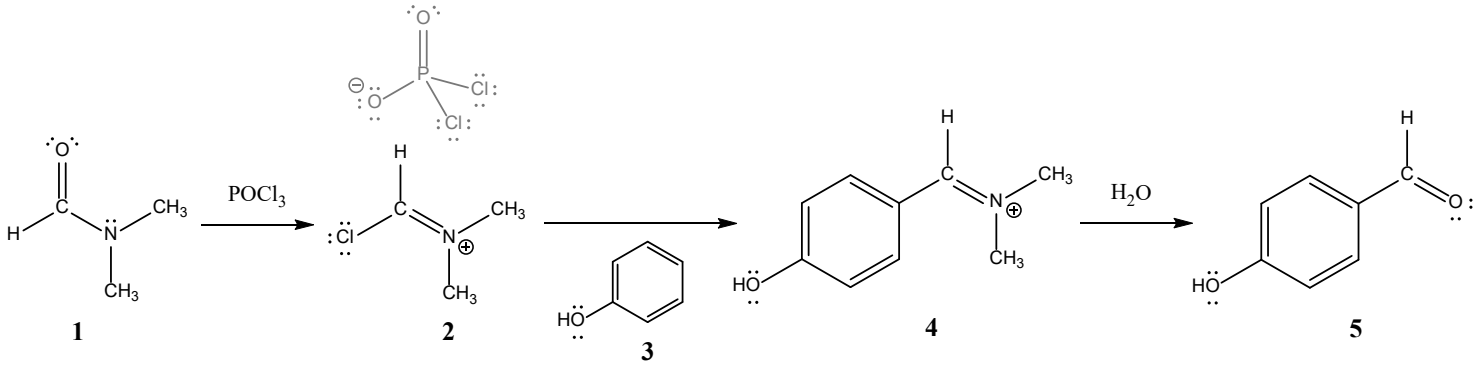
4. *…continued from previous page*

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**.




**1** **2** **3** **4** **5**

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

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

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

*more space on next page…*

5. *…continued from previous page*

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

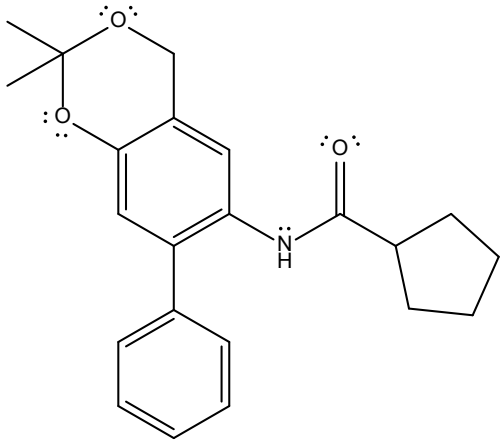
*Your answers should take the form of a retrosynthetic analysis followed by chemical equations for the reactions in the synthesis itself. Show all required reagents, and number steps within a reaction if order of addition is important.*

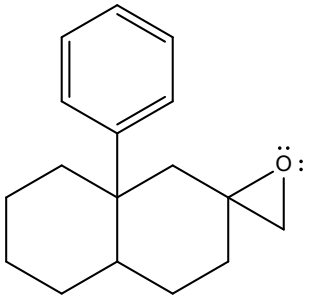
*You may use any reagents that you could reasonably expect to be commercially available <u>and</u> that contribute no more than 7 carbon atoms to the final product.*

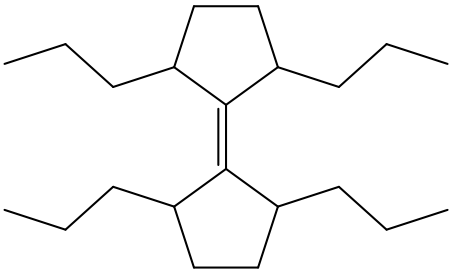
*If you are suggesting a multi-step synthesis, write an equation for each step.*

*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.*

**<u>Options</u>**







6. *continued…* *[10 marks]*

**First Retrosynthesis and Synthetic Proposal**

6. *continued…* *[10 marks]*

**Second Retrosynthesis and Synthetic Proposal**

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]*

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

(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]*

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!**