

Problem Set 2

Cycloadditions and Photochemistry

2.1 Problems 2 and 5

9/6: • We begin with Problem 5.

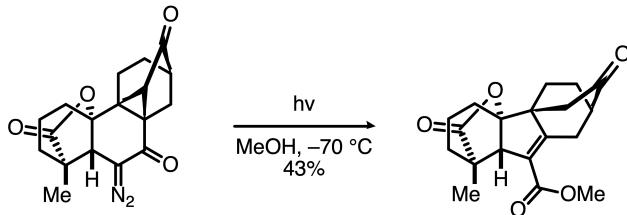


Figure 2.1: PSet 2, Q5.

- The first step — and the light-activated step — is a photolytic **Wolff rearrangement**.
 - Specifically, the light will photoexcite the diazo functional group. We don't really need to show this, though.
- After that, we have methanol addition to the ketene.
 - By using two methanol molecules, we can access a six-membered transition state.
 - On ketenes.
 - The $\text{C}=\text{O}$ and $\text{C}=\text{C}$ π -bonding orbitals are orthogonal.
 - More specifically, this means that the $\text{C}=\text{O}$ π -bond orbital lies in the plane of the page, and the $\text{C}=\text{C}$ π -bond orbital lies out of the plane of the page.
 - Implication: We must be careful about choosing the side of the ketene to which the methanol adds.
- Hydrogen bonding from methanol stabilizes many of the steps, as drawn in the third intermediate.
- There may be a **retro-Michael addition** somewhere in here. However, this was said to form an enolate, and thus be a step we'd like to avoid??
- Jasmin: Where can we learn about photoexcitation problems?
 - There are two types of photoexcitation regimes: Broad spectrum and specific wavelength.
 - The majority of productive photochemical processes use lower energy photons.
 - As a consequence, photochemistry is rare among unsaturated systems because anything powerful enough to drive something there will rupture bonds everywhere.

- By contrast, conjugated systems are more easily photoexcited.
- Example: The most reliable way to generate 4-membered rings is with photoexcitation! We can form 4-membered rings in such a system because we're pumping more than enough energy to overcome the ring strain. Here's how it works.

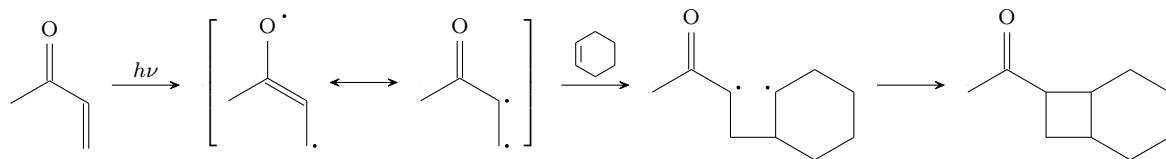
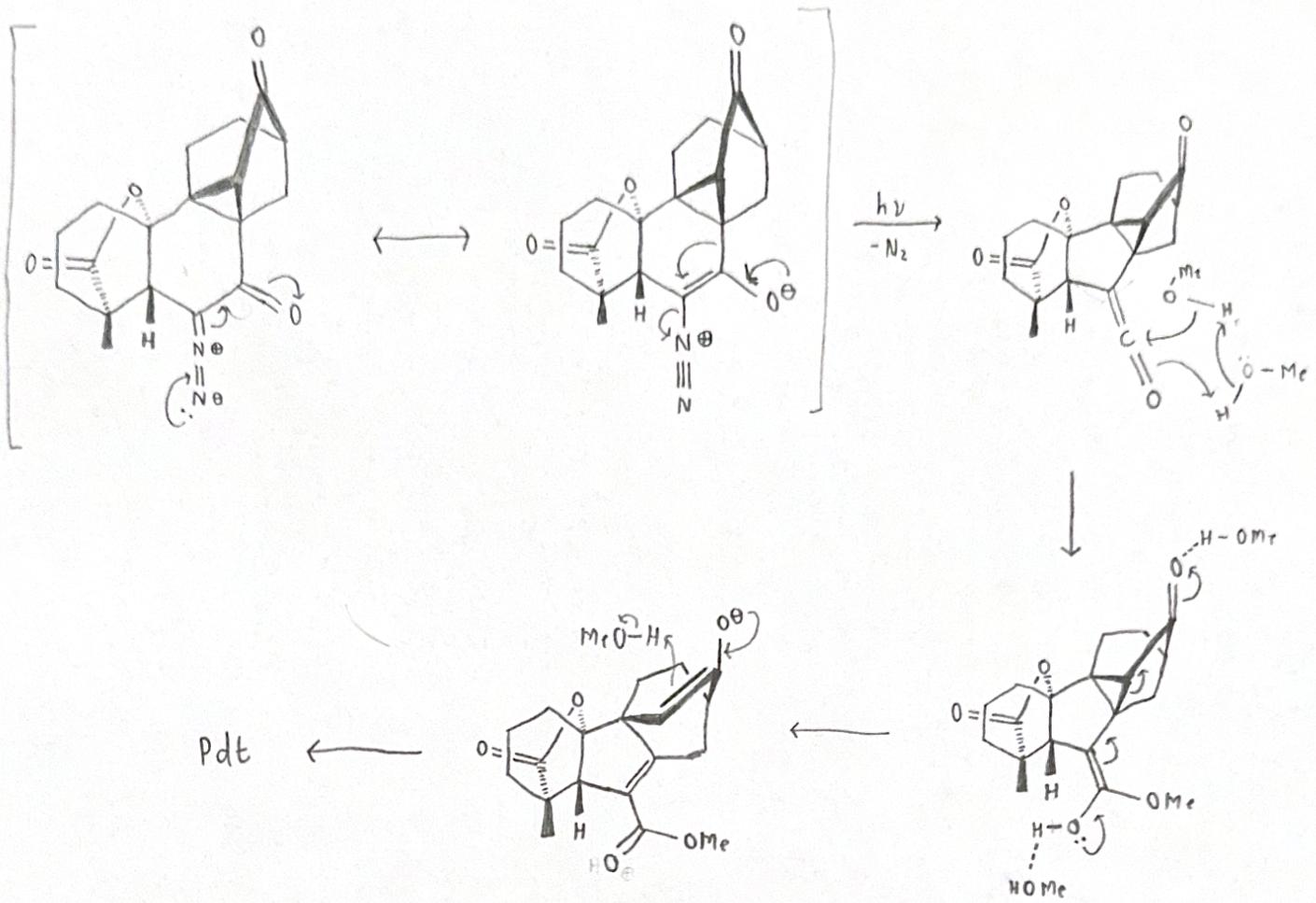


Figure 2.2: Forming 4-membered rings via photochemistry.

- A β -unsaturated carbonyl can be excited to a diradical, which can also be thought of as an excited state of the π -bond.
 - Note that the unconjugated alkene does *not* get photoexcited!
- Then we can do radical chemistry with the ketone, which is hard to excite.
 - You could also have photoexcitation followed by intersystem crossing (singlet to triplet state).
 - We will likely learn more about photoexcitation in 5.53.
 - Takeaway: Looking at the starting material, we should identify conjugated systems, like how the ketone is conjugated to the $\beta\text{-C}=\text{N}$ bond.
- Aside: Rhodium can do very similar chemistry under thermal conditions. Instead of a carbene, we'd get a metal alkylidene, but it'd be the same end product.
 - So this can be transition-metal catalyzed.
- Reference: King et al. (1997).
- Altogether, the full solution to PSet 2, Q5 is on the next page.



- We now begin Problem 2.

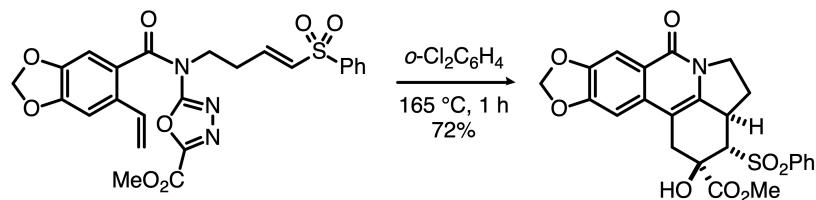
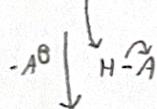
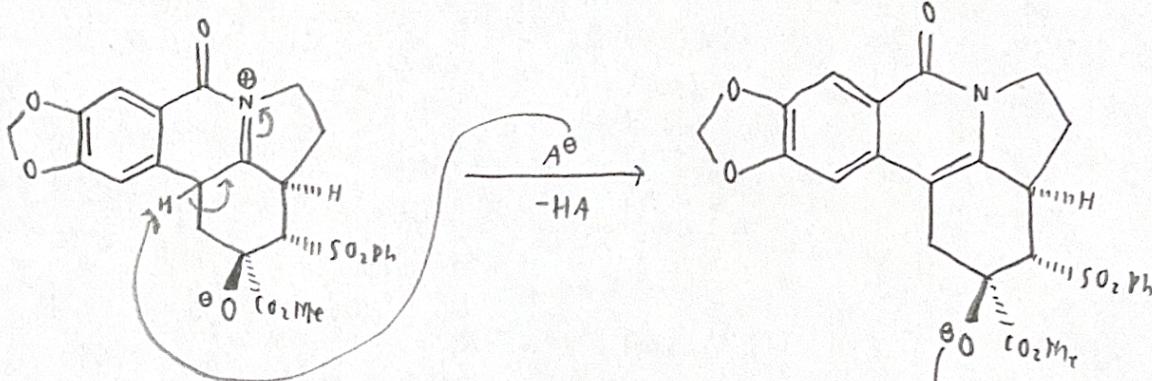
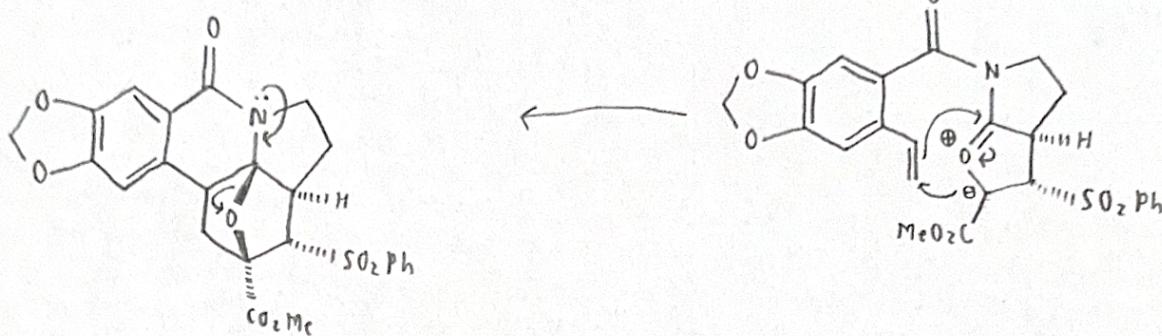
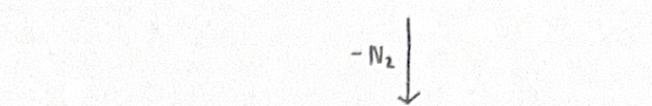
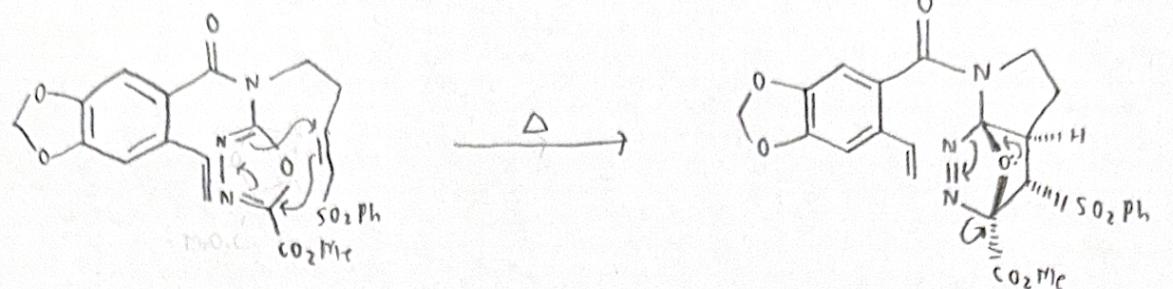


Figure 2.3: PSet 2, Q2.

- Starts off with a [4 + 2] cycloaddition, which will follow similar rules to the analogous Diels-Alder.
 - For example, this cycloaddition will also be diastereoselective, and hence will prefer to have the phenylsulfonyl EWG be *endo* in the transition state.
 - This sets the stereochemistry of the right side of the molecule.
 - This is an antarafacial/suprafacial reaction, not a suprafacial/suprafacial reaction.
 - Read up on the **Woodward-Hoffmann rules!!**
 - Forming a 5-membered ring is better than a six-membered ring??
 - Note that we choose to react with the more electron-poor alkene because it has a lower, more energetically accessible LUMO.
- After the cycloaddition, we rearrange the electrons and spit out nitrogen.
- We then do another [4 + 2] cycloaddition.
 - How do we retain the stereochemistry at the carbanion?? What's the alternate mechanism?
- At high temperature, the N–O ketal can drop down and (reversibly) expel the oxygen.
 - The formation of the N-acyl iminium will seriously stabilize the α -carbon's hydrogens. The stabilization effect is so extreme that any base in solution — from the starting material, to something intramolecular, to the unsilylated glass of the reaction vessel — will pick it off.
 - Then we just have to protonate the oxygen and we're done!
 - Altogether, the full solution to PSet 2, Q2 is on the next page.



Pdt

- Definitely have all of PSet 2 ready for next Monday!! And have at least looked at PSet 3.
 - PSet 2, Q3 is gonna need really good 3D transition state structures. Make sure to try this one!!
 - Hints:
 - You start with a Diels-Alder. Lewis acid activates the ketone.
 - This lowers the energy of the LUMO; sets the stage for an intramolecular Diels-Alder.
 - Following this, draw the intermediate, put it in a chair scenario, and then sort out the azide.
 - Azides and Lewis acids can add into the carbonyl. This will lead to loss of N_2 , and how can we facilitate this?
 - Schmidt reaction.
 - Lots of antiperiplanar interactions that are responsible for product distribution.
 - This problem is something of a sequel to PSet 1, Q3.
 - We will start next time with PSet 2, Q3.
 - Remember to take more pictures!!
 - Use whatever time we have for this class to think about future problems, not clean copying notes.
 - Jasmin and I will start next time with two PSet 2 problems; one of us will take Q3, the other Q1.
 - Focus on PSet 2, but we can start PSet 3.

2.2 Problems 1, 3, 4, and 6

- 9/9:
- What is the up/down arrow symbol in Problem 4?

– Means reflux (e.g., heat).

- We now begin discussing Problem 3.

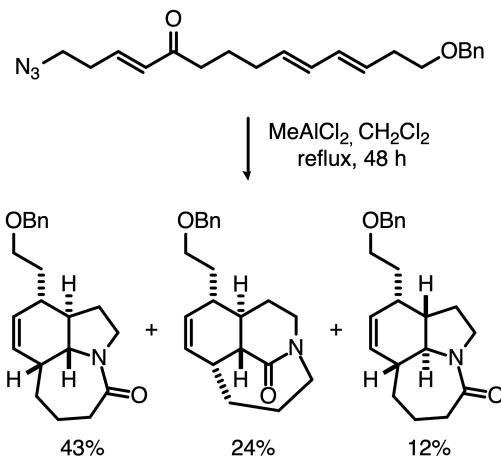
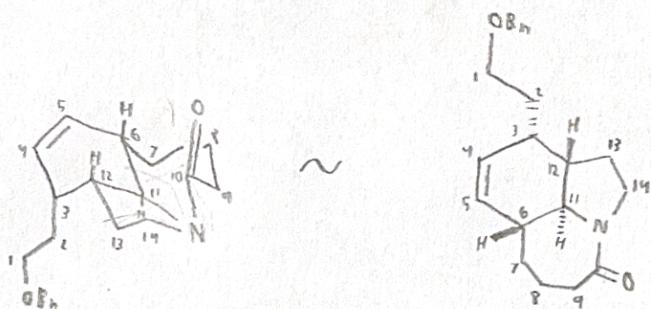
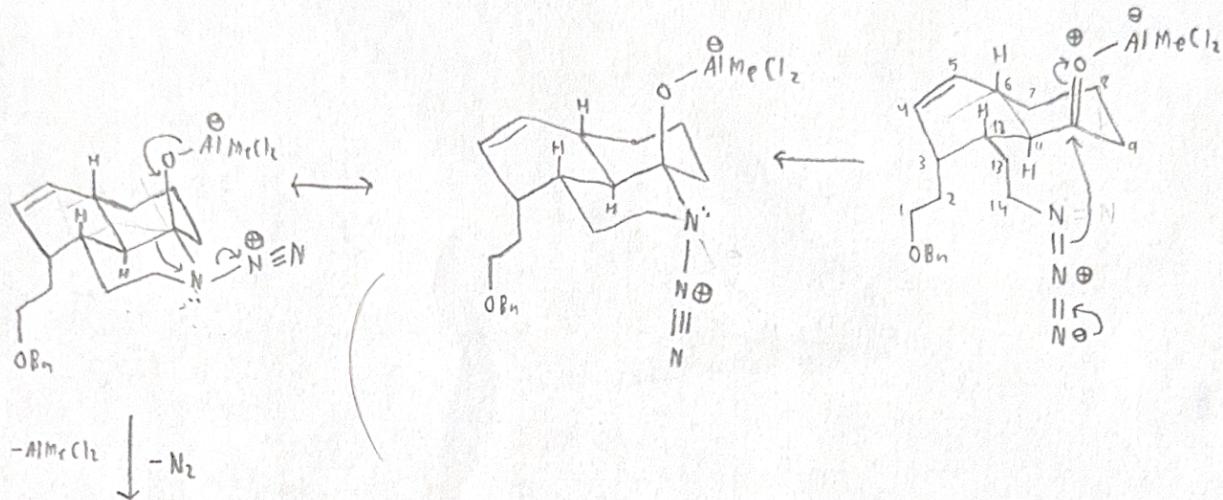
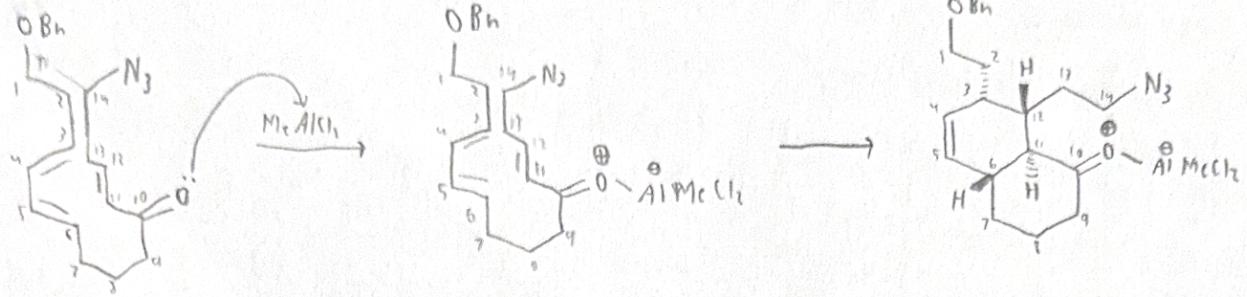


Figure 2.4: PSet 2, Q3.

- MeAlCl_2 is a common Lewis acid catalyst for Diels-Alder reactions. As such, we will begin with coordination of the ketone EWG on the dienophile to MeAlCl_2 to further activate it.
 - This activated EWG will lower the LUMO of the dieneophile.
- Even after this activation step, however, we will still need reflux conditions for this Diels-Alder to proceed because the diene is only activated inductively through hyperconjugation.

- Also note that to lead into the Diels-Alder, we may need to redraw the substrate in the more favorable s-*cis* conformation.
 - We also bring the diene closer to the dienophile spatially.
 - Numbering the carbons can help with drawing this change.
- It is important to note that there are two possible Diels-Alder conformations: *exo* and *endo*.
 - The transition state with the ketone (the EWG) on the outside is the *exo* TS.
 - The transition state with the ketone over the diene is the *endo* TS.
 - *endo* is favored by electronics and will lead to the two major products.
 - *endo* transition state is preferred for intermolecular, but for intramolecular, we may see more of the *exo* transition state!
 - Let's look at the *exo* pathway first since it only leads to one product.
- We now proceed with the Diels-Alder.
 - Because the Diels-Alder is famously diastereoselective, the product's stereochemistry is set here.
 - More specifically, the Diels-Alder is **stereospecific**, not **stereoselective**.
 - Also notice that we have 3 *E* alkenes in the starting material.
 - We will, however, obtain (+/-)-products, depending on whether the diene attacks the dienophile from the top face or bottom face.
 - To yield the entantiomer shown, we need the diene to attack the dienophile from the top.
- **Stereospecific** (reaction): A chemical reaction that yields a single stereoisomer as the sole product.
- **Stereoselective** (reaction): A chemical reaction that favors one stereoisomer over others but can still produce a mixture of stereoisomers.
- We should recognize that the Diels-Alder forms the equivalent of a substituted decalin.
 - Thus, we can choose between *cis*-decalin and *trans*-decalin for our chair conformation.
 - When we draw decalins, it is good to draw the stereodetermining hydrides, too.
 - This is a bit of a stretch as the alkene will enforce a flat *cis* conformation where it is, but we can just modify the chair structure.
 - It is also good to work out the stereochemistry in 2D first, and then translate it to 3D.
 - Pay attention to chair conformations, too: You want to make sure that your substituents are arranged in the more energetically favorable conformation and not clashing.
- Immediately after the Diels-Alder, we begin an intramolecular Schmidt reaction.
 - The negative charge at the end of the azide helps push the near double bond electrons toward the activated carbonyl.
- After this first step, the rest of the azide can be either axial or equatorial on the 6-membered heterocycle, and we'll likely have rapid epimerization because stereochemistry is not fixed at nitrogen atoms.
- When the rest of the azide is equatorial, it is antiperiplanar to one of the C–C bonds adjacent to the oxygen.
 - In this conformation, that bond can disengage to attack the σ^* -orbital of the N–N single bond.
- This final step yields the most minor product.
- The other two products will come from the *endo*-pathway. We will get two products in the other pathway because the azide epimerization puts *two* C–C bonds antiperiplanar to the N–N single bond.
- Altogether, the full *exo* pathway for PSet 2, Q3 is on the next page.
 - Note that the rewrite to the 3D form and the rewrite back both accidentally involve shifts to the other enantiomer.



- We now begin discussing Problem 1.

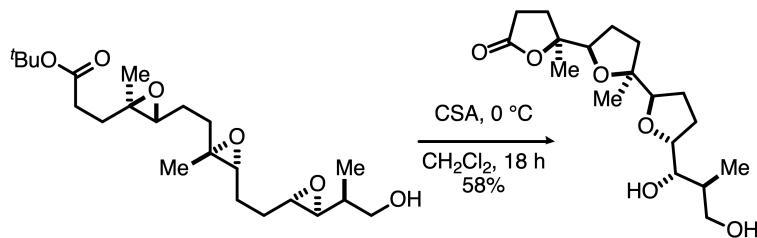


Figure 2.5: PSet 2, Q1.

- The distal epoxide carbons with methyl groups attached could hold stable carbocations, and thus be the beginning of an S_N1 mechanism.
 - Alternatively, the distal epoxide carbons without methyl groups attached are open to S_N2 attacks.
- There appears to be a stereoinversion at C3. Could this be due to attack by the conjugate base after activation?
 - But then how would CSA snap off to leave behind an alcohol?
- It probably would make the most sense to have the cascade go up the chain, terminating by kicking out *t*-butoxide.
 - How is the stereochemistry set?
 - This is an example from Ian Patterson in the 1970s.
 - Jasmin's overall strategy is correct.
 - Acid-catalyzed loss of a *t*-butyl group is correct! We have a *t*-butyl cation that will either be trapped (solvation), or it will eliminate to regenerate the acid.
- Epoxides aren't super reactive on their own; they will need to be protonated to react.
 - We do indeed have an S_N1 mechanism.
 - The p*K*_a of an epoxide is -2 , but for CSA, it's 1.2 !
 - We can't easily do an S_N2 on epoxides!
 - Epoxides are unique under electrophilic conditions in that they can draw in a nucleophile (even to a sterically hindered site) because there is so much energy in releasing the ring strain.
 - You get more bond elongation on the tertiary distal carbon.
 - The first step is a 5-exo-tet cyclization; epoxides *can* do this chemistry.
- Stereochemistry is inverted at every step; this is consistent with a stereospecific process.
- We should protonate the oxygen of the carbonyl; better, like in the amide because it doesn't break conjugation.
- The *t*-butyl ester can add in, which is even better because *t*-butyl stabilizes a positive charge. We'll always use the carbonyl lone pair as a nucleophile; we don't use a carboxylic acid as a nucleophile.
- Very rapid protonation of all epoxides (relative to the protonation of the carbonyl). Once the end one is protonated, we'll have intramolecular addition.
- Amides and ethers both have lone pairs that can't be used.
 - The lone pairs on the oxygen are equivalent.

- We don't use the bottom resonance picture because even if the ether oxygen is resonance-delocalized in with sp^2 hybridization, that oxygen is positively charged, so there's no way we'll use it as a nucleophile.
- Good thing to observe about the starting material: Every step is stereoinvertive.
- Altogether, the full solution to PSet 2, Q1 is on the next page.

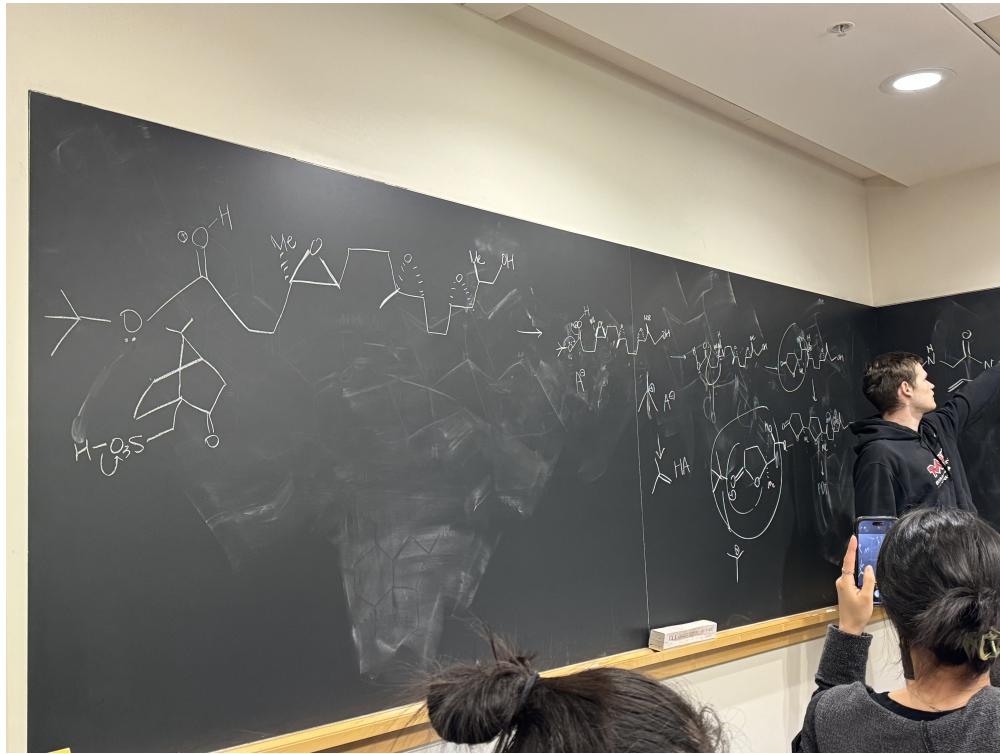


Figure 2.6: PSet 2, Q1 solution.

- We now begin discussing Problem 4.

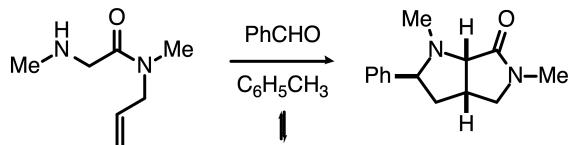


Figure 2.7: PSet 2, Q4.

- The heat is approximately 110 °C.
- In *some* order, we probably have aldehyde condensation to the iminium, a keto-enol tautomerization, and a [3 + 2] cycloaddition.
- Stereochemistry gets set during the final cycloaddition analogous to the Diels-Alder.
 - 5-5 ring system wants to be *cis*-fused. And the phenyl will want to be on the outside.
- The hydrogens are not too easy to enolize; the nitrogen pairs add electron density and make this $pK_a = 25$ vs. $pK_a = 20$ of acetone.
- We won't lose hydroxide and then use it; it will be intramolecular.
 -
- This is a dipolar [3 + 2] cycloaddition. You get a dipolarophile.
 - You have true carbanion formation from deprotonation of the α -hydrogen by the hydroxide in the hemiaminal intermediate; the hydroxide is our base.
 - The α -hydrogen will be stabilized by both the iminium and the amide!
- Altogether, the full solution to PSet 2, Q4 is on the next page.

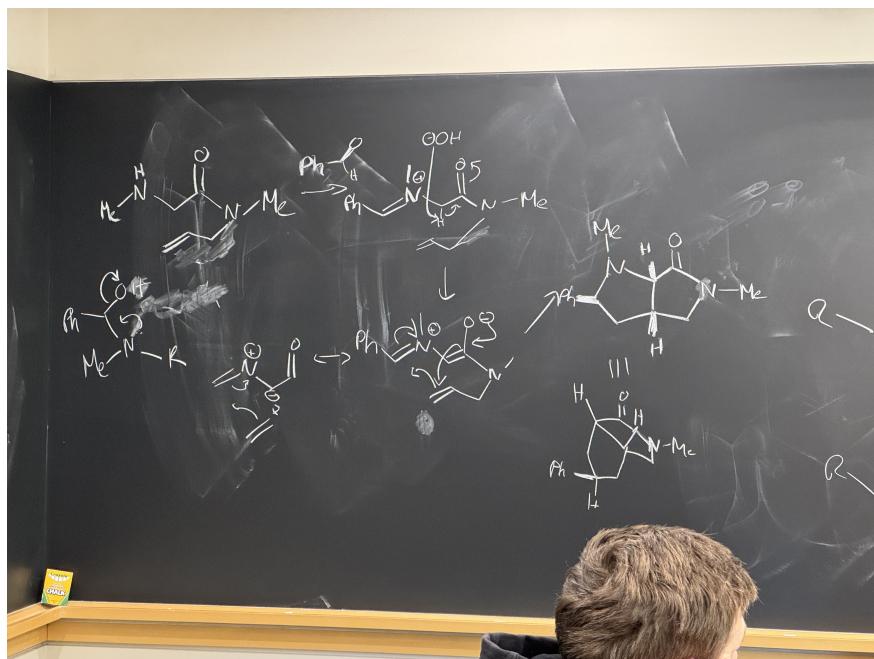


Figure 2.8: PSet 2, Q4 solution.

- We now begin discussing Problem 6 (Ivan).

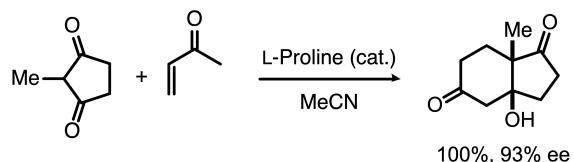


Figure 2.9: PSet 2, Q6.

- The core of this reaction is — once again — a cycloaddition. We get there by activating the α,β -unsaturated ketone into a diene and the other species into a good dienophile. Then the chirality of the proline organocatalyst combined with the Diels-Alder diastereoselectivity gives us what we want.
- What provides the regioselectivity?? The diene does not have its EDG in an optimal position...
- The first step is conjugate addition, not condensation. You don't even need proline here before condensation. We do not form a stereocenter.
- The proline species in solution (by pK_a 's) is the carboxylate and the ammonium.
- Why the enamine targets the one ketone.
 - It is more kinetically viable.
- Altogether, the full solution to PSet 2, Q6 is on the next page.

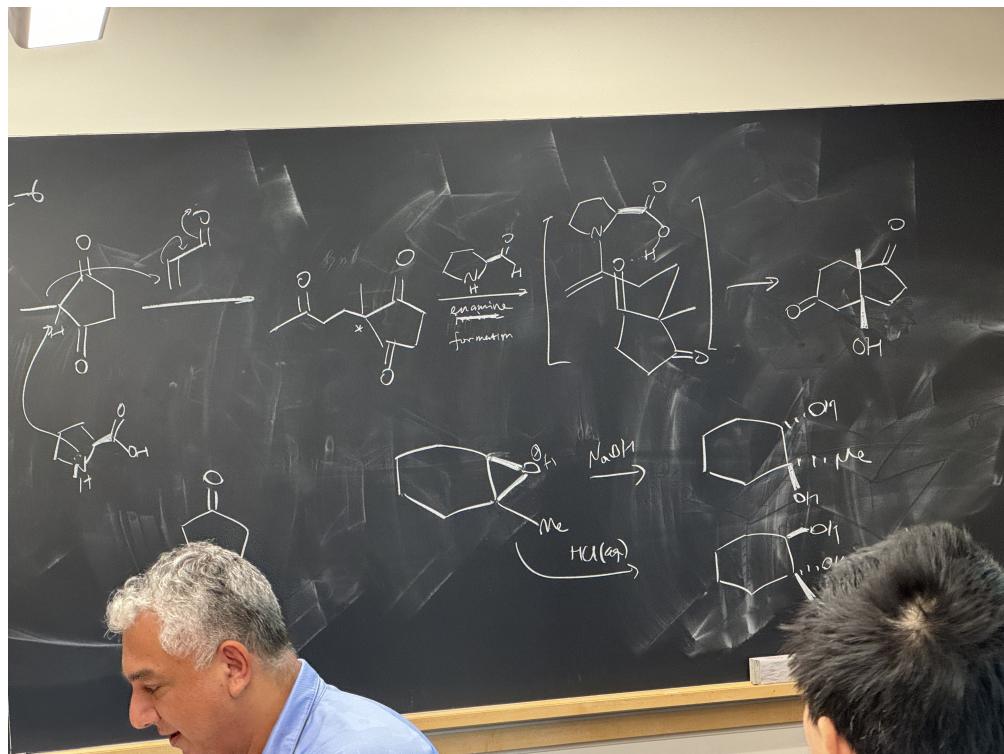


Figure 2.10: PSet 2, Q6 solution.

- Actually have a *fully* worked out mechanism for any problem I'm supposed to present. Sketch it out *and* try to fully work it out. Drawing it all out will end up saving time and catching mistakes!!
- He'll ask us at the beginning of next class which PSet 3 problems we found the most difficult/interesting.
- Jeremiah will be here on Wednesday; Mo will be back on Friday.
 - Jeremiah will send us a PSet for Wednesday. Mo will pick up with PSet 3 on Friday.
- Frank and Ivan started PSet 3; nobody else did.
 1. Really good use of 3D transition states. Note the use of the semicolon; other reagents aren't present in the first step. Something happens with the acid, then with the diazo, then with the DMSO. Consider the Swern oxidation. Perchloric acid is useful for a reason.
 2. More of a carbocation pathway. Think about the coordination of the ??, ring strain release, no NaBH₄ before the skeleton is formed. Last step is just reduction.
 3. Very interesting. Consider Friedel-Crafts type chemistry, and a symmetrical intermediate. This helps explain the product distribution/formation of product over SM. Protonation states are important here.
 4. Two consecutive photochemical steps. Aminal intermediate, H-atom abstraction chemistry.
 5. The ynone (negatively charged oxygen center) is like an enolate; very nucleophilic, very sterically accessible. Notice the refluxing condition. Silica gel indicates protic conditions.
 6. Aldol chemistry.