

5.47 (Tutorial in Organic Chemistry) Notes

Steven Labalme

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Part I

Movassaghi

Problem Set 1

Carbocations, Carbanions, and Radicals

1.1 Problems 1, 2, and 6

9/4:

- Logistics.
 - The list of topics is the syllabus.
 - We'll cover everything we need to know in discussion, but we can supplement what we discuss here with our own readings.
 - Mo recommends the OChem II textbook.
 - Students: Frank, Christina, Jasmin, Alex (senior undergrad), and Ivan.
 - PSet 2 passed out on paper.
 - The locked door code for 18-578 is 9344, if we ever get here before him.
 - He'll ask us at the beginning of class which problems seem the most interesting to us.
 - We should try every problem on the PSet before class.
 - We'll probably put multiple problems up at the same time.
 - This is a team effort to sort out the board, not one person defending their solution.
 - We will not get through six problems every time.
 - These problems are basically ice breakers for discussion.
 - He encourages us to compare notes and compare solutions, but we must try all the problems first by ourselves.
 - Do not search for the solutions on Google; this takes away from the discussion.
 - Mo will send PSet 2 as a PDF!
 - These examples were chosen to start because Mo wants to begin with bond dissociation energy, carbocations, carbanions, and radical chemistry.
- We now begin discussing Problem 1.

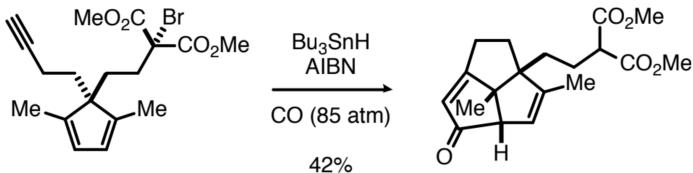
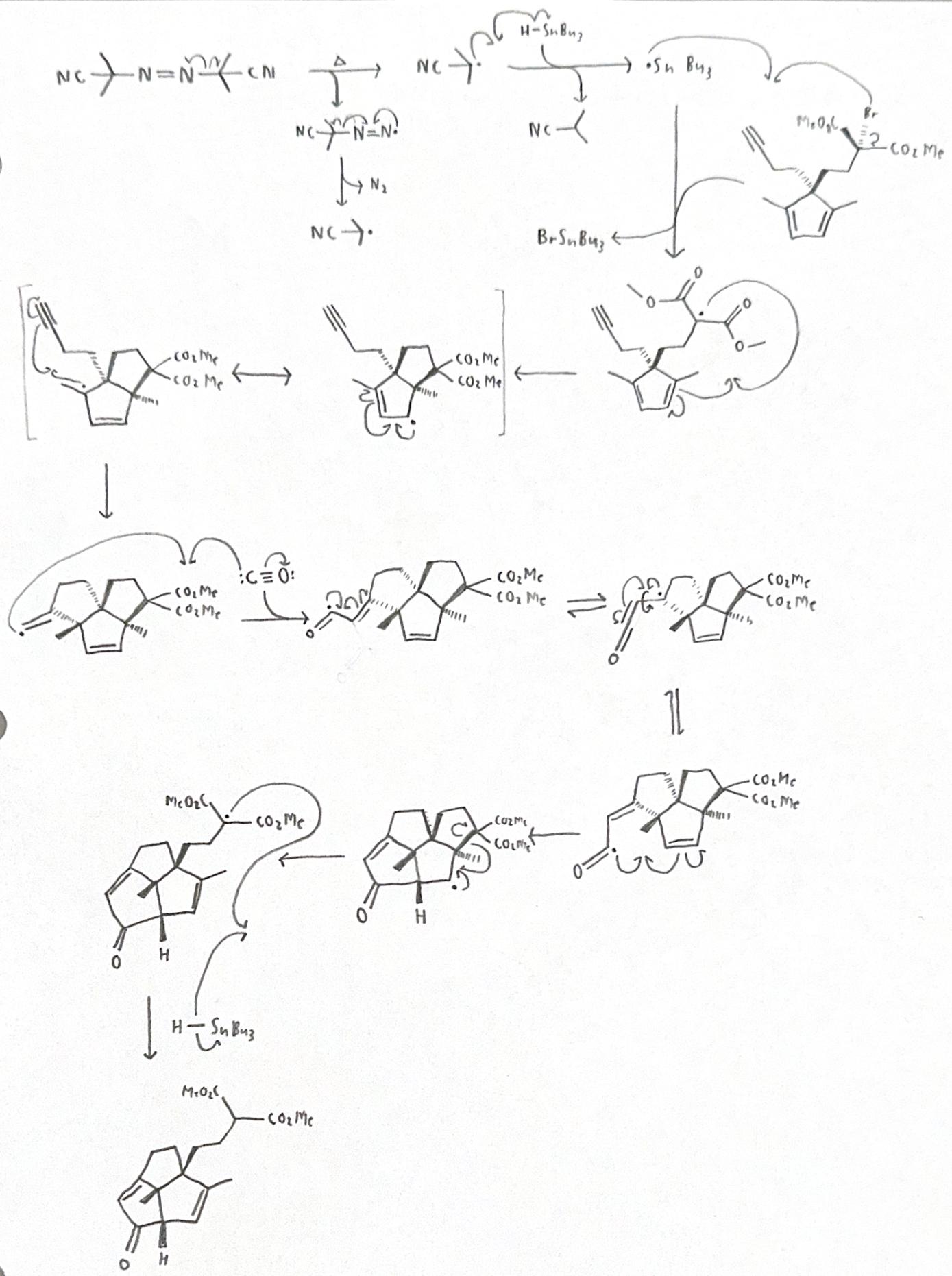


Figure 1.1: Movassaghi PSet 1, Q1.

- A key technique for thinking about, rationalizing, and solving this problem is **bond dissociation energy** (BDE).
 - In fact, we can apply BDE from the very beginning: AIBN's C–N bond is the first to break because its BDE is an extremely low $\sim 30 \text{ kcal/mol}$.
 - Additionally, AIBN's C–N bonds do not have to break symmetrically. Rather, one bond may break first (driven by its vibrational modes) to generate the stable tertiary carbon-centered radical *and* a nitrogen radical.
 - After some finite time (from picoseconds to much longer), the second C–N bond will split, off-gassing N₂.
 - At this point, we must remember that this is a three-step radical reaction (initiation, propagation, termination), and AIBN is our initiator.
 - Thus, we don't have *equivalents* of AIBN to speak of, but rather a tiny amount in a sea of everything else.
 - Our AIBN radical is very stable, but the H–SnBu₃ bond is so weak that it will still break when the two bump into each other.
 - Indeed, BDE can justify why this bond breaks over any of the reactant C–H's.
 - H₃C–H is 100 kcal/mol.
 - HR₂C–H is $\sim 90 \text{ kcal/mol}$.
 - Tributyl tin hydride BDE is a whopping $\sim 73 \text{ kcal/mol}$.
 - Know BDEs!! [Here](#)'s a great resource for C–H bonds on Wikipedia.
 - The ·SnBu₃ radical is halophilic, and does indeed head straight for the bromine to form a resonance-stabilized radical on the reactant.
 - A typical C–Br BDE is 68 kcal/mol.
 - Why does AIBN pick off the H–SnBu₃ over the bromine, then??
 - Alexander Müller suggested it could be because tin and bromine are closer on the periodic table than they preferentially react (think hard/soft acid base theory).
 - Once we create the stabilized radical on the compound, we have to think about where it could go.
 - Do a C–H abstraction analysis to see what hydrogens the radical might be able to pick off.
 - The methyl hydrogens are relatively accessible and allylic, but the transition state would be seven-membered, which is less than ideal. Same with the propargyl hydrogens.
 - Indeed, 1,5-H atom transfer is the most favorable because it's a six-membered transition state.
 - Linear, intermolecular is the most stable transition state.
 - But when we get to 1,5-abstraction, intermolecular concentration dependencies (think chelate effect) start to compete with linearity.
 - However, 5-exo-trig is favorable addition chemistry.
 - 6-endo-trig will be more stable thermodynamically (secondary radical formation).
 - When 5-exo-trig is irreversible, we form that (the kinetic product).
 - When 5-exo-trig is reversible, we form exclusively the 6-endo-trig product.
 - Look up Baldwin's Rules!!
 - Exo/endo because the radical is outside/inside the formed ring.
 - dig/trig/tet naming is due to the hybridization of the carbon we're attacking (*sp*, *sp*², *sp*³ — respectively).
 - Be able to switch fluently between pK_a's and BDEs.

- An *sp* carbanion is more stable because we're holding that electron density tight near the positive nucleus.
 - An *sp* radical is extremely unstable because it has nowhere to draw electron density from.
 - Hyperconjugation stabilizes a primary radical over the methyl radical.
 - The AIBN radical is not stabilized by an EWG (EWGs destabilize radicals), but it is stabilized by resonance with the cyano group.
- So if hydrogen abstraction is less than ideal, let's think about what other kinds of chemistry radicals can do.
 - Addition chemistry is one major such option! Double bonds are nucleophilic sites that a radical will naturally be attracted to, so our achiral compound can undergo a radical attack at either of the quaternary carbons with essentially the same effect.
 - Thus, we will have a racemic mixture of products, but the stereochemistry of each molecule will be set by this attack.
 - That's why Mo wanted the stereochemistry indicated; to show that the attack will lead to a syn product.
 - Indeed, the *cis*-fused 5-membered ring is 15 kcal/mol more stable than the *trans* equivalent.
 - We can now resonate the radical over to the more stable tertiary position.
 - Now we begin the abstraction analysis over again.
 - No good-looking hydrogens to abstract, so it's probably addition chemistry again.
 - If we add into the alkyne, we can do a kinetically favored 5-exo-dig.
 - Additionally, there *will* be a thermodynamic driving force for this reaction: Compare bond energies! A C–C σ -bond is stronger than a C≡C π -bond.
 - Maxim: Whenever we have the opportunity to form a C–C σ -bond, we like to do that.
 - Now is a good time to pick up a CO.
 - Again, we are thermodynamically driven by the breaking of a C≡O triple bond to form a C–C single bond.
 - How about the stereochemistry?
 - We need the *Z* alkene to complete the cyclization, but in fact, the *Z* and *E* alkenes are equivalent! This is because resonance with the radical allows unrestricted rotation around the “alkene” bond in the other resonance structure.
 - Note that equilibrium arrows are good for E/Z isomerism because we are moving the atoms, not just the electron density as in resonance.
 - The rate of cyclization of the acyl radical must outcompete reduction by the tin hydride.
 - Then we can break a bond to form a more stable radical.
 - Finally, we can react with tributyltin hydride in a propagation step.
 - Altogether, the full solution to PSet 1, Q1 is on the next page.



- We now begin discussing Problem 2.

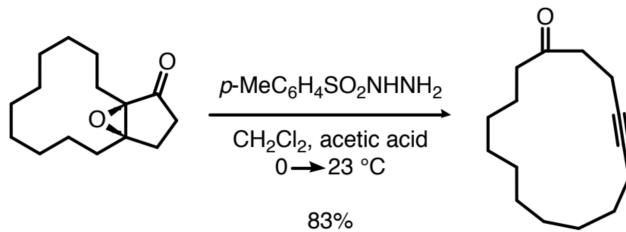
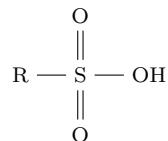
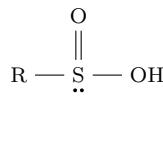


Figure 1.2: Movassaghi PSet 1, Q2.

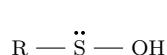
- Aside: The naming of the reagent.



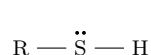
(a) Sulfonic acid.



(b) Sulfinic acid.



(c) Sulfenic acid.



(d) Thiol.

Figure 1.3: The oxidation states of sulfur.

- There are four different oxidation states of sulfur.
- They are referred to as (from most oxidized to most reduced) **sulfonic acid**, **sulfinic acid**, **sulfenic acid**, and **thiol**.
- Now back to the problem at hand.
- In acidic solution, the first thing we can do is make the carbonyl more reactive via protonation.
 - Note that the hydrazide may get protonated with the acid (and perhaps 90% of it will be!), which would shut down nucleophilicity.
 - But whatever hydrazide remains can do the demonstrated chemistry.
- Then our hydrazine species can come in and add via nucleophilic addition.
- After this, we're fairly stable. But a negatively charged oxygen (like the epoxide) in acidic species can be protonated!
- After protonation, we'll want to break the epoxide ring. But where can we draw the electron density from?
 - Looking around, notice that the second hydrazine nitrogen has a lone pair that can be used!
 - Additionally, we can start building toward our alkyne located three carbons away from the position that could become the ketone after our new alcohol undergoes some modification.
- Specifically, that modification will be kicking down the oxygen electrons to form the triple bond, kick out the leaving group, and break the leaving group in half all in one concerted step. This bond breaking process is still favorable because...
 - The relevant orbitals align in an **antiperiplanar** fashion;
 - We are strengthening and weakening consecutive bonds;
 - Antibonding molecular orbitals receive donations of electron density, specifically the σ^* -antibonding orbital of the S–N bond;

- The entropic gain in going from one molecule to three favors this step thermodynamically.
- Aside: 4-membered transition states.

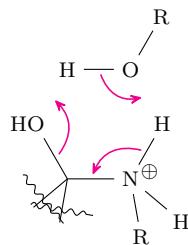
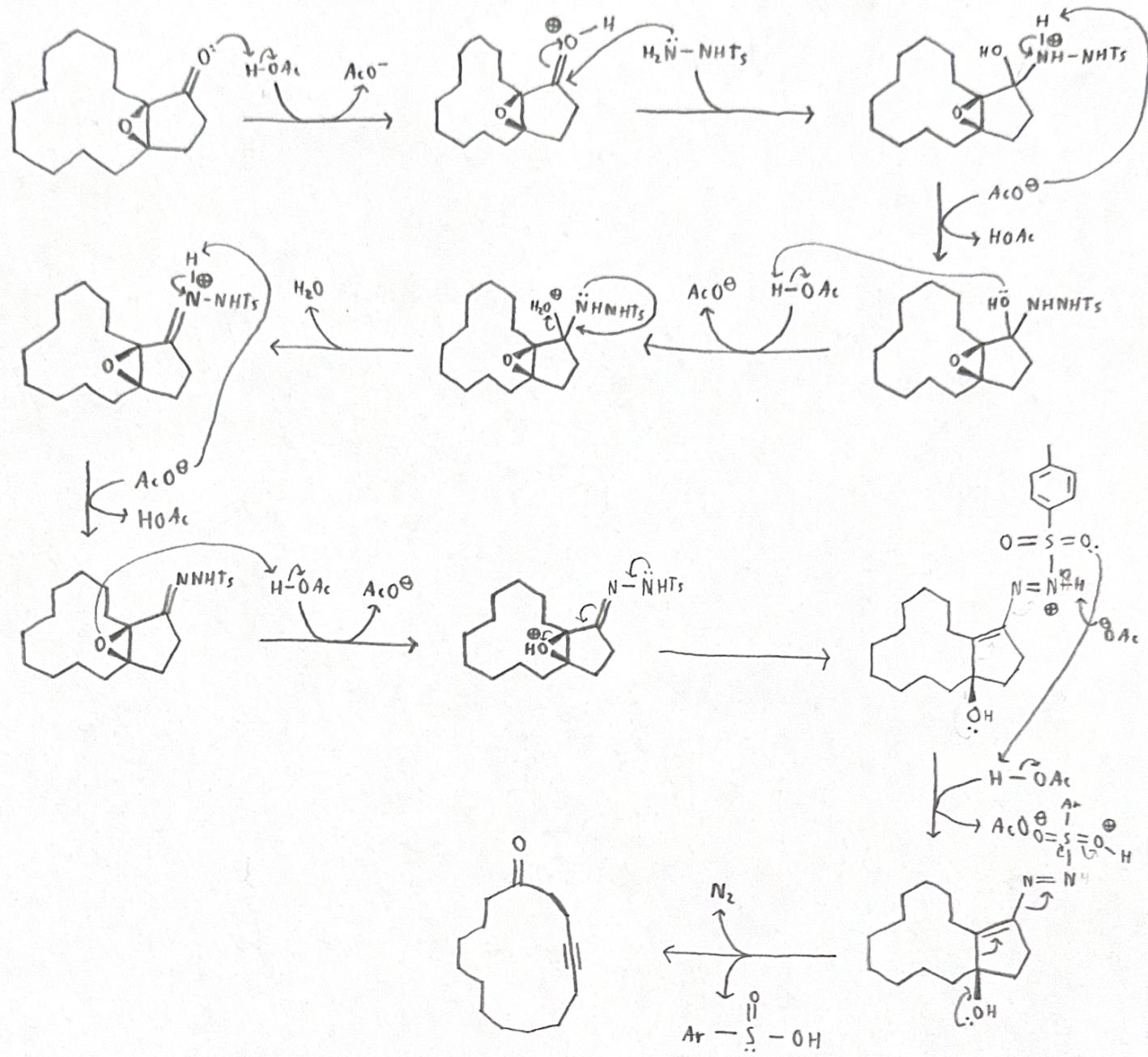


Figure 1.4: Using an acid as a proton transfer agent.

- At a minimum, look to add an O–H to the ring to make it a six-membered transition state.
- We could also do this in a two-step intermolecular process.
- As a specific example, amide bond hydrolysis under basic conditions is more reminiscent of the six-membered ring, though.
- Aside: Protonation and pK_a 's.
 - Ketones are much harder to protonate than comparable species.
 - pK_a of hydronium is -1.7 .
 - pK_a of protonated ethylene oxide (the simplest epoxide) is -2 .
 - pK_a of protonated carbonyl is -6 to -8 .
 - Protonated THF is more easily stabilized by solvation effects than protonated diethyl ether because the “arms” are being held back in THF, so the oxygen lone pairs are more accessible.
 - Carboxylic acid derivatives vary in terms of how hard they are to protonate.
 - Acid chloride is -9 .
 - Amide is 0 (resonance stabilization of the positive charge to the nitrogen).
 - Ether is in the middle (still has resonance stabilization, but oxygen is more electronegative).
- Random note: Strain for a 5-membered ring is about 5 kcal/mol .
- Altogether, the full solution to PSet 1, Q2 is on the next page.



- We now begin discussing Problem 6.

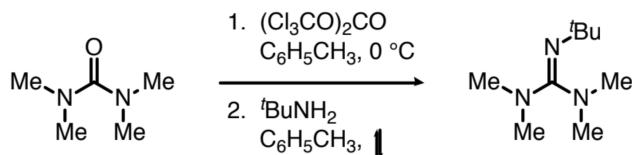
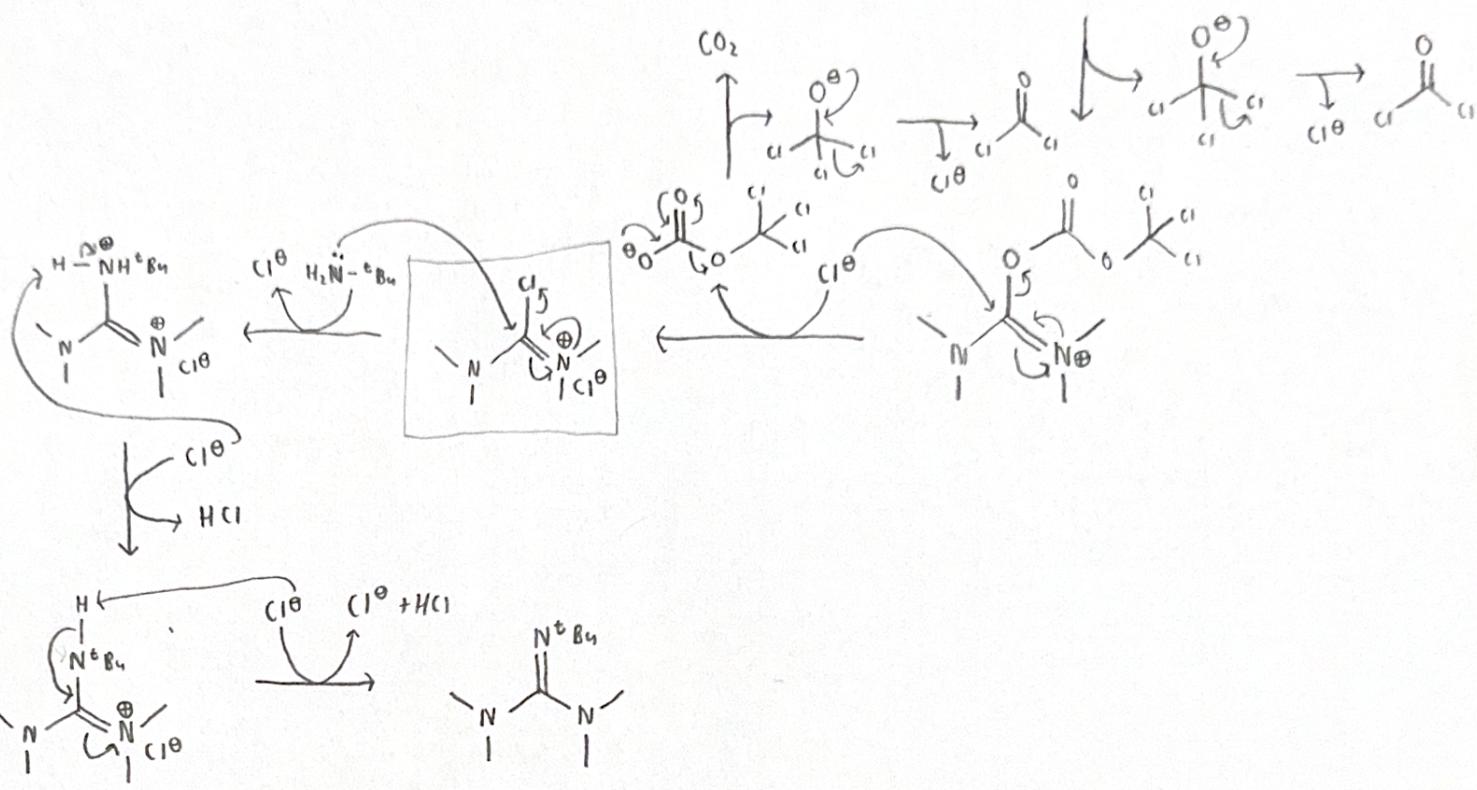
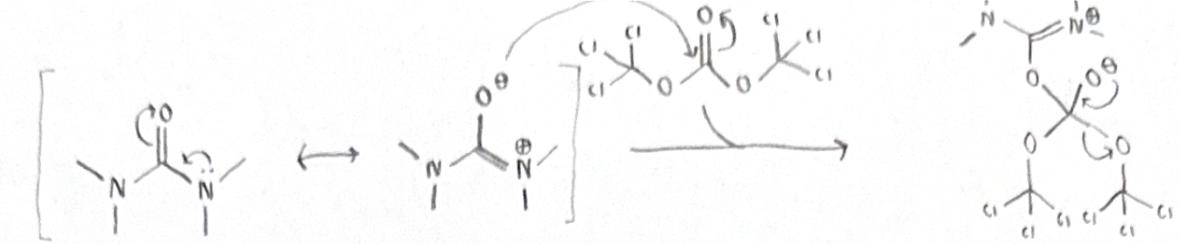


Figure 1.5: Movassaghi PSet 1, Q6.

- The first reagent is triphosgene. We use it because...
 - It is far less toxic than phosgene;
 - It generates phosgene *in situ*.
- First, make the reactant more nucleophilic via resonance.
- The reactant then attacks the reagent.
 - Note that Mo is fine with us drawing out a nucleophilic substitution as electrons kicking up and back down in one step instead of in two (as Levin required). As such, I have done a bit of both in the final mechanism for this problem.
- The leaving group is unstable, and undergoes α -elimination of one chlorine.
- Chloride then attacks the positive center, kicking electrons up and down and kicking out a leaving group.
- CO_2 then leaves, and we get another phosgene and chloride.
- The chloride salt is where we end (the boxed intermediate in the final mechanism).
 - Note that overall at this point, we've generated 2 equivalents of phosgene and 1 equivalent of CO_2 ; all chloride generated has been reincorporated into the molecule.
- Now we add the second species.
 - It attacks the iminium ion and kicks out the chloride.
 - Chloride then neutralizes the molecule, generating HCl .
 - Finally, one more chloride attacks the remaining nitrogen hydrogen.
 - Decide which way we go based on the $\text{p}K_a$'s of the relevant acids.
- Note that we need one extra equivalent of *tert*-butylamine to sequester the HCl .
- Altogether, the full solution to PSet 1, Q6 is on the next page.



- Next time.
 - We'll start next time with problems 4-5 of PSet 1.
 - First 5 sessions are with Mo, then Alison has 6-10.
 - 10 total sessions in this class.
- Memorize more pK_a 's!!

1.2 Problems 3, 4, and 5

- 9/6:
- PSet 2 PDF, please?
 - Mo sent PSets 2-3 via email a minute before class.
 - We will work all the PSets in order, as opposed to mixing and matching problems.
 - Mo: Prioritize working on new problems instead of clean copying old problems.
 - We now begin discussing Problem 5.

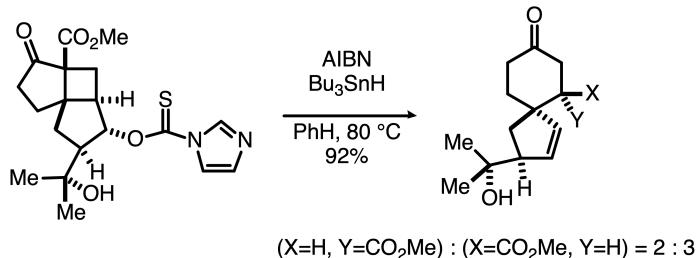
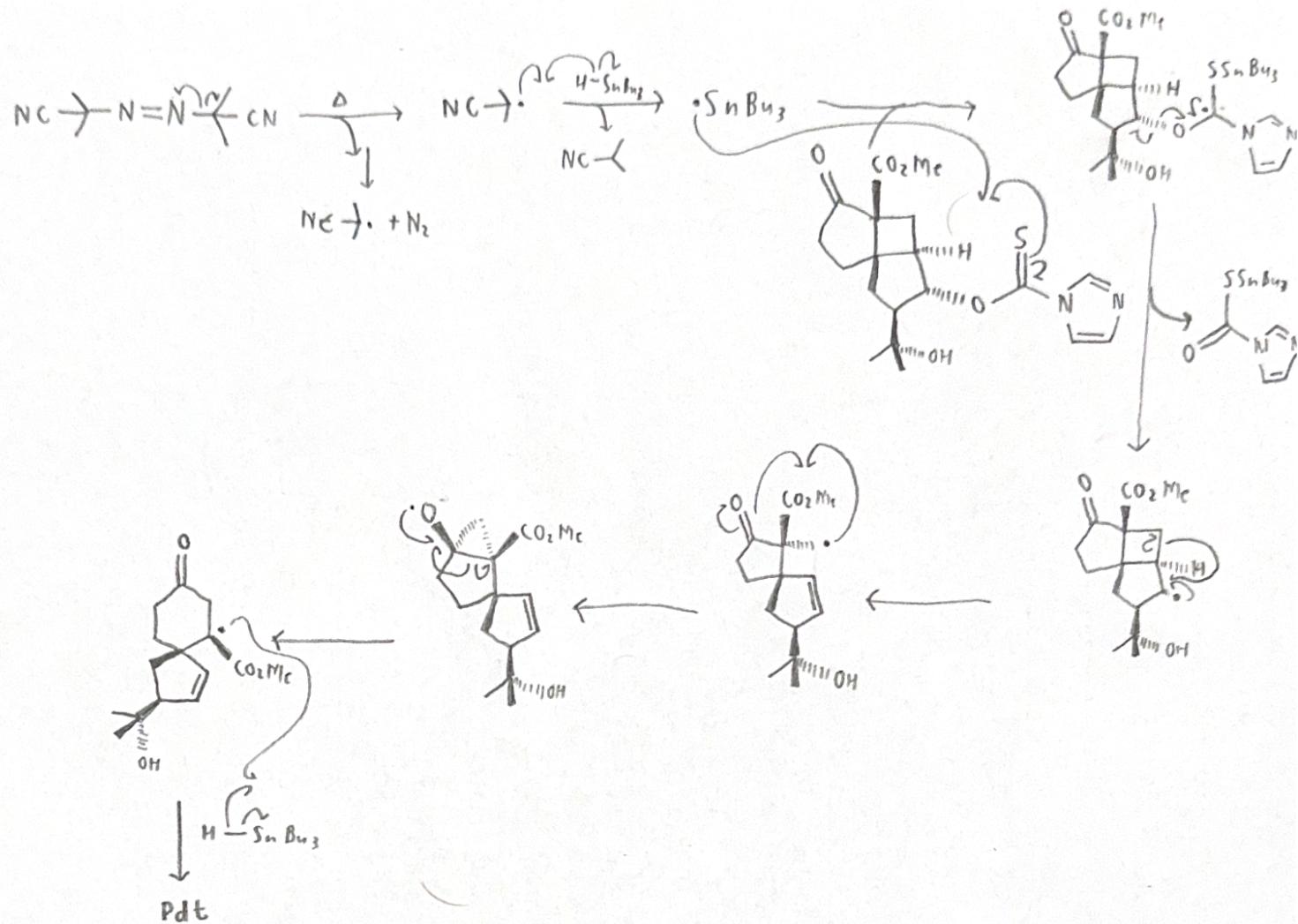


Figure 1.6: Movassaghi PSet 1, Q5.

- As in PSet 1, Q1 (Figure 1.1), we start by cleaving AIBN and abstracting the hydride from $HSnBu_3$.
- Then like we went after the bromine last time, we go after the sulfur this time. Let's discuss the driving force to go after the sulfur.
 - The sulfur atom, itself, is a big soft atom with orbitals that are easily accessible to the tin radical.
 - The product is also extremely stable for several reasons.
 - For starters, it's a tertiary radical.
 - It's also a 5-electron, 3-centered radical once you take the oxygen and the sulfur into account.^[1] Essentially, all of the nearby heteroatoms can donate electron density to stabilize the radical.
 - Note that among the nearby heteroatoms, the nitrogen is least likely to donate its electron pair. This is because its electron pair is part of the aromatic ring. Thus, to donate it, you would have to break aromaticity, and that would be extremely unfavorable.
- Next, you kick out the whole sulfur-containing moiety as a leaving group and form a secondary radical on the compound.
 - It's not immediately obvious why this step should be favorable: You're breaking a (very strong) C–O single bond. However, you are also forming a C=O double bond, and it's this bond-forming process which provides the driving force to split off the leaving group.

¹ Aside: This is why the methine C–H bonds in THF are weaker than the other ones, i.e., because breaking one of them generates a 3-electron, 2-centered radical.

- Aside: The last two steps together are known as a **Barton-McCombie deoxygenation**.
 - This method works really well for tertiary alcohols.
 - However, if you just have a primary alcohol, you will reduce the stable radical with tin hydride because it is not favorable to form a primary radical. Then under acidic work up conditions, you kick out the alcohol from the thioester.
- Once again, it is now not immediately obvious how to proceed.
 - We can't really have a 5-endo-trig cyclization (under ordinary OChem conditions).
 - One thing we can do is form the double bond in the product, break a C–C σ -bond, and form a methyl radical.
 - This seems like it would be very uphill at first, but it will be driven by the release of the cyclobutane ring strain. Indeed, so much strain release is the only thing that could drive primary radical formation.
- Then we have a 3-exo-trig cyclization.
 - This is a kinetically favorable (but reversible) cyclization.
 - It is also favorable because it eliminates the primary radical.
 - Radicals abstract atoms that have spherical orbitals (I, Br, Cl, H).
 - Radicals don't abstract methyl groups because it would have to invert the carbon atom and navigate the C–H orbitals to get to the C–C σ^* orbital.
 - Adding into the C=O π -bond is just gonna be more favorable, even though we're forming a 3-membered ring.
 - How fast is the formation of the three-membered ring?
 - Going to a primary oxygen centered radical is uphill.
 - Exchanging a π -bond for a C–C σ -bond is favorable.
 - We are also helped by the fact that fragmentation is very exothermic, so even though we have to go through a high-energy intermediate, we get a very stable product one step later. In fact, the energetic stability of the product *lowers* the energy of the transition state (and hence the activation energy).
 - Know rates, too!!
 - Releasing ring strain in the radical clock radical is 10^8 /s.
 - 5-exo-trig is 10^5 /s.
 - Radical-radical coupling is almost barrierless; diffusion controlled at 10^9 /s.
 - Going from the strained, primary radical to a doubly benzylic radical can happen faster than diffusion at 10^{11} /s.
 - Relearn radical clocks!!
- Because the 3-exo-trig is reversible, we could just reverse it. However, there is another, more favorable route.
 - Indeed, the last step is driven by the release of cyclopropane ring strain and the formation of a tertiary, resonance-stabilized radical.
- We get a rearrangement and fragmentation.
- The spiro group and sterics could account for the ratio of stereoisomers.
 - Alkene vs. alkane already favors the stereochemistry; we don't *need* the R group. The alkene is so much smaller (2 hydrogens vs. 4 hydrogens).
- Altogether, the full solution to PSet 1, Q5 is on the next page.



- We now begin discussing Problem 4.

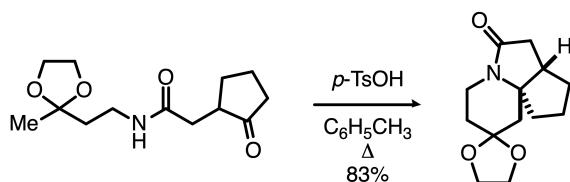


Figure 1.7: Movassaghi PSet 1, Q4.

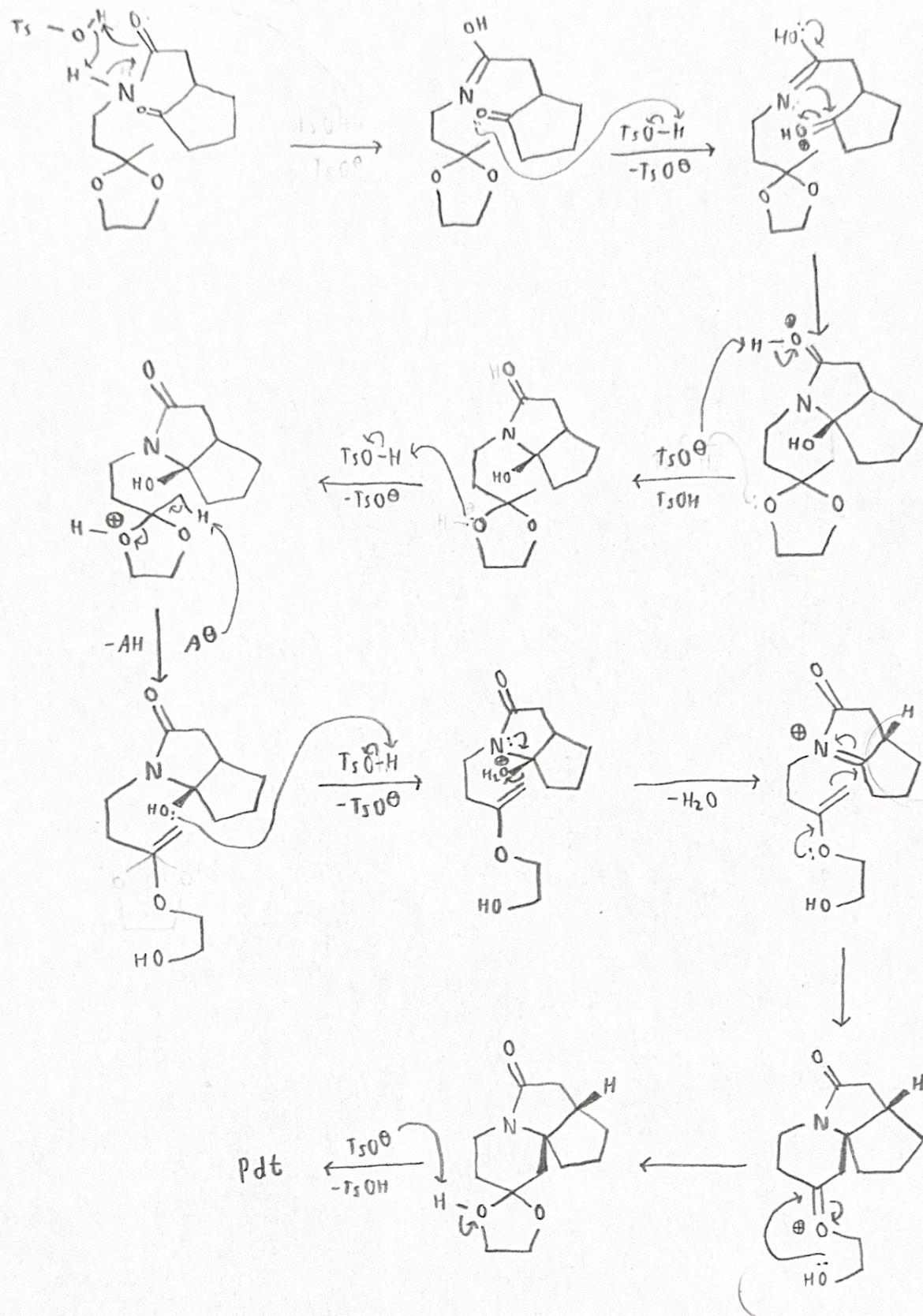
- The provided reagents are strong acid and heat. As such, the first step will be a protonation. But which site will we protonate?

- There are five possible positions we could protonate, and four distinct types. Let's order them from least-likely to most-likely to be protonated.
 - Least likely: The amide nitrogen.
 - This nitrogen's lone pair is conjugated with the C=O π -bond, and breaking this conjugation will take a ton of energy.
 - The ketone.
 - Recall that the pK_a of a protonated carbonyl is -6 to -8 .
 - Either of the ethers.
 - Recall that the pK_a of a protonated ether is -2 .
 - The amide oxygen.
 - Recall that the pK_a of a protonated amide is 0 .
 - This is because the positive charge we create is resonance-stabilized by the α -nitrogen.
 - Thus, while protonating the ketone would seem like a logical first step to accelerate nucleophilic addition, the pK_a values tell us that it is *over a million times* more likely that we will protonate the amide first.
 - Moreover, this protonation actually is helpful!
 - Specifically, it can help tautomerize the amide into an **imidic acid**.
 - The imidic acid's nitrogen will then have an unconjugated lone pair in an sp^2 orbital that is ideally positioned to attack the ketone once we protonate it. This imidic acid/**imidate**^[2] nitrogen is a superb nucleophile.
 - Thus, after the tautomerization, we activate the ketone and add into it.
 - This forms a fairly stable hemiaminal that can hang around for a while.
 - In particular, we will *not* want to convert this to an N-acyliminium just yet (see below).
 - We then deprotonate the intermediate so that we can protonate it elsewhere.
 - It is important to deprotonate *before* charging ahead into the next protonation because multiply charged intermediates are difficult to access.
 - Once we activate the ketal, multiple species in solution could pick off the α -hydrogen.
 - It could be the conjugate base, tosylate. However, it could also be the original amide in the starting material!
 - At this point, our enol ether is a prepared and ready nucleophile.
 - Now we activate the electrophile by having water leave to create an N-acyliminium.

²Clear up the naming!

- N-acyliminiums are even more electrophilic than iminiums due to their combined dipole with the adjacent carbonyl.
 - Thus, it is important that we form the enol ether first and the N-acyliminium second, because the N-acyliminium will react as soon as it forms. In other words, the N-acyliminium will not want to hang around for too many steps before reacting again.
- The last step is a 5-endo cyclization, which is not feasible in radical chemistry but *is* feasible in carbocation chemistry.^[3]
 - Comment: When working in acidic regimes, try not to have carbanions in your mechanism.
 - This whole transformation is related to the **Pictet-Spengler reaction**.
 - Altogether, the full solution to PSet 1, Q4 is on the next page.

³Is it not a 6-endo cyclization??



- We now begin discussing Problem 3.

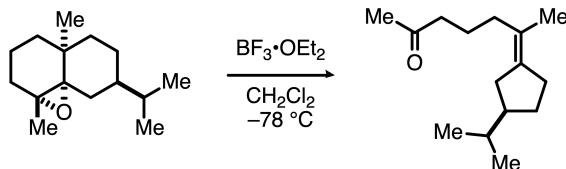
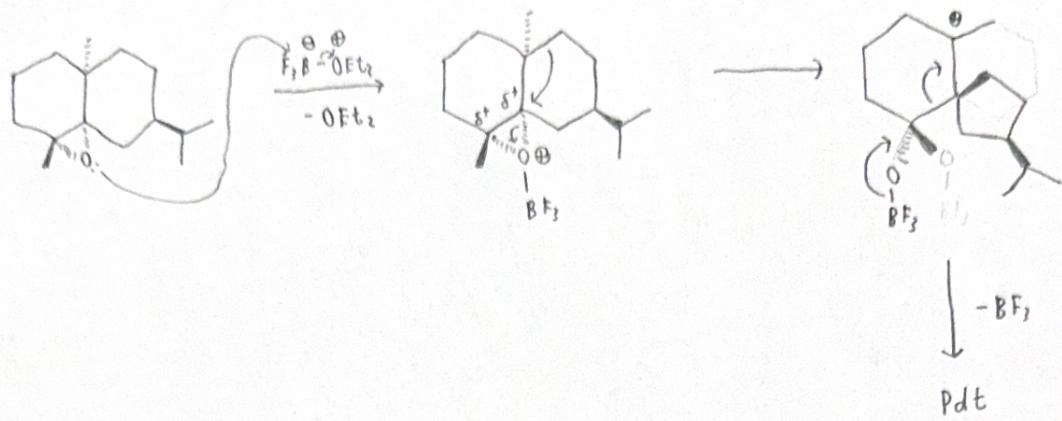


Figure 1.8: Movassaghi PSet 1, Q3.

- Looking at the reagents, observe that BF_3 is a strong Lewis acid. Thus, it will seek out the most nucleophilic site on the substrate first, which in this case happens to be oxygen.
 - When the oxygen coordinates to the boron, a number of subtle changes begin to take place.
 - For starters, the two C–O bonds will elongate because oxygen withdraws electron density from them. This lowers the activation energy for C–O bond cleavage.
 - Additionally, when oxygen has a positive charge, it becomes more electronegative and puts partial positive charges on the **distal** carbons. This makes them more promising electrophilic sites.
- Drawn toward the electrophilic distal carbon, a C–C σ -bond engages the C–O σ^* -orbital in an antiperiplanar fashion.
 - Geometry is important here: If the stereochemistry were switched at the top carbon, this reaction would be much less likely to proceed.
 - It is also important to note that epoxide opening and ring shrinking happen in a concerted step — driven by the favorable bonding/antibonding interactions — instead of in a stepwise fashion.
 - Indeed, antiperiplanar geometry and concerted steps often go hand-in-hand!
 - We can also rationalize why we have an intramolecular nucleophilic attack on the C–O bond instead of an intermolecular one. This mainly comes down to sterics: Nucleophilic addition will be disfavored at a quaternary carbon.
- At this point, we have a tertiary carbocation as our most reactive site.
 - This could induce a hydride shift, but a hydride shift would form a secondary carbocation and hence this is disfavored. The only time that a hydride shift would happen here is if we could get to a much more stable product through this hydride shift.
 - There is also no methyl shift here because the methyl group is *syn*; if it were *trans*, it could benefit from antiperiplanar interactions and would be more likely to shift. What does this mean??
- Thus, we kick off the leaving group, form a C=O bond and a C=C bond, and neutralize the carbocation. All of these favorable effects are enough to compensate for breaking the C–C σ -bond.
- Altogether, the full solution to PSet 1, Q3 is on the next page.



Problem Set 2

Cycloadditions and Photochemistry

2.1 Problems 2 and 5

9/6: • We begin with Problem 5.

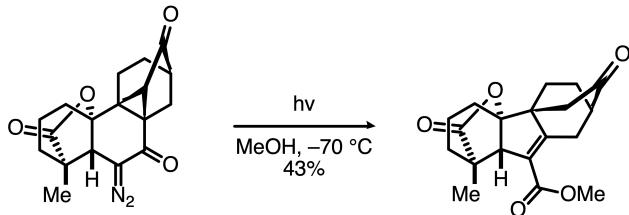


Figure 2.1: Movassaghi PSet 2, Q5.

- 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.

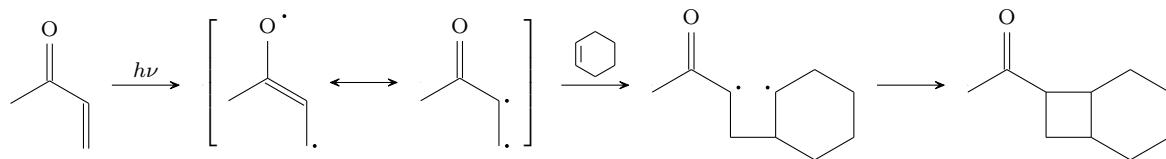
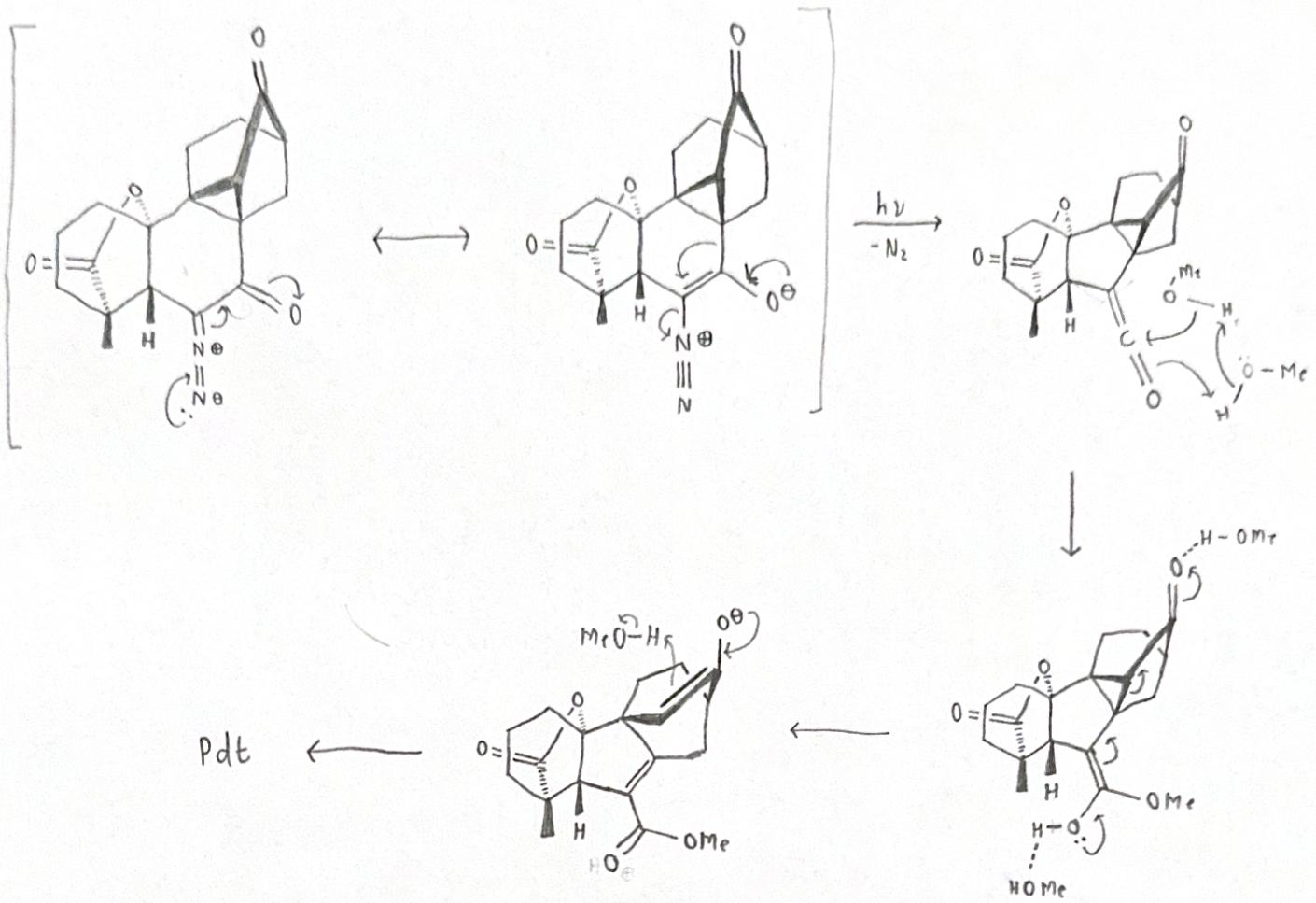


Figure 2.2: Forming 4-membered rings via photochemistry.

- 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.

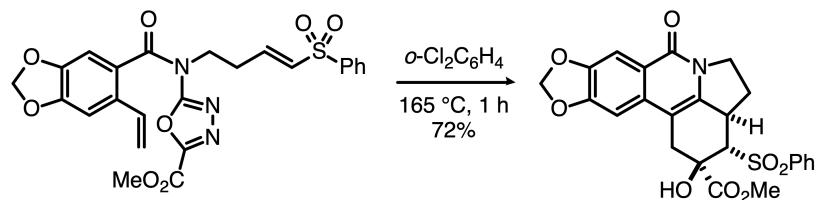
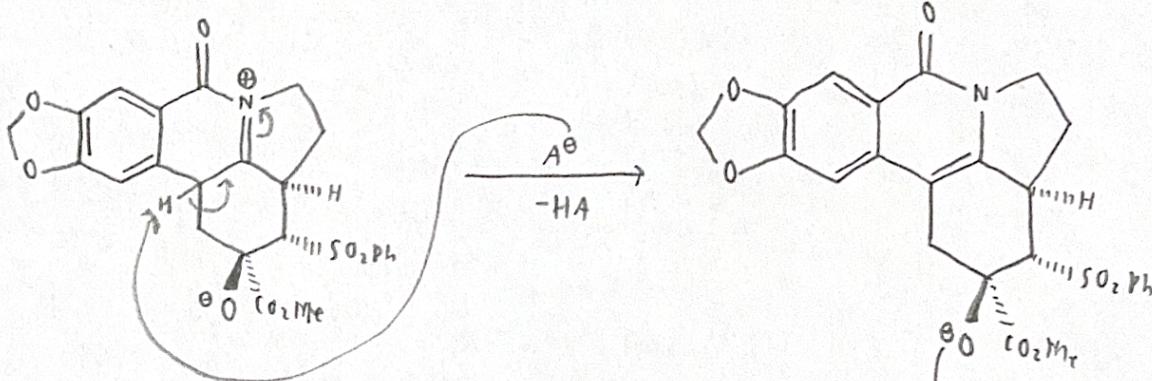
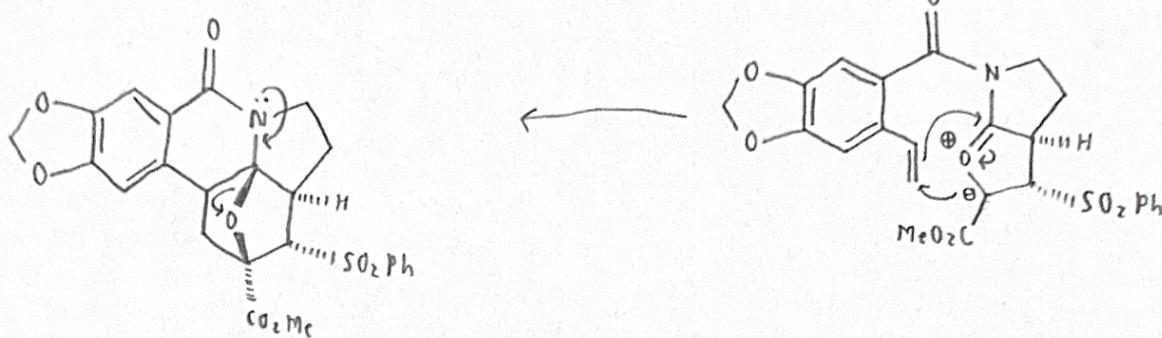
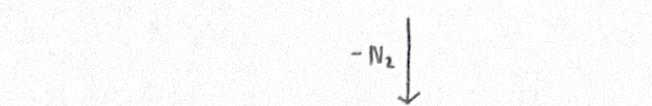
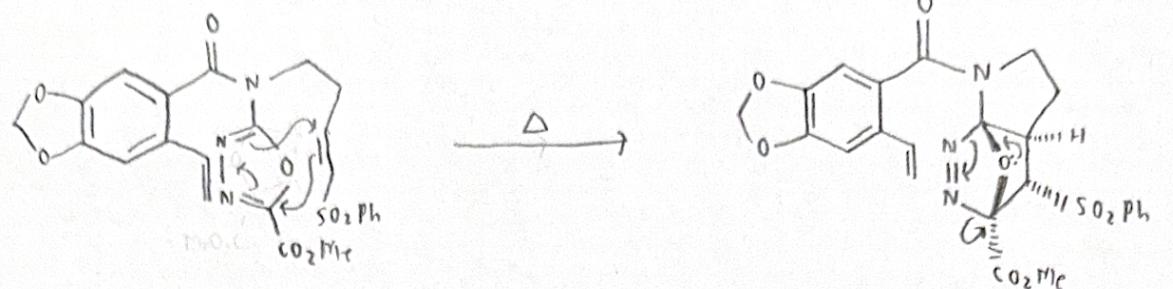


Figure 2.3: Movassaghi PSet 2, Q2.

- 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.

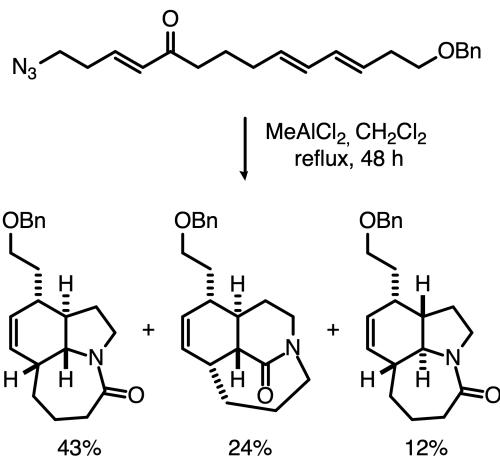
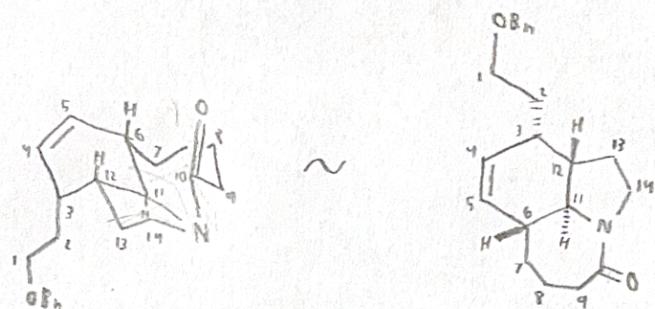
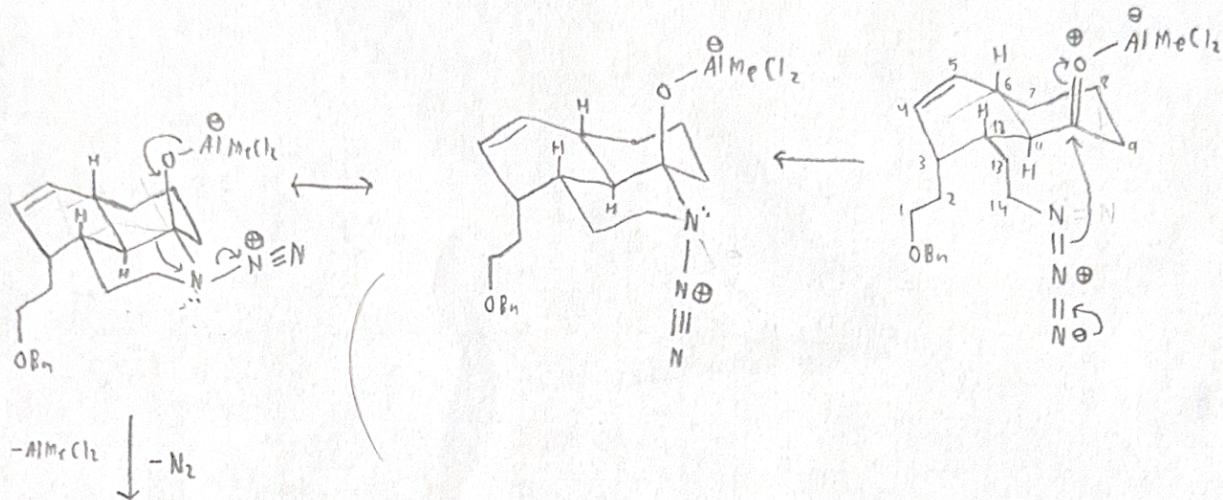
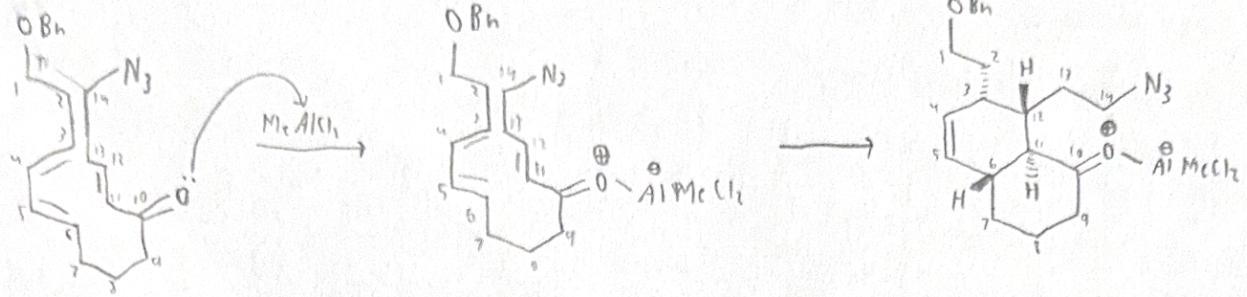


Figure 2.4: Movassaghi PSet 2, Q3.

- 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.

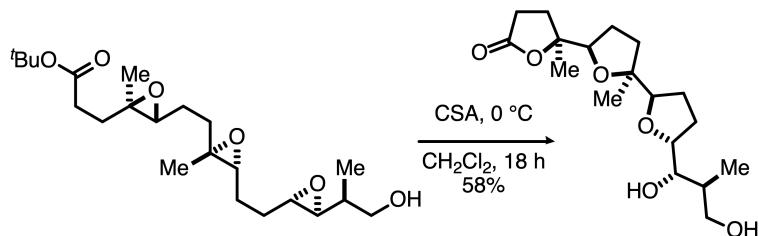


Figure 2.5: Movassaghi PSet 2, Q1.

- The distal epoxide carbons with methyl groups attached could hold stable carbocations, and thus begin 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.

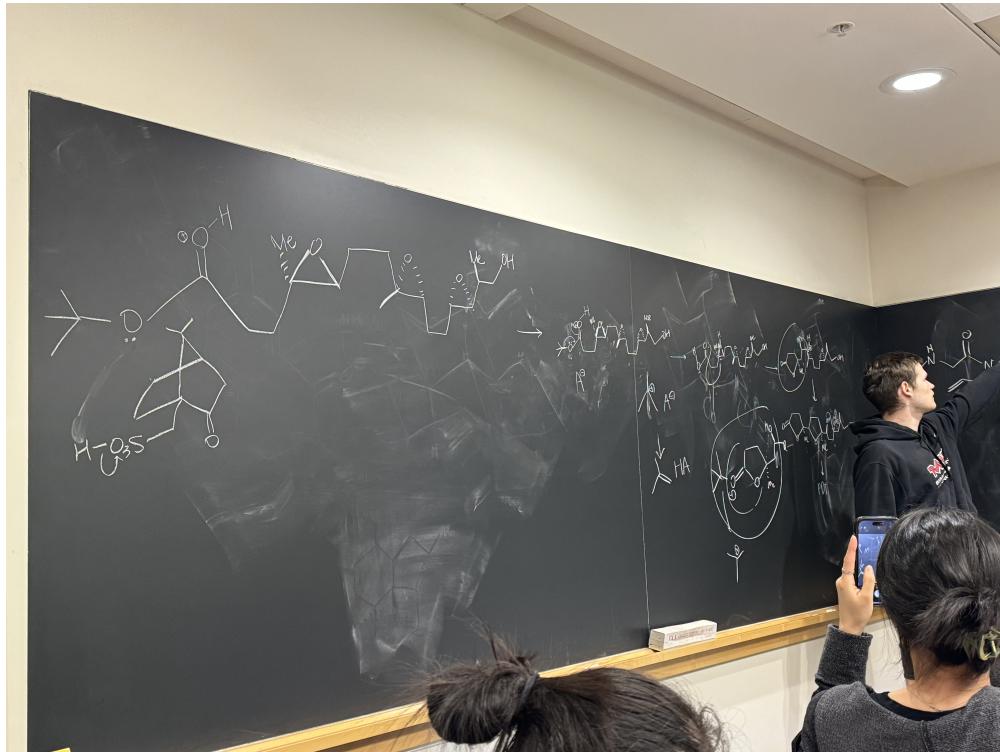


Figure 2.6: Movassaghi PSet 2, Q1 solution.

- We now begin discussing Problem 4.

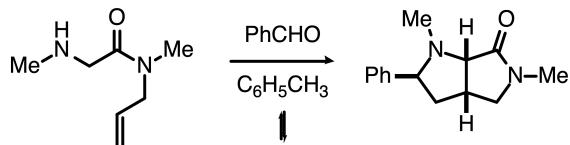


Figure 2.7: Movassaghi PSet 2, Q4.

- 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.

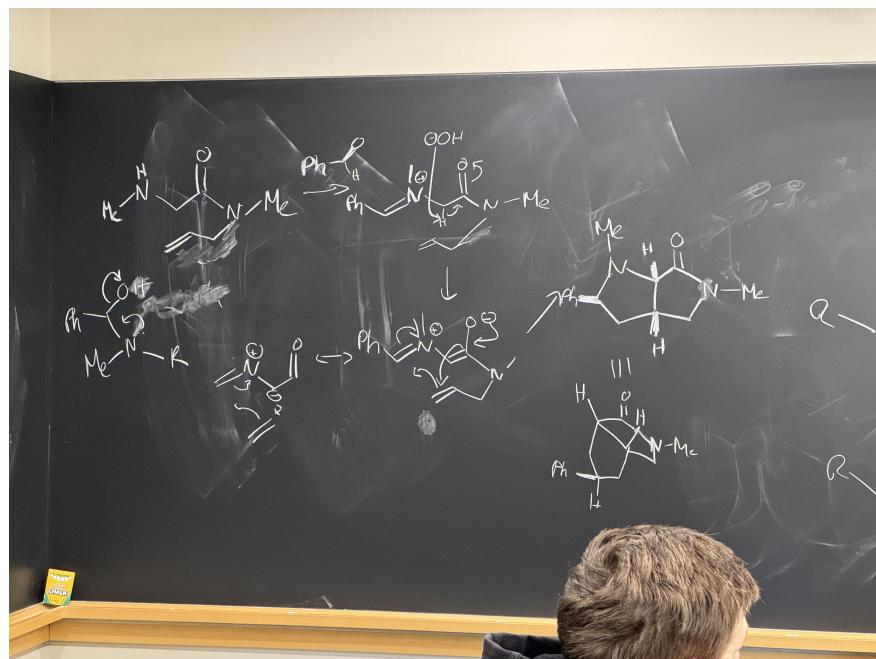


Figure 2.8: Movassaghi PSet 2, Q4 solution.

- We now begin discussing Problem 6 (Ivan).

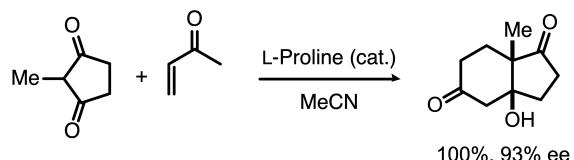


Figure 2.9: Movassaghi PSet 2, Q6.

- 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.

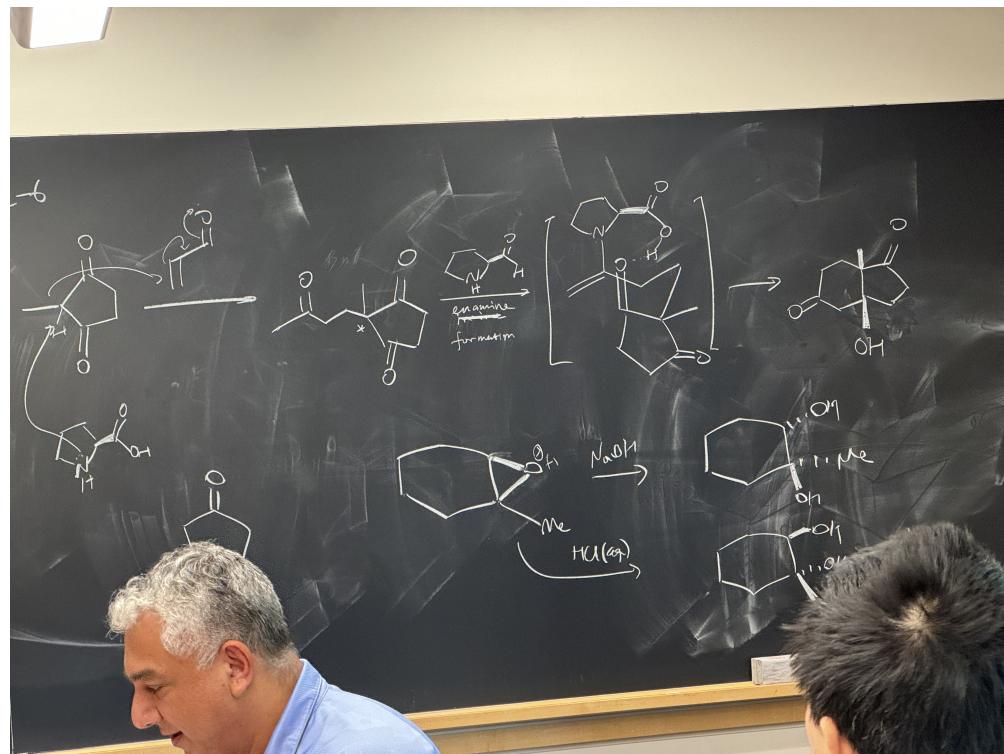


Figure 2.10: Movassaghi PSet 2, Q6 solution.

- 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.

Problem Set 3

Cyclic Intermediates

3.1 Problems 1, 2, 3, 4, 5, and 6

9/13: • We begin with Problem 3.

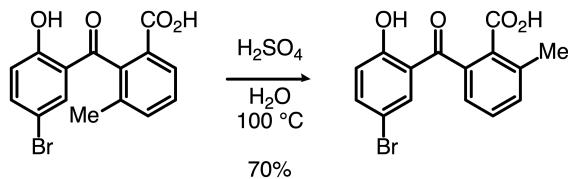


Figure 3.1: Movassaghi PSet 3, Q3.

- Fairly acidic conditions; fairly high temperature. So fairly forcing.
- First step could be electrophilic aromatic substitution. In Friedel-Crafts, the π -system acts as a nucleophile.
- We go through a spiro-fused bicyclic juncture. Without the methyl group, it'd be fully symmetric.
- You can't acylate an aromatic system with a carboxylic acid.
- To get to an acylium ion in the starting material, protonate at the less favored position of the carboxylic acid OH. This will happen at 1 in a billion molecules, and that's what the forcing conditions get us. Then water leaves.
- Ask myself: What sites could you protonate, and where would this get us?
 - Reversible protonation of the carbonyl does nothing, so move on.
 - Few reagents implies an intramolecular reaction.
 - In an intramolecular reaction, think about which atoms could go where without something breaking off fully.
- The OH of the phenol could hydrogen-bond to the carbonyl and planarize the system.
- Dearomatizing the ring is uphill. The bonds will be fairly labile. This first step could well go backwards! The point is that pretty much every step here is reversible. But why do we get dominant formation of the product?
 - The left molecule (with two ortho substituents) has rotation about the right phenyl-carbonyl bond. With the product substituents, the molecule can be planar and we get additional stabilization via full conjugation.

- In Friedel-Crafts chemistry, phenols are ortho- and para-directing, so remember that our phenol can have some nucleophilicity.
- Altogether, the full solution to PSet 3, Q3 is on the next page.

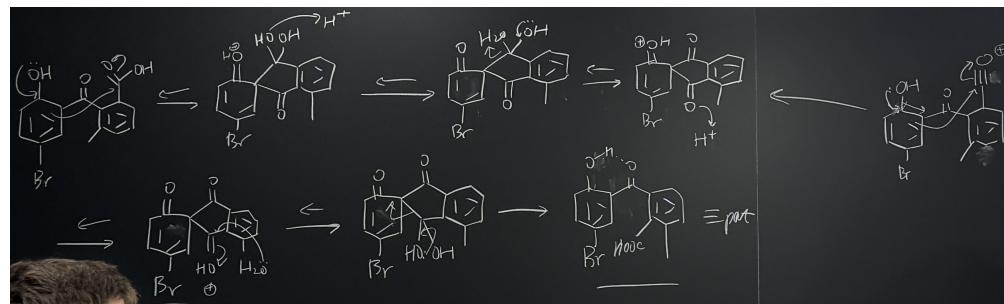


Figure 3.2: Movassaghi PSet 3, Q3 solution.

- We now begin discussing Problem 1.

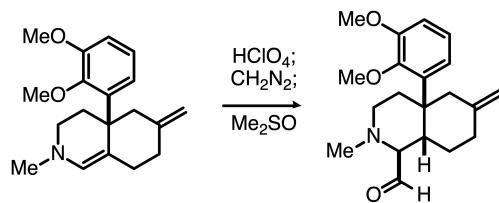


Figure 3.3: Movassaghi PSet 3, Q1.

- Perchloric acid is a very strong acid with a weak, nonnucleophilic counterion. Thus, protonation is correct.
- However, what protonating the enamine might not be favorable.
 - The enamine is more nucleophilic than the enol because the nitrogen can stabilize positive charge better than the oxygen.
 - Lone pair donation to the enamine will override any alkene selectivity.
 - This is why we protonate the tertiary position.
- Then the nucleophilic diazomethane attacks the iminium.
- Losing dinitrogen provides the energy you need to form a three membered aziridinium.
- Aziridine → aziridinium intermediate.
 - Thus, nucleophilic addition and rupture of one of the bonds could relieve ring strain.
- The DMSO oxygen attacks the less sterically hindered position.
- Positively charged sulfur has perchlorate as a counteranion.
- We don't need oxalyl chloride because we already have the key intermediate.
- Swern: The triethylamine actually deprotonates at the methyne; then the carbanion diprotonates at the ipso carbon.
 - Retro [3 + 2] dipolar cycloaddition.
 - Involvement of ylides??
- The methylamine in the structure can act as internal base; we could also have another molecule come by to do the deprotonation.
- Protonating the bicycle will lead to either a *cis*-decalin derivative or a *trans*-decalin derivative.
 - The *cis*-decalin has the aryl group being equatorial, which is energetically favorable.
 - The aryl is not 1,3-interacting with the bottom ring because the double bond is bending the 3-hydrogen away.
 - The approach coming from the top of diazomethane is much more favorable, because it's less hindered by the inside/underside of the *cis*-decalin.
- We should consider the stereochemistry at each step, because it impacts what chemical options are available at each step.

- Altogether, the full solution to PSet 3, Q1 is on the next page.

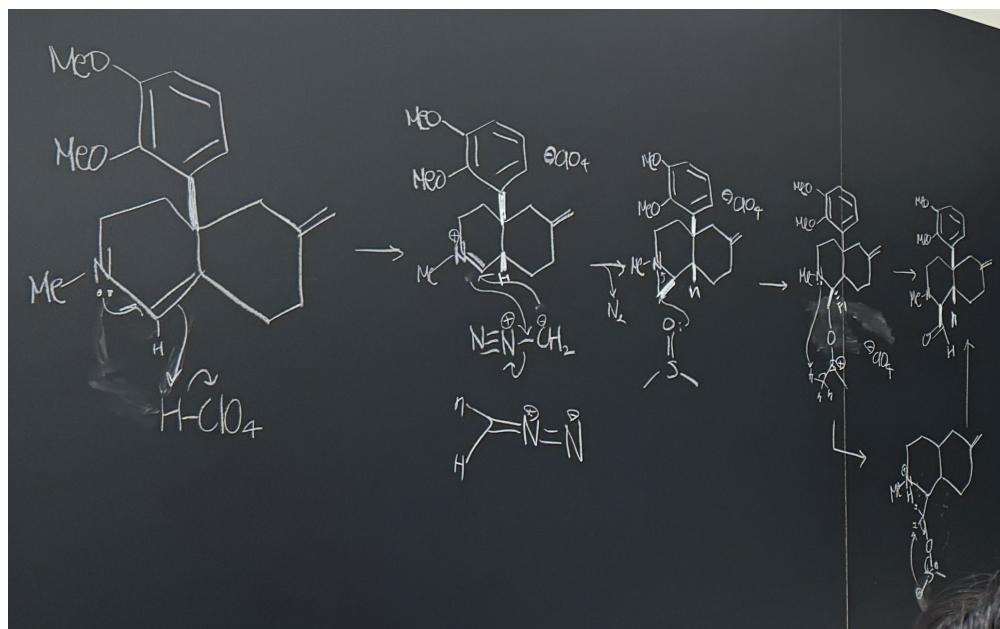


Figure 3.4: Movassaghi PSet 3, Q1 solution.

- We now begin discussing Problem 4.

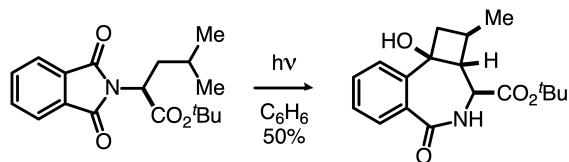


Figure 3.5: Movassaghi PSet 3, Q4.

- Photoexcitation makes the carbonyl into a diradical. Then we have 1,5-H atom abstraction (which is optimal, as we've discussed previously).
 - We will photoexcite either of the two carbonyls in the phthalimide.
 - It's easier to photoexcite conjugated systems because we've got a larger box (particle in a box QM analogy). Larger boxes have lower excitation energy. *check the math!!*
 - Once you photoexcite the carbonyl, you'll go back, do α -cleavage to form an acyl radical, or do 1,5-H atom abstraction.
 - David: Where is the intersystem crossing?
 - Singlets or triplets can form a bond; the aromatic system will help enable the ISC exchange.
- Two carbon radicals quickly form a 4-membered ring, driven by killing radicals and forming a C–C σ -bond.
 - The 4-membered ring is an azocyclobutane.
- Then we get another 1,5-H atom abstraction, and another ring-closing reaction.
- Altogether, the full solution to PSet 3, Q4 is on the next page.

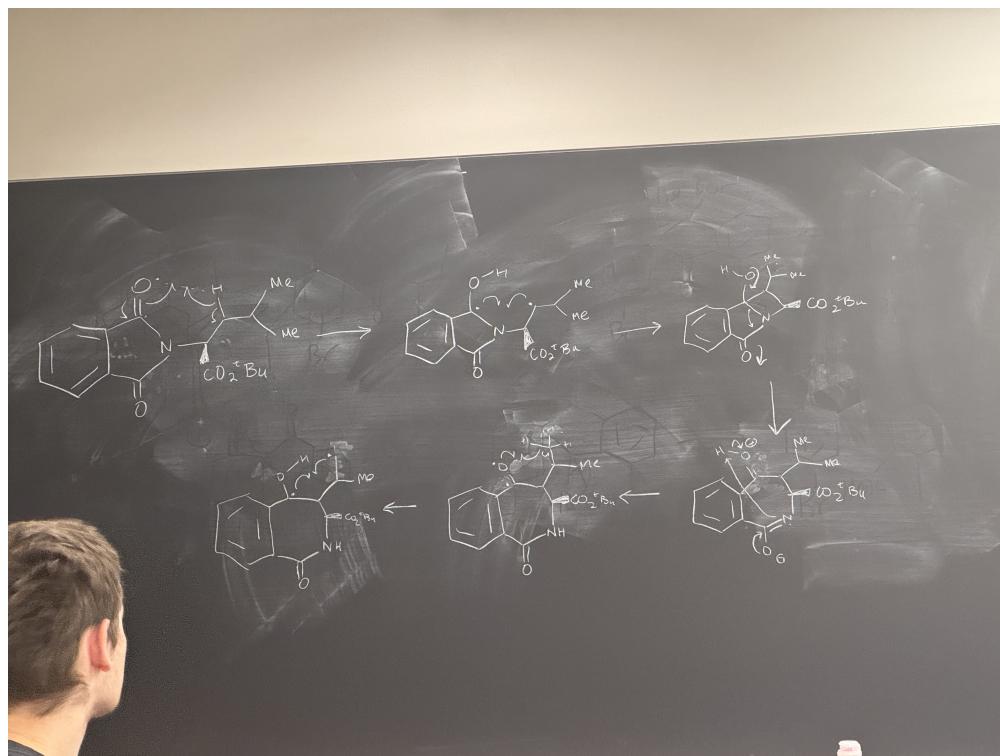


Figure 3.6: Movassaghi PSet 3, Q4 solution.

- We now begin discussing Problem 2.

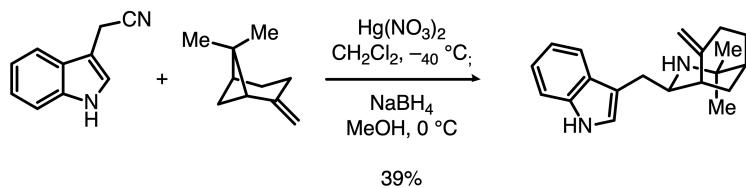


Figure 3.7: Movassaghi PSet 3, Q2.

- Look at quaternary carbons as places that a C–C σ -bond could leave behind a carbocation.
- We form the mercurinium ion.
 - The tertiary carbocation is less stable than the mercurinium ion.
 - Focus on what's reversible.
 - Releasing ring strain drives the formation of the tertiary carbocation.
 - We need an antiperiplanar orientation between the C–C bond that's breaking and the C–Hg bond that's breaking.
 - If mercury attacked from the top: (1) that's less likely due to steric bulk at the top of the molecule, and it would just have to reverse because no antiperiplanar orientation for the shift.
- Nitrilium ion has $\text{p}K_{\text{a}} = -10$.
- An analysis of pyrrole.
 - Protonating it: Positive charge is on 1, 2, or 3 atoms.
 - The most nucleophilic position is the α -carbon.
- Indole is just a variant of pyrrole. Indoles are very nucleophilic at the β -position.
- Thus, the indole nitrile is not the most nucleophilic species, but it is the most kinetically accessible.
- Indolyl group wants to be equatorial.
- Better to just kick out the mercury than use its lone pair.
 - Look up oxymercuration mechanism!!
- This reaction is a report of Clayton-Hithcock, even though it has mechanistic similarities to the Ritter reaction.
- Altogether, the full solution to PSet 3, Q2 is on the next page.

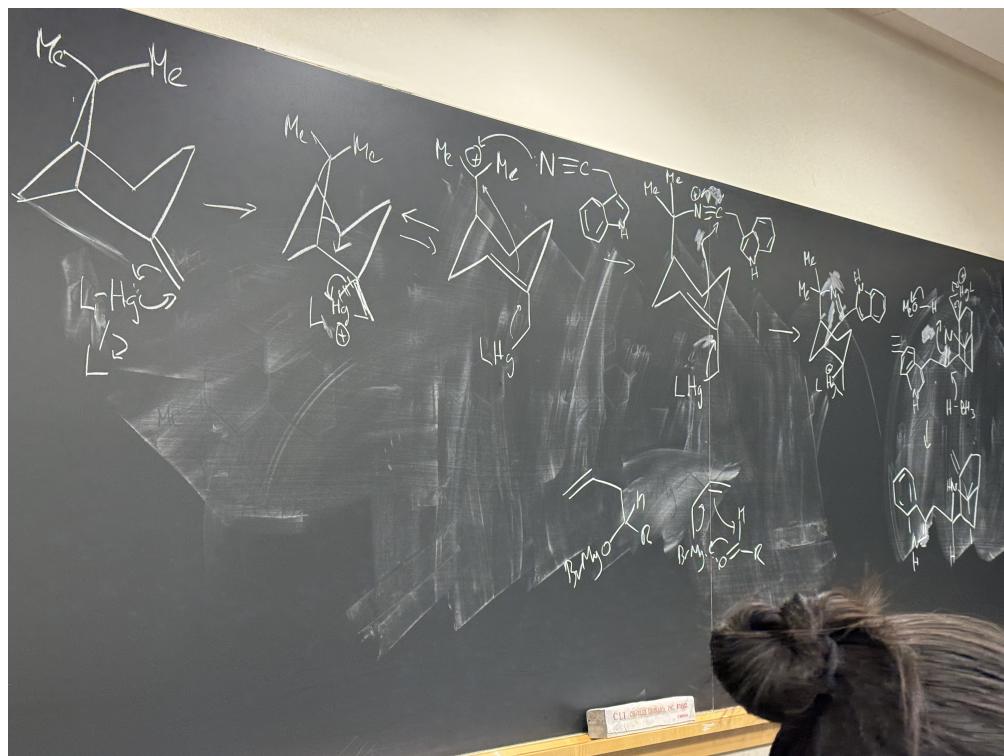


Figure 3.8: Movassaghi PSet 3, Q2 solution.

- We now begin discussing Problem 5.

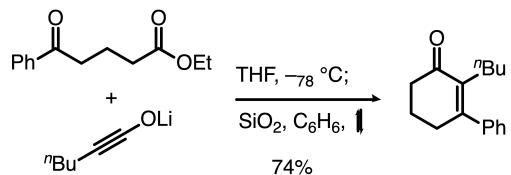


Figure 3.9: Movassaghi PSet 3, Q5.

- The ynolate could react like an enolate, but more likely it will be a concerted [2 + 2] cycloaddition. Good to keep the counteranion on the oxygen to assist in the cycloaddition.
- The reaction stops at the lactone in the first step. Then the addition of the acid, benzene, and heat weakens bonds and drives off CO₂.
- Altogether, the full solution to PSet 3, Q5 is on the next page.

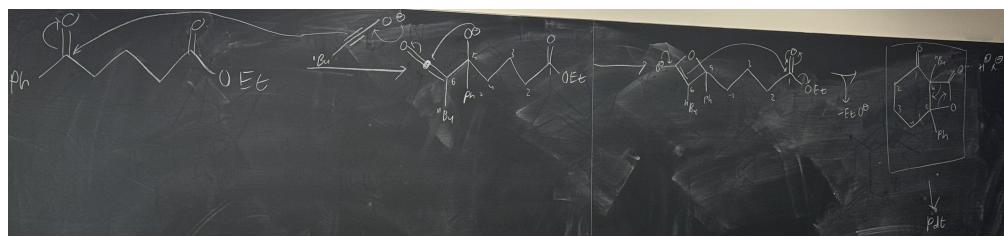


Figure 3.10: Movassaghi PSet 3, Q5 solution.

- We now begin discussing Problem 6.

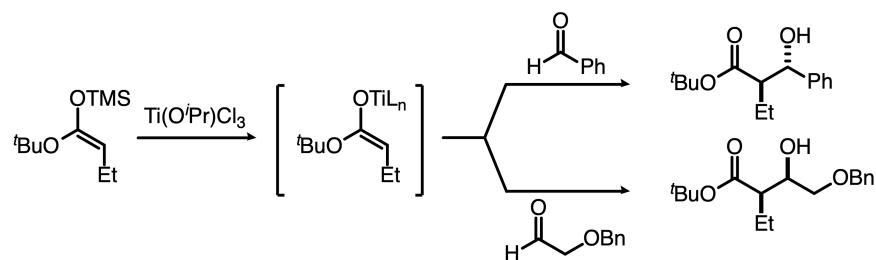


Figure 3.11: Movassaghi PSet 3, Q6.

- First step is just a deprotection.
- Then the transition state is a six-membered ring.
 - Closed transition states: **Zimmerman-Traxler transition states**. Dave Evans helped a lot with understanding this reactivity!
- What does the Lewis acid do?
 - The aldehyde becomes more electrophilic if we put a Lewis acid on the oxygen. When they coordinate to titanium, they become more electrophilic.
 - If something coordinates to the titanium, this also reactivates the enolate!
 - This is **dual activation**, leading to maximum rate enhancement. This is a very important concept in boron chemistry: We'll come back to it in 5.511
- Altogether, the full solution to PSet 3, Q6 is on the next page.

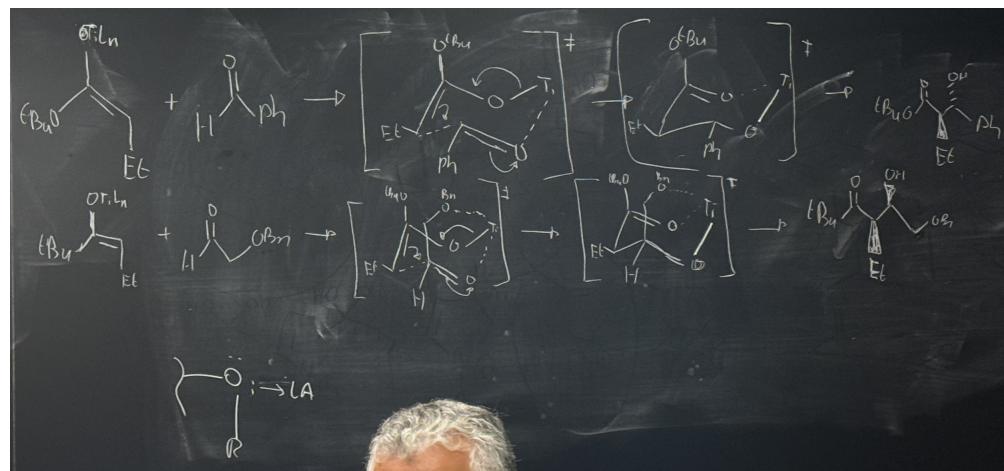


Figure 3.12: Movassaghi PSet 3, Q6 solution.

- Look over 5.43 - Advanced Organic Chemistry MIT OCW in the weeks before I begin 5.511!!

Part II

Johnson

Problem Set 1

Carbonyls

1.1 Problems 18 and 19

9/11:

- We should still continue reviewing the list of topics (at least before second year orals)!!
 - I should also continue reading the textbook!!
 - Come in with good solutions on Friday!!
- Problem 22 is the **Dakin-West reaction**, if we want to look it up after class.
- We now begin discussing Problem 19.

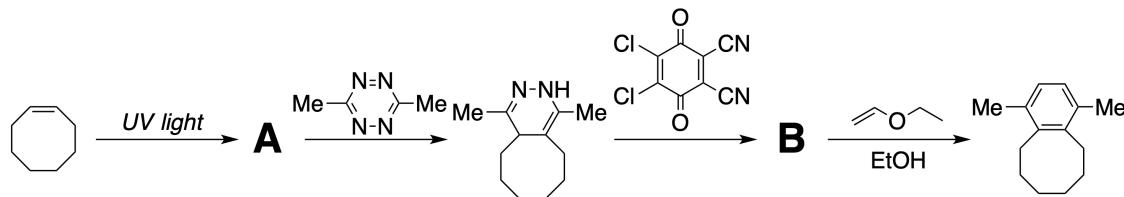


Figure 1.1: Johnson PSet 1, Q19.

- With UV light, we'll get isomerization to *trans*-cyclooctene. *picture; Frank's HOMO/LUMO diagram.*
 - *trans*-cyclooctene is a pretty strained molecule.
 - Jeremiah has us draw out the HOMO and LUMO of the alkene, i.e., matching phases and unmatching phases.
 - Jeremiah thinks the Woodward-Hoffmann rules are hard to understand without HOMO/LUMO diagrams.
 - Light excites an electron to a higher energy state, in a process in which a spin is conserved.
 - Learn **Jablonski diagrams!!**
 - Absorption of a photon happens on a femtosecond timescale, way faster than any other process can happen.
 - The flip of an electron spin is called **intersystem crossing**. This gets you from a singlet to a triplet state. ISC (flipping a spin) is technically a **forbidden** process, because a change in spin angular momentum must be matched by a change in orbital angular momentum or some such thing.
 - The electrons are still paired, even after excitation.
 - **Fluorescence** and **internal conversion** are by far the fastest and most favorable processes (photorelaxation and vibrational relaxation, respectively).

- The double bond does break into a biradical, and now the molecule is much more conformationally flexible.
- Jeremiah likes to show a biradical as the unpaired electrons with their spins.
- What is the driving force for this thermodynamically uphill reaction?
 - The *trans* and *cis* molecules absorb different wavelengths, so we need to shine exactly the wavelength that *cis* can absorb so that the reaction doesn't go backwards.
 - Once the *trans* species forms, it will form in a 75:25 ratio or something like that because “the energy difference is matching the extinction coefficient” or something like that.
 - Trans alkenes coordinate strongly to silver, and then we can flush it off of a silica column.
 - The trans coordinates more to silver because...
- An isolated double bond will need high intensity, low wavelength UV light be activated.
 - If you wanted to get this to work with lower energy light, you'd need a photocatalyst.
 - The reaction might start to have a bright color because the absorption peaks shift.
- The *trans*-cyclooctene does a cycloaddition to form an intermediate.
 - How do we do the proton shuffle? Perhaps using one of the nitrogens as a base.
 - **Inverse electron demand Diels-Alder.** Here, the dieneophile is electron rich and the diene (a tetrazine) is electron poor.
 - For this kind of reaction, we care about the LUMO of our diene and the HOMO of our dienophile (inverse of the regular Diels-Alder!).
 - And we do see that the symmetry matches.
 - Kicking out N₂ and forming the double-bonded intermediate happens concerted; the zwitterion Frank drew probably doesn't exist.
 - Then this intermediate tautomerizes to the intermediate in the question.
 - Use an external molecule (or the solvent) to do the tautomerization. The second tautomer is more stable!
- The third step is a **DDQ reaction**.
 - There is no established mechanism for this reaction!
 - Net driving force: Taking two quinones and aromatizing both of them.
 - It's also a dehydrogenation reaction.
 - We believe the mechanism is radical-enabled.
 - A π-bond (relatively nucleophilic) on the intermediate can do a single-electron transfer and become a radical cation.
 - Single-electron transfer from a π-bond can and will happen if it's thermodynamically favorable because DDQ is such a good electron acceptor.
 - You might also use light to accelerate this reaction.
 - There's a nice resonance structure that's aromatic, even though oxygen-centered radicals are unstable. But then this leads to rapid proton transfer of the resonance-stabilized positive proton.
 - **Semiquinone intermediate.**
 - Then the O radical steals an electron, becoming a negatively charged O that can steal a proton for aromaticity.

- There is also a proposed two-electron mechanism.
 - Start with a hydride transfer of the most electron-rich hydride to DDQ.
 - Using resonance structures to predict nucleophilic sites! Draw an aromatic resonance structure, which puts a positive charge on oxygen.
- Why couldn't we use TEMPO to disprove the radical mechanism?
 - It's a matter of relative rates; these radicals could only be formed transiently, far faster than TEMPO could interfere.
- There are computational papers in the last few years on DDQ mechanisms, but they are heavily substrate dependent.
- Some calculations suggest an **asynchronous** process.
- There are some reactions that would almost definitively suggest asynchronous mechanisms.
 - SRN1 reaction fills the gaps where SN1 and SN2 don't work.
 - Trigonal pyramidal carbocation is very unstable.
 - Tertiary radical is much more simple.
 - Doughtery and Anslyn has a whole chapter on SRN1 reactions!
 - Prior to photoredox catalysis, these reactions were more just a curiosity; now we're trying to make them useful.
 - Corey Stephenson's work on the early photoredox reactions.
- Lastly, we get another Diels-Alder reaction followed by a retro-Diels-Alder to kick out N₂.
- Then six-membered transition state proton transfer.
 - Heat or acid would help the end.
 - Jeremiah ran this reaction when he first got to MIT, and thought that the spontaneous aromatization was quite interesting.
- Altogether, the full solution to PSet 1, Q19 is on the next page.

- We now begin discussing Problem 18.

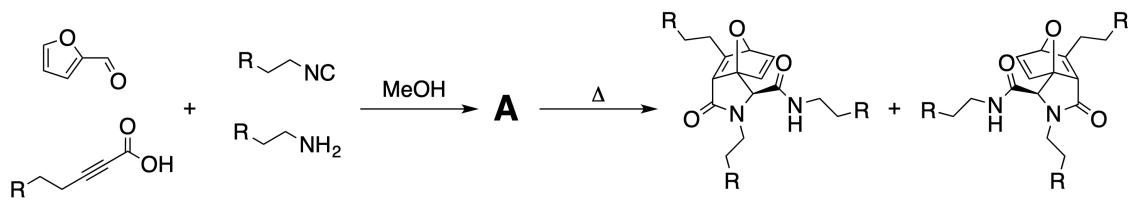


Figure 1.2: Johnson PSet 1, Q18.

- Altogether, the full solution to PSet 1, Q18 is on the next page.

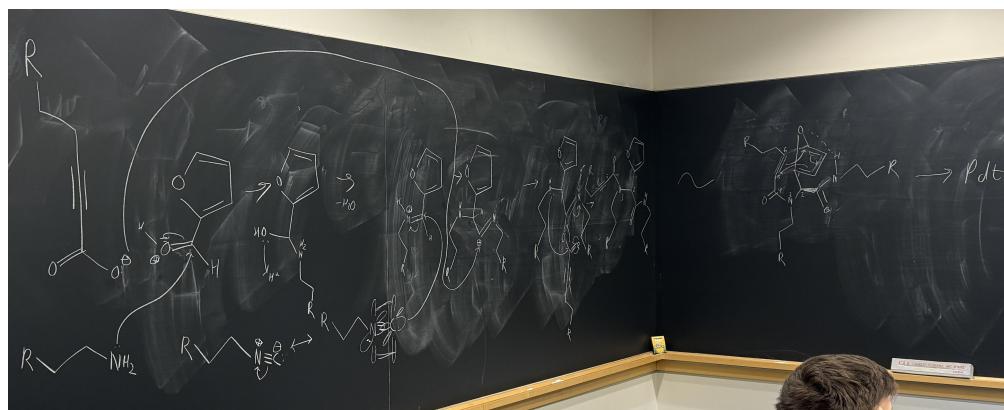


Figure 1.3: Johnson PSet 1, Q18 solution.

- We now begin discussing Problem 21.
- The first step is a **Fischer indole synthesis**.
- That's all we got to today.
- Jeremiah's list of named reactions.
 - 15: Benzoin condensation reaction.
 - 18: Ugi reaction followed by Diels-Alder.
 - 19: Inverse electron-demand Diels-Alder and another Diels-Alder.
 - 20: A Michael addition and Mannich reaction.
 - 22: A Dakin-West.
 - 21: Fischer indole synthesis.

References

King, G. R., Mander, L. N., Monck, N. J. T., Morris, J. C., & Zhang, H. (1997). A new and efficient strategy for the total synthesis of polycyclic diterpenoids: The preparation of gibberellins (\pm) -GA₁₀₃ and (\pm) -GA₇₃. *Journal of the American Chemical Society*, 119(16), 3828–3829. <https://doi.org/10.1021/ja963935h>