

# 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.

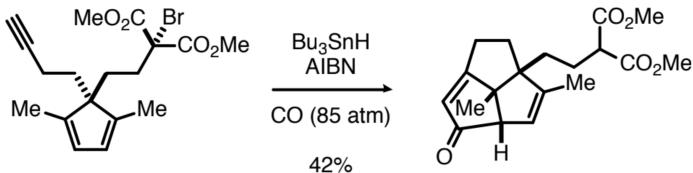
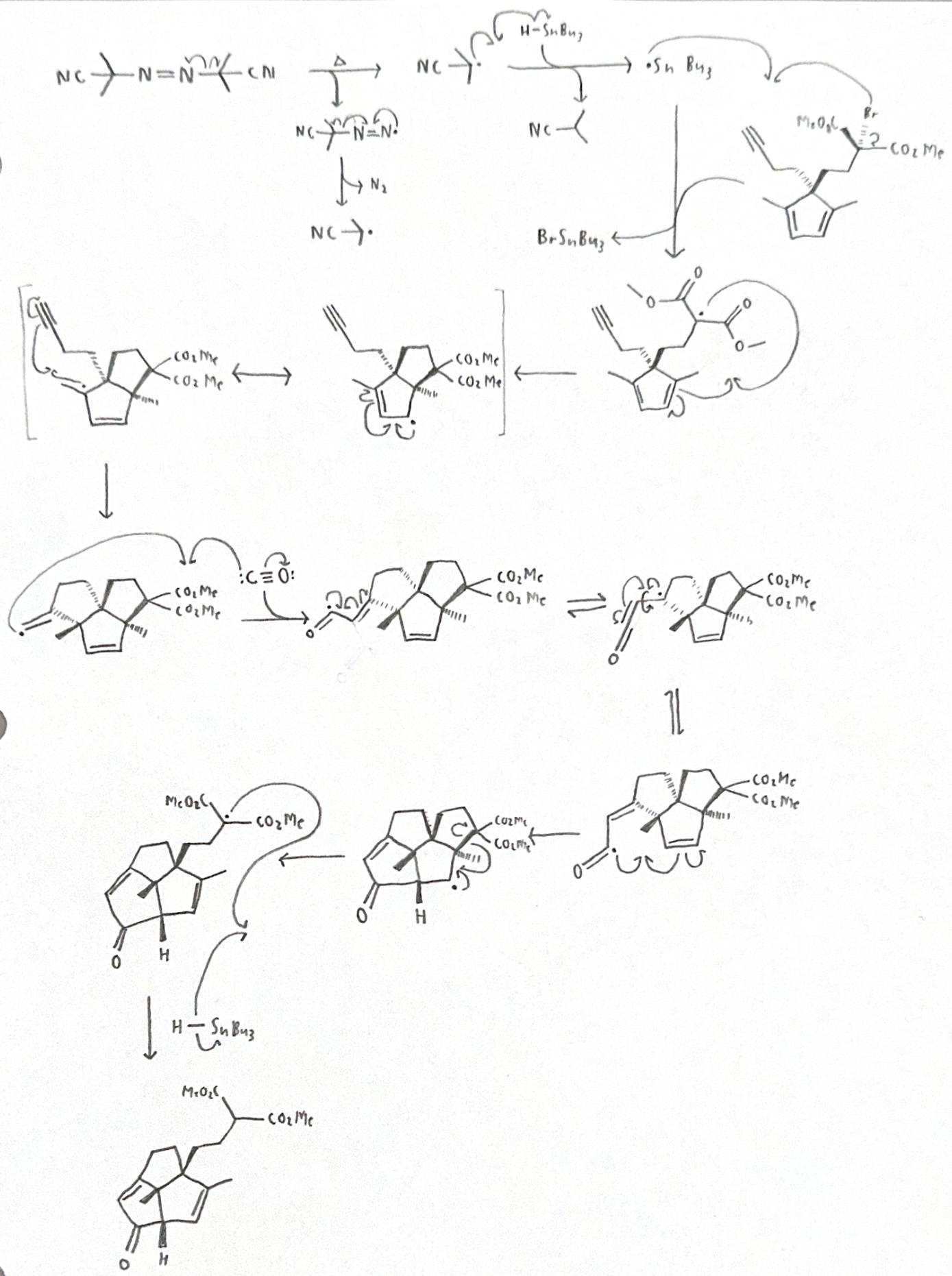


Figure 1.1: PSet 1, Q1.

- 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  $\sim 30$  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 N<sub>2</sub>.
- 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–SnBu<sub>3</sub> 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.
  - H<sub>3</sub>C–H is 100 kcal/mol.
  - HR<sub>2</sub>C–H is  $\sim 90$  kcal/mol.
  - Tributyl tin hydride BDE is a whopping  $\sim 73$  kcal/mol.
  - Know BDEs!! [Here](#)'s a great resource for C–H bonds on Wikipedia.
- The ·SnBu<sub>3</sub> 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–SnBu<sub>3</sub> 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*<sup>2</sup>, *sp*<sup>3</sup> — respectively).
  - Be able to switch fluently between p*K*<sub>a</sub>'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  $\sigma$ -bond is stronger than a C≡C  $\pi$ -bond.
  - Maxim: Whenever we have the opportunity to form a C–C  $\sigma$ -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.

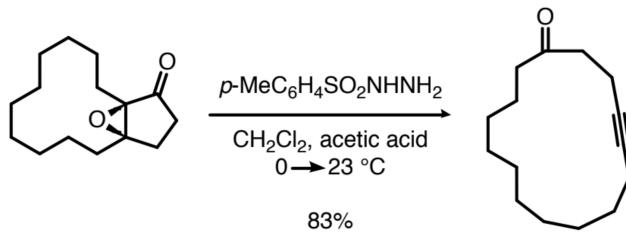
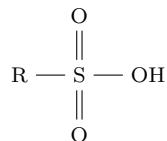
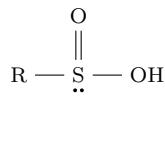


Figure 1.2: PSet 1, Q2.

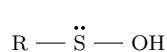
- Aside: The naming of the reagent.



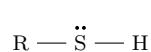
(a) Sulfonic acid.



(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  $\sigma^*$ -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.

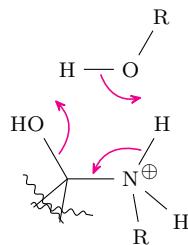
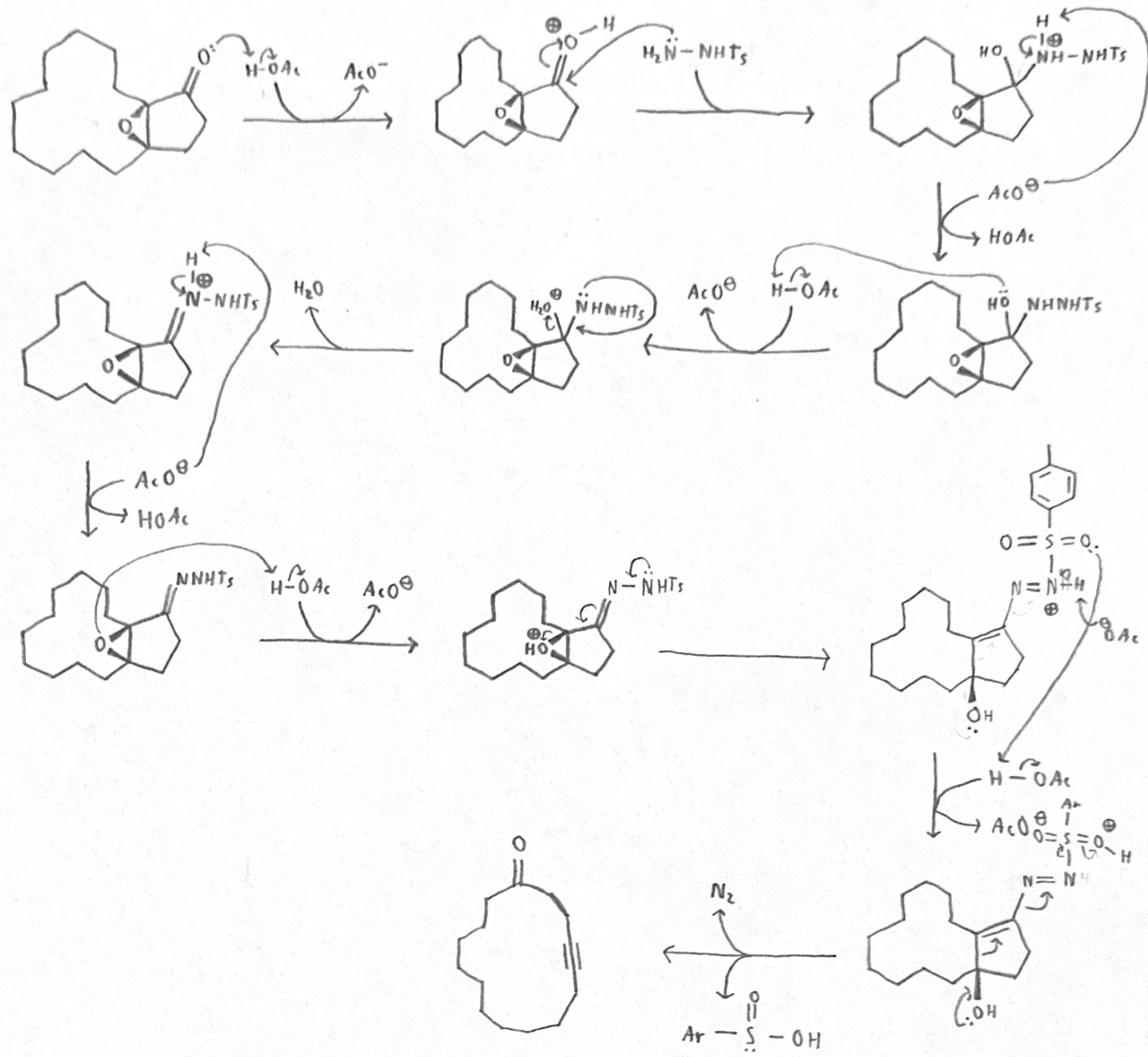


Figure 1.4: Using an acid as a proton transfer agent.

- 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  $5\text{ kcal/mol}$ .
- Altogether, the full solution to PSet 1, Q2 is on the next page.



- We now begin discussing Problem 6.

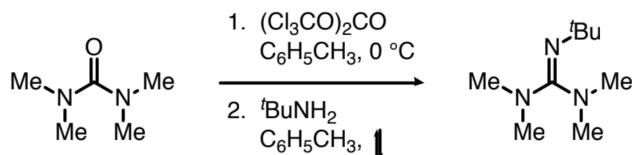
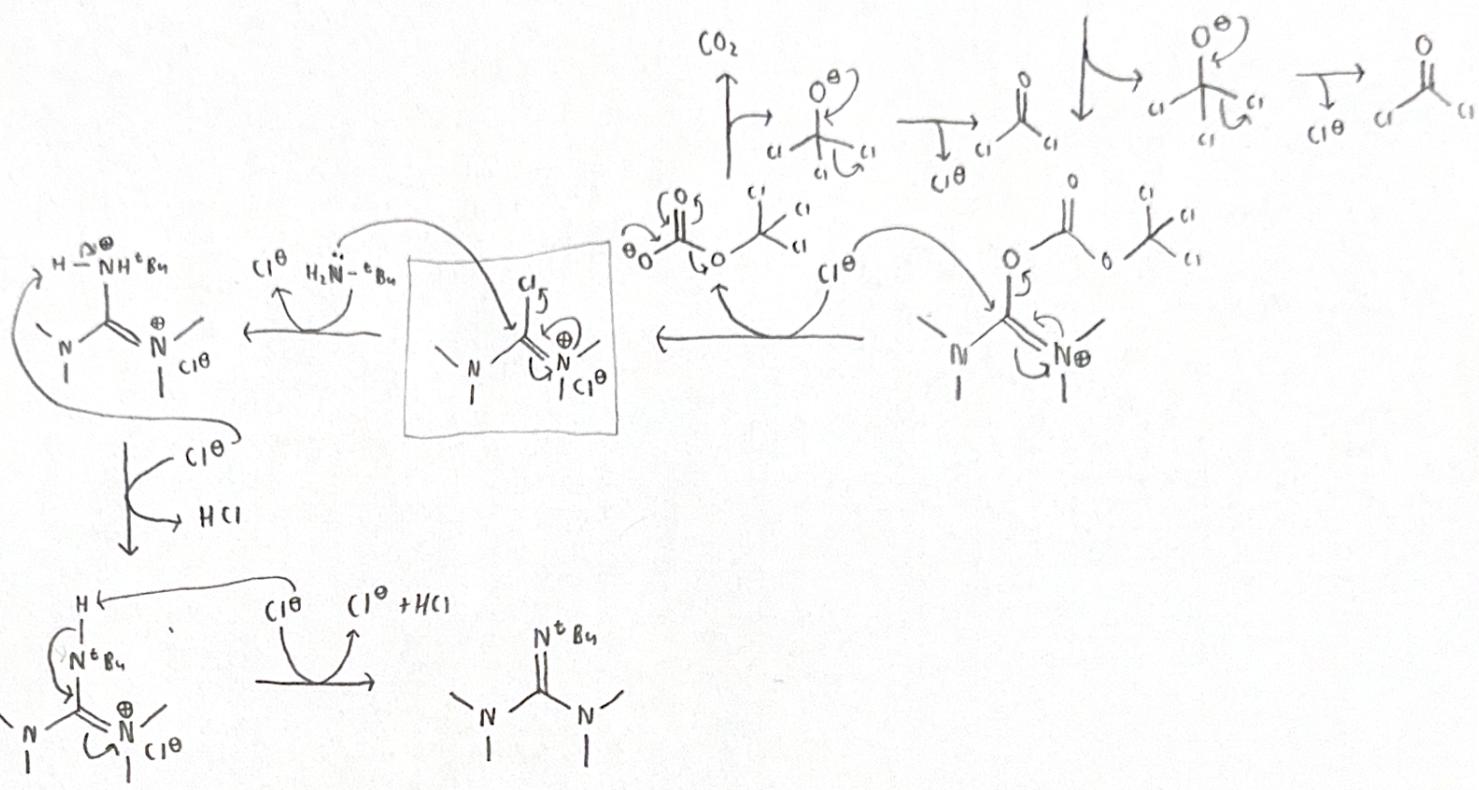
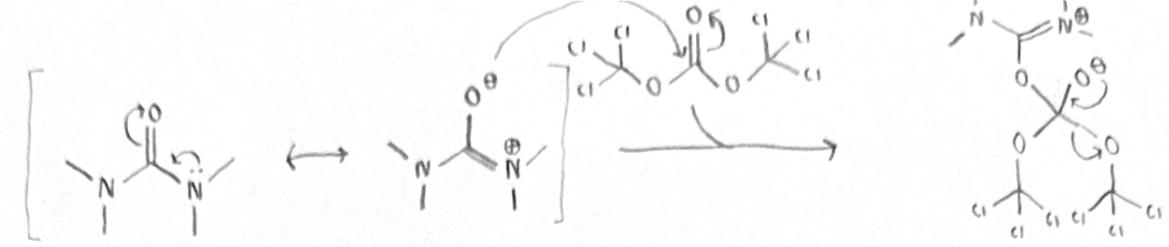


Figure 1.5: PSet 1, Q6.

- 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  $\alpha$ -elimination of one chlorine.
- Chloride then attacks the positive center, kicking electrons up and down and kicking out a leaving group.
- $\text{CO}_2$  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  $\text{CO}_2$ ; 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  $\text{HCl}$ .
  - 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  $\text{HCl}$ .
- 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.

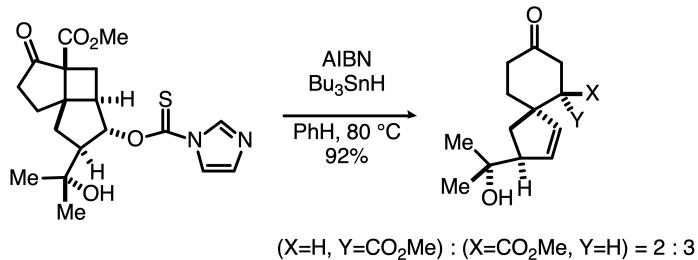
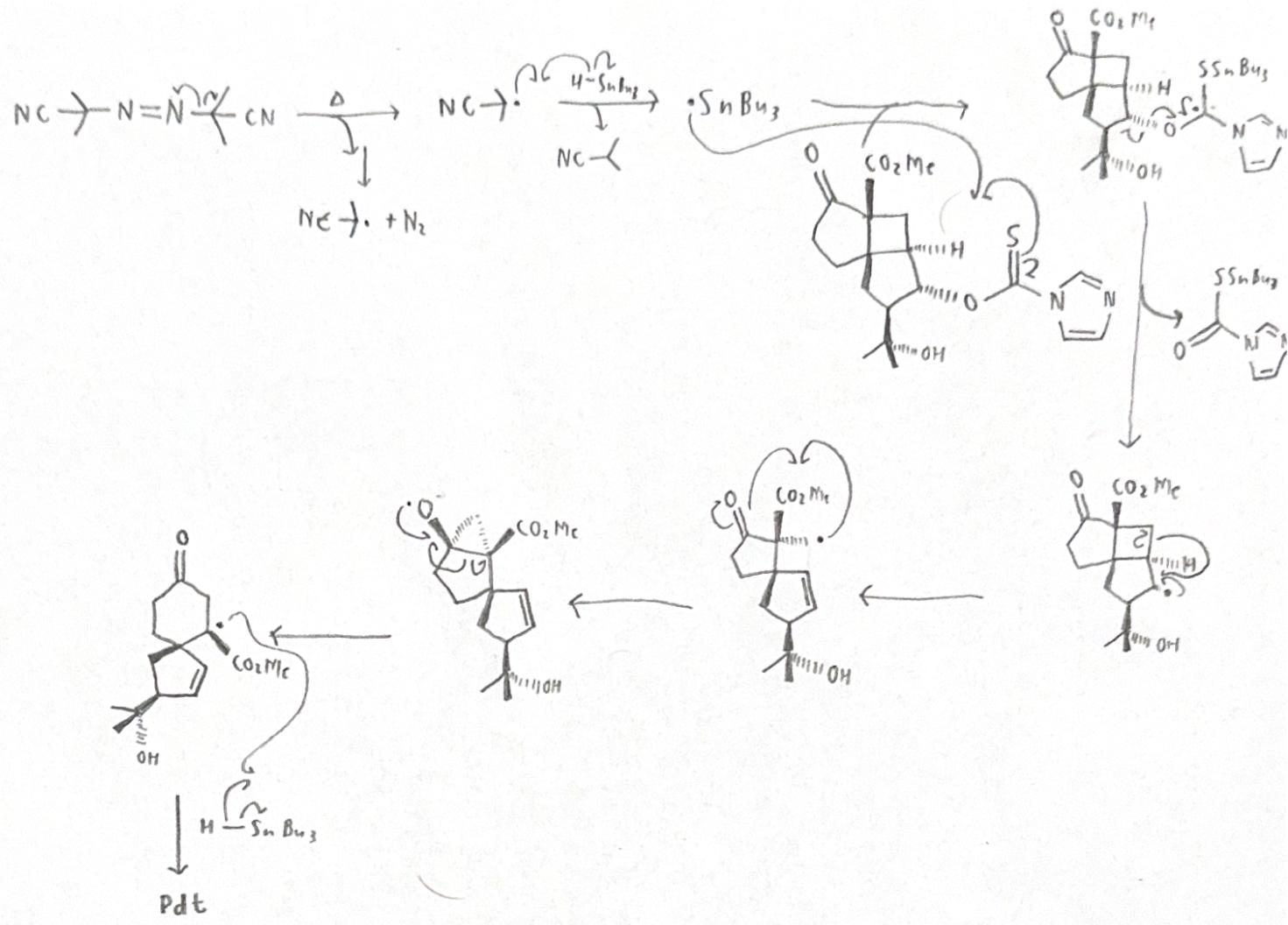


Figure 1.6: PSet 1, Q5.

- 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.<sup>[1]</sup> 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.

<sup>1</sup> 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  $\sigma$ -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  $\sigma^*$  orbital.
    - Adding into the C=O  $\pi$ -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  $\pi$ -bond for a C–C  $\sigma$ -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.

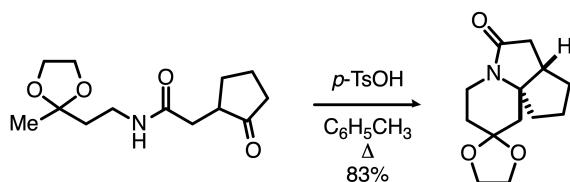


Figure 1.7: PSet 1, Q4.

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

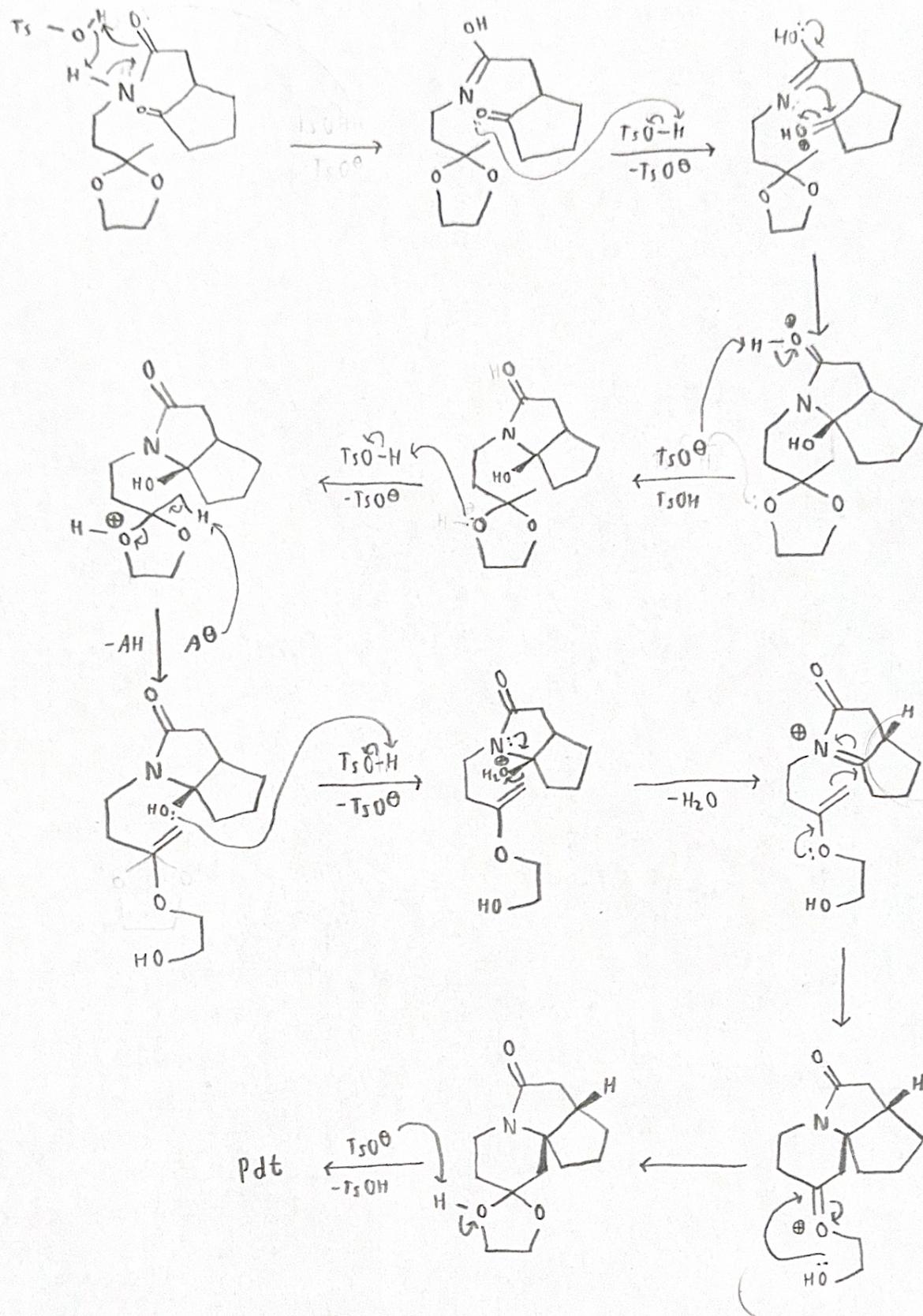
- There are five possible positions we could protonate, and four distinct types. Let's order them from least-likely to most-likely to be protonated.
    - Least likely: The amide nitrogen.
      - This nitrogen's lone pair is conjugated with the  $\text{C}=\text{O}$   $\pi$ -bond, and breaking this conjugation will take a ton of energy.
    - The ketone.
      - Recall that the  $\text{p}K_{\text{a}}$  of a protonated carbonyl is  $-6$  to  $-8$ .
    - Either of the ethers.
      - Recall that the  $\text{p}K_{\text{a}}$  of a protonated ether is  $-2$ .
    - The amide oxygen.
      - Recall that the  $\text{p}K_{\text{a}}$  of a protonated amide is  $0$ .
      - This is because the positive charge we create is resonance-stabilized by the  $\alpha$ -nitrogen.
  - Thus, while protonating the ketone would seem like a logical first step to accelerate nucleophilic addition, the  $\text{p}K_{\text{a}}$  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**<sup>[2]</sup> 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  $\alpha$ -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.

<sup>2</sup>Clear 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.<sup>[3]</sup>
- 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.

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<sup>3</sup>Is it not a 6-endo cyclization??



- We now begin discussing Problem 3.

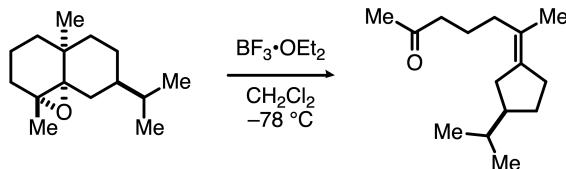


Figure 1.8: PSet 1, Q3.

- Looking at the reagents, observe that  $\text{BF}_3$  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  $\sigma$ -bond engages the C–O  $\sigma^*$ -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  $\sigma$ -bond.
- Altogether, the full solution to PSet 1, Q3 is on the next page.

