

Problem Set 3

Condensations

3.1 Problems 1, 4, and 8

- 9/16:
- David works with Rick Danheiser.
 - We now begin discussing Problem 1.

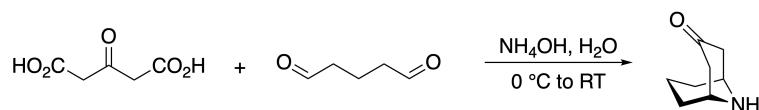


Figure 3.1: Wendlandt PSet 1, Q1.

- The reagents: NH₄OH in water is approximately pH = 11.
- Keto-enol tautomerization and amine condensation gets the carbons bonded in the right way.
 - Dialdehyde forms an imine.
 - The enol is not unreasonable because hydrogen bonding stabilizes a 6-membered ring.
 - Then the enol can be a H-bond acceptor from the other carboxylate.
- Watch out for reversible steps!!
- Loss of CO₂ helps drive some of the steps.
- There are multiple right answers; David's sequence of events works, but others could be valid, too.
- Aldehyde is more electrophilic than the monoprotonated imine, so if we're gonna react with an imine, we need to change both aldehydes into imines first. Alternatively, we need to diprotonate the imine.
- It's not clear whether decarboxylation happens earlier or later in the mechanism.
- Altogether, the full solution to PSet 1, Q1 is on the next page.

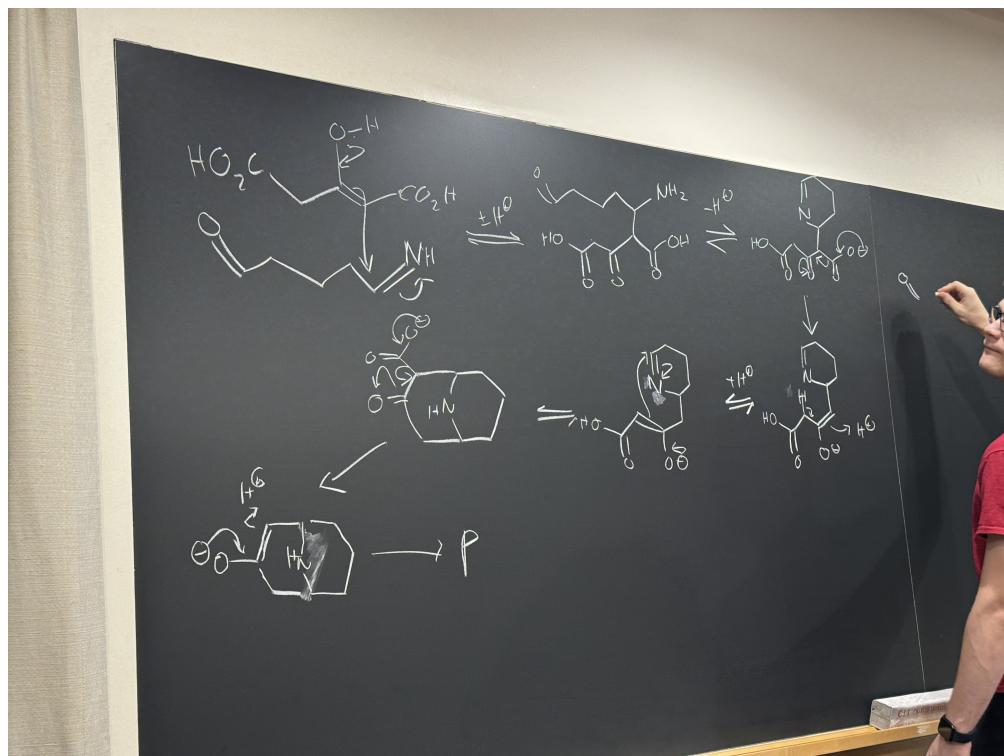


Figure 3.2: Wendlandt PSet 1, Q1 solution.

- We now begin discussing Problem 4.

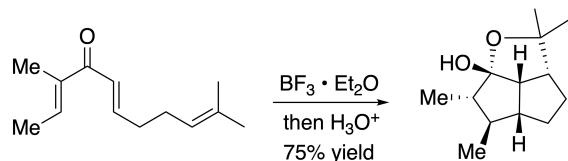


Figure 3.3: Wendlandt PSet 1, Q4.

- This is a **Nazarov reaction**, which is covered in Clayden.
- The initial electrocyclization is conrotatory; we need a continuous sequence of π -orbitals to get this.
- The Nazarov is a very powerful tool for making 5-membered rings, but the cation that it leaves oblates a ton of the stereochemical information.
- Torquoselective reaction:** ...
- Orbital analysis yields a structure with the stereochemistry that
- 5,5-trans ring fusions aren't known outside of very unique synthetic constructs. The difference in energy is a huge 5 kcal/mol to 7 kcal/mol.
- Scott Denmark has developed strong Lewis acid activation of strong Lewis bases.
 - Thus, from the perspective of both the activated Lewis base heteroatom and the perspective of the carbocation, this C–O bond-forming reaction should proceed before the acid workup.
- Whenever you see a cycloaddition, start thinking about the orbital structure of the HOMO and LUMO.
- Altogether, the full solution to PSet 1, Q4 is on the next page.

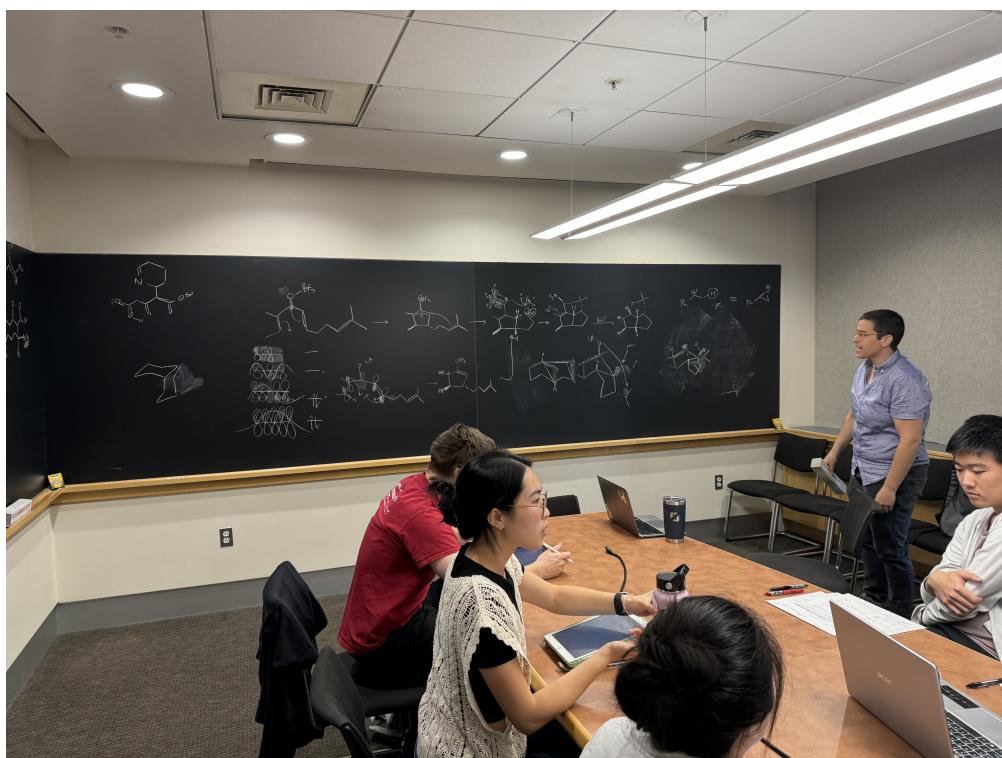


Figure 3.4: Wendlandt PSet 1, Q4 solution.

- We now begin discussing Problem 8.

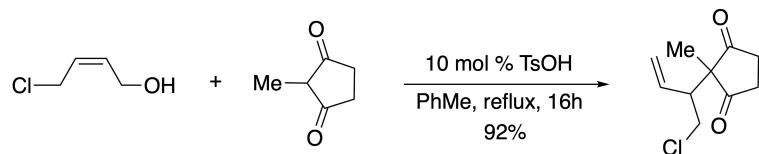


Figure 3.5: Wendlandt PSet 1, Q8.

- The thing I proposed is called an $\text{S}_{\text{N}}2'$ reaction, i.e., the attack of one species not on the leaving group but on the conjugated position a couple of carbons away.
 - My mechanism is *plausible* but not *defensible*.
 - The OH is not the most Lewis basic species in solution.
- Protonating a hemiacetal will be easier than Frank's proposition of protonating the alcohol.
 - Alison proposed 1,2-addition and 1,4-addition.
- We end with a **Claisen rearrangement**.
- You get a *stabilized* enol structure. Enol is better than enolate for acidic solution.
- You use the nucleophilic part to rearrange the electrophilic part.
- Altogether, the full solution to PSet 1, Q8 is on the next page.

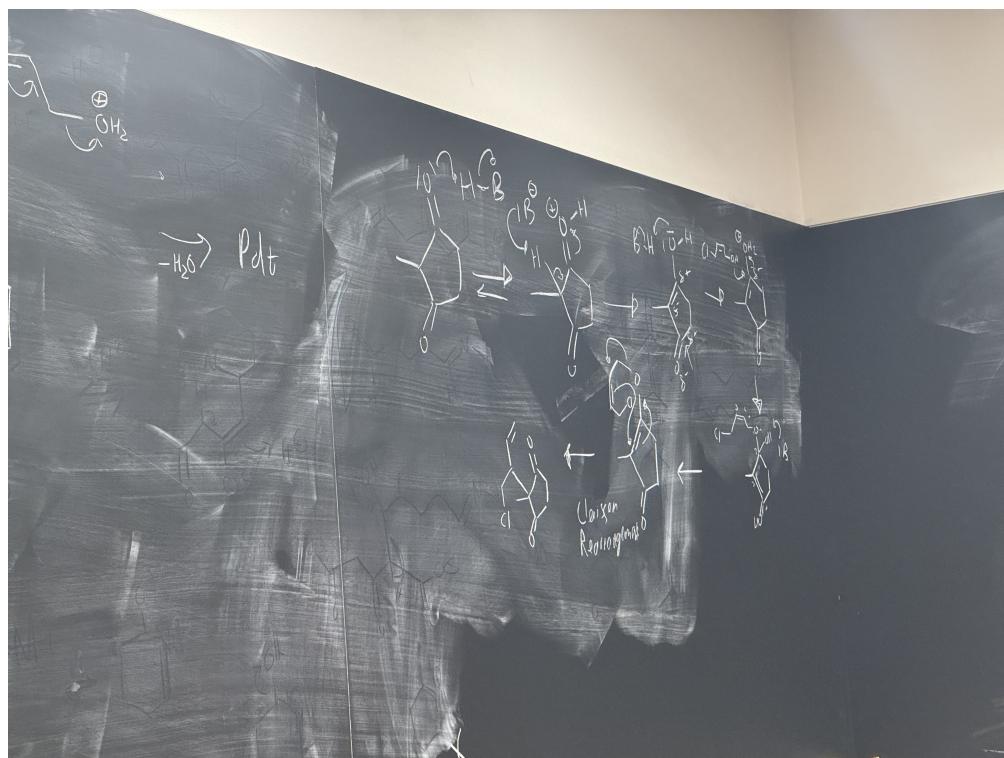


Figure 3.6: Wendlandt PSet 1, Q8 solution.

3.2 Problems 3, 5, 6, and 7

9/18: • Alison used to play ice hockey!

- We now begin discussing Problem 6.

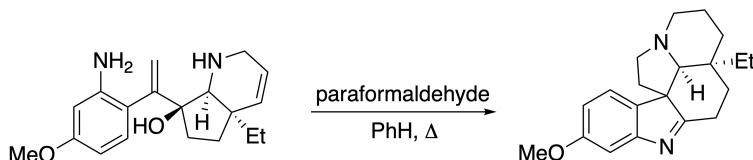
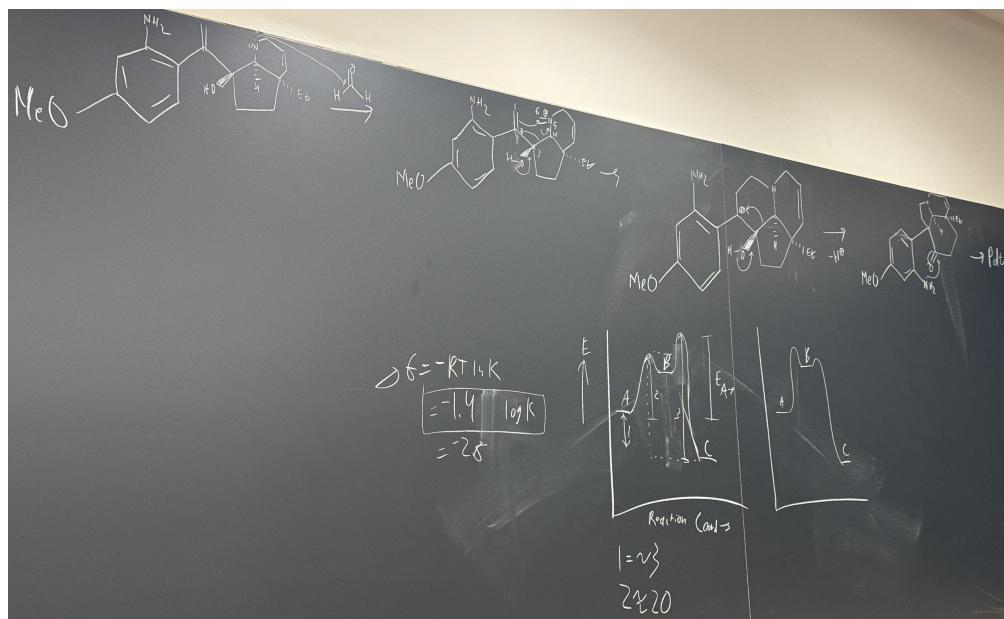


Figure 3.7: Wendlandt PSet 1, Q6.

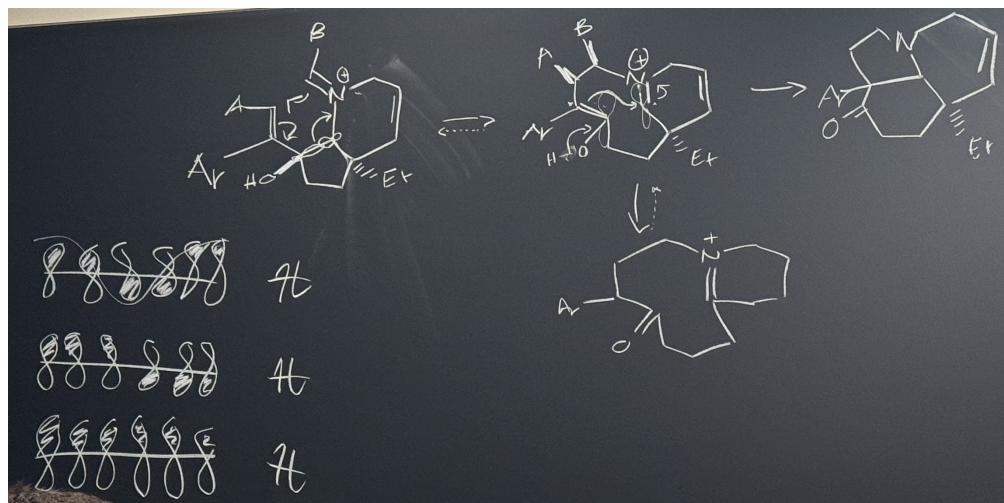
- I was the only person to have an idea for 6!
- There was a typo in the PSet.

- **Sigmatropic step.**

- The sp^3 hybrid orbitals become p 's. At some point in the transition state, they look p -like enough.
- It will be **conrotatory**, so fake substituents come out on the same side.
- Don't remember the rules; just draw the orbitals and figure it out.
- David's pneumonic: 64 disco: 6 disrotatory, 4 conrotatory. Then for light, you just reverse it.
- Does everything happen very quickly, or do things pull apart first and we tautomerize to a ketone before we go back to an enol and react.
- Nonpolar solvent and high temperature often implies pericyclic reaction!
- Where are acids and bases coming from? The molecule itself? How does the condensation occur?
 - Protonated piperidine: $pK_a = 10$.
 - Protonated aniline: $pK_a = 8$.
 - Learn the [Evans](#) pK_a table!!
 - The aniline probably forms the iminium with the formaldehyde, and that's just reversible until we can do the entropically favorable step.
- Altogether, the full solution to PSet 1, Q6 is on the next page.



(a) My proposition.



(b) Sigmatropic correction.

Figure 3.8: Wendlandt PSet 1, Q6 solution.

- We now begin discussing Problem 7.

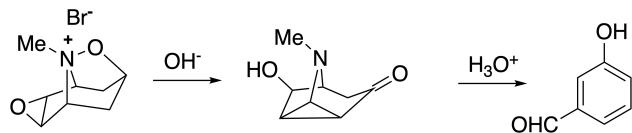


Figure 3.9: Wendlandt PSet 1, Q7.

- Somebody prepared a beautiful molecule, and then it just decomposed into this basic AF benzaldehyde derivative.
- This is probably a classic case of working in a lab, finding the decomposition product, going back to your PI, and then having to resort to arrow pushing to figure out what happened.
- The first step is helped by an antiperiplanar arrangement and the fact that the iminium wants its electron pair back.
- Altogether, the full solution to PSet 1, 7 is on the next page.

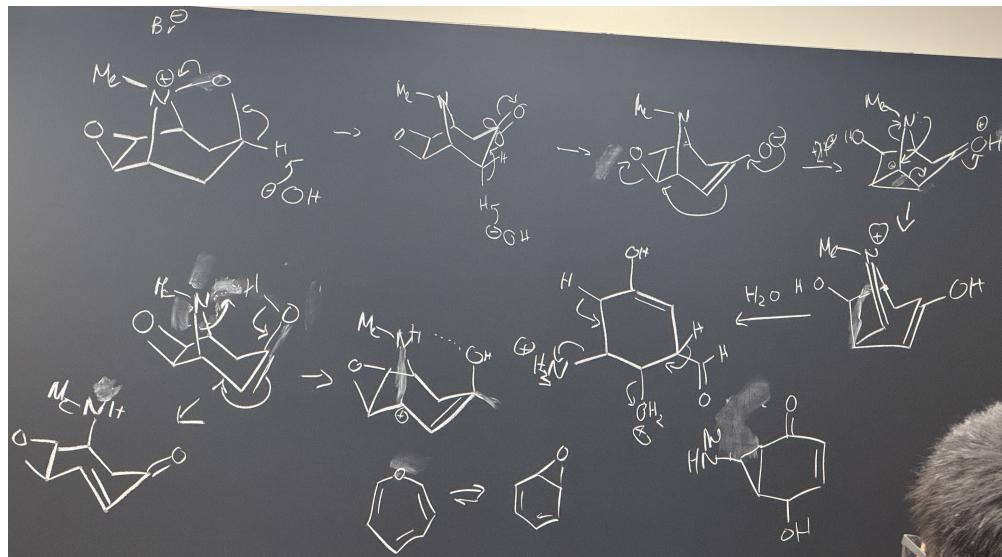


Figure 3.10: Wendlandt PSet 1, Q7 solution.

- We now begin discussing Problem 5.

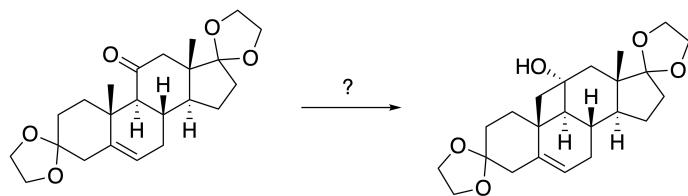


Figure 3.11: Wendlandt PSet 1, Q5.

- Noorish 2 reaction.**

- Why is O· less stable than C·?
- Bond dissociation energies.
 - 10 kcal/mol driving force to form O–H and break C–H.
 - 50 kcal/mol favorability for deprotonating isopropanol at the alcohol vs. the methine C–H.
 - Derived by 35-fold difference in pK_a , so $\Delta G = -1.4 \log(10^{35}) \approx 50$.
- Altogether, the full solution to PSet 1, Q5 is on the next page.

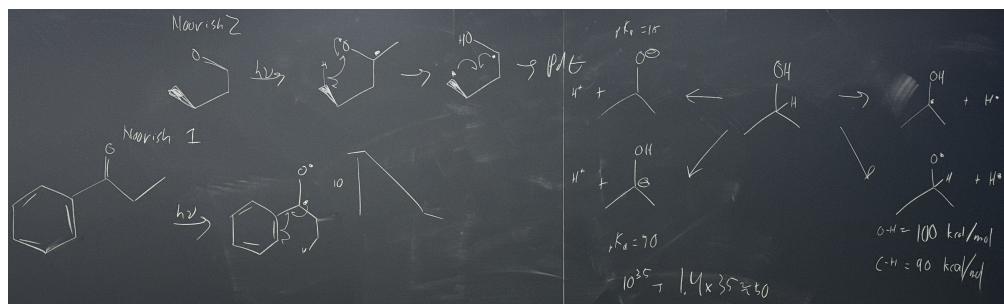


Figure 3.12: Wendlandt PSet 1, Q5 solution.

- We now begin discussing Problem 3.

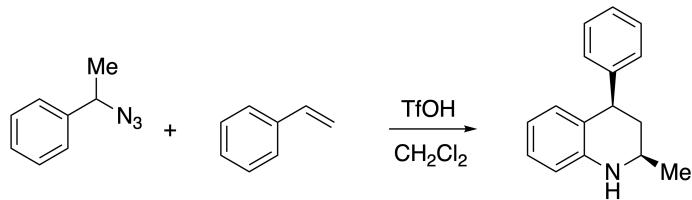


Figure 3.13: Wendlandt PSet 1, Q3.

- This reaction has a name, per Alison.
- When can C–C bonds migrate?
- The second resonance structure explains why you protonate the internal nitrogen instead of the terminal one.
- The second step is α -elimination; electrons flow from the atom to itself.
- Aside: Drawing an unprotonated **nitrene** (nitrogen analogue of a carbene).

 - Nitrenes are electrophiles because they have one lone pair and two unpaired electrons.
 - Nitrenes are sp^2 -hybridized; we know this because ??.

 - We'll cover this next time.
 - 3 vs. 2 regions of electron density?

 - Lone pair in both sp^2 orbitals, vs. lone pair in one sp -orbital and two single electrons in orthogonal p orbitals. Singlet vs. triplet nitrene.
 - Triplet nitrene is low energy per Hund's rule; singlet nitrene is higher energy.
 - Orbital mixing in singlet vs. triplet states. Draw an MO diagram! Next time, we'll build MOs from the ground up for nitrene.

- Altogether, the full solution to PSet 1, Q3 is on the next page.

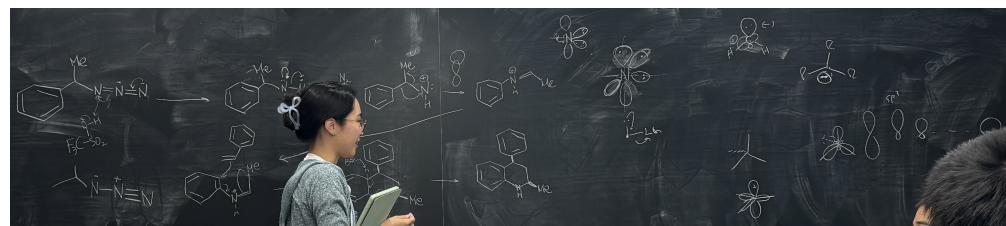


Figure 3.14: Wendlandt PSet 1, Q3 solution.

- Alison will send out PSet 2 over the weekend.