

Problem Set 1

Condensations

1.1 Problems 1, 4, and 8

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

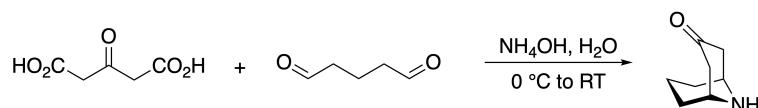


Figure 1.1: Wendlandt PSet 1, Q1.

- 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.

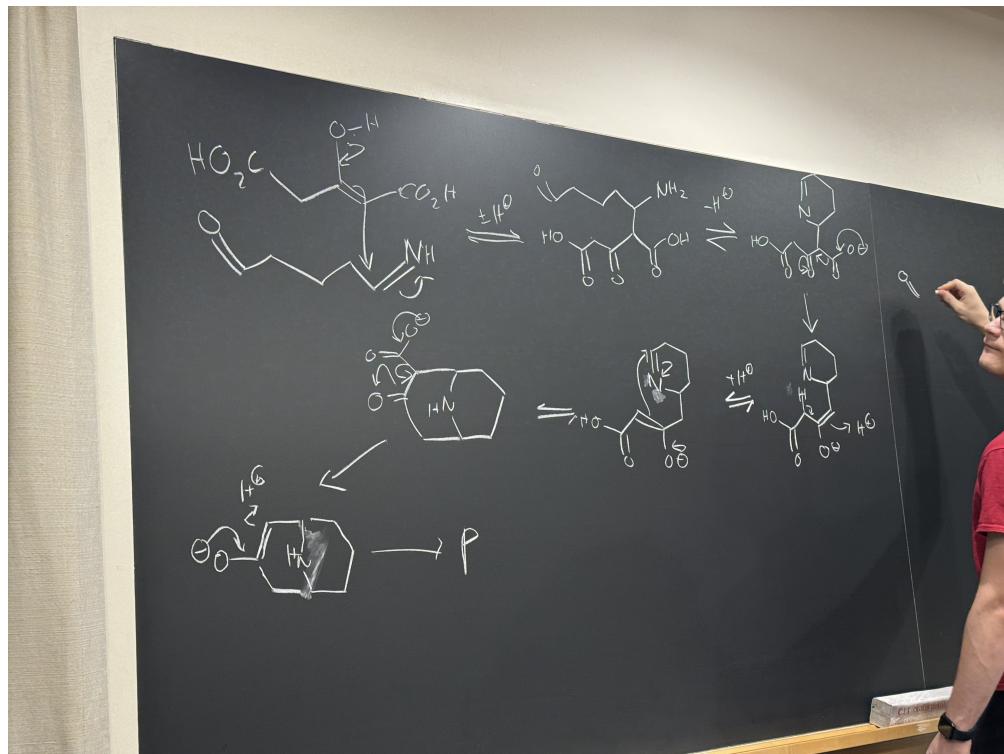


Figure 1.2: Wendlandt PSet 1, Q1 solution.

- We now begin discussing Problem 4.

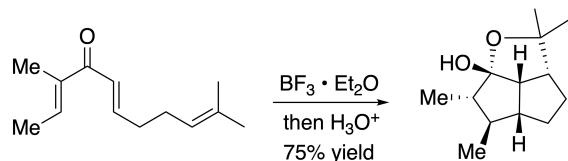


Figure 1.3: Wendlandt PSet 1, Q4.

- 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.

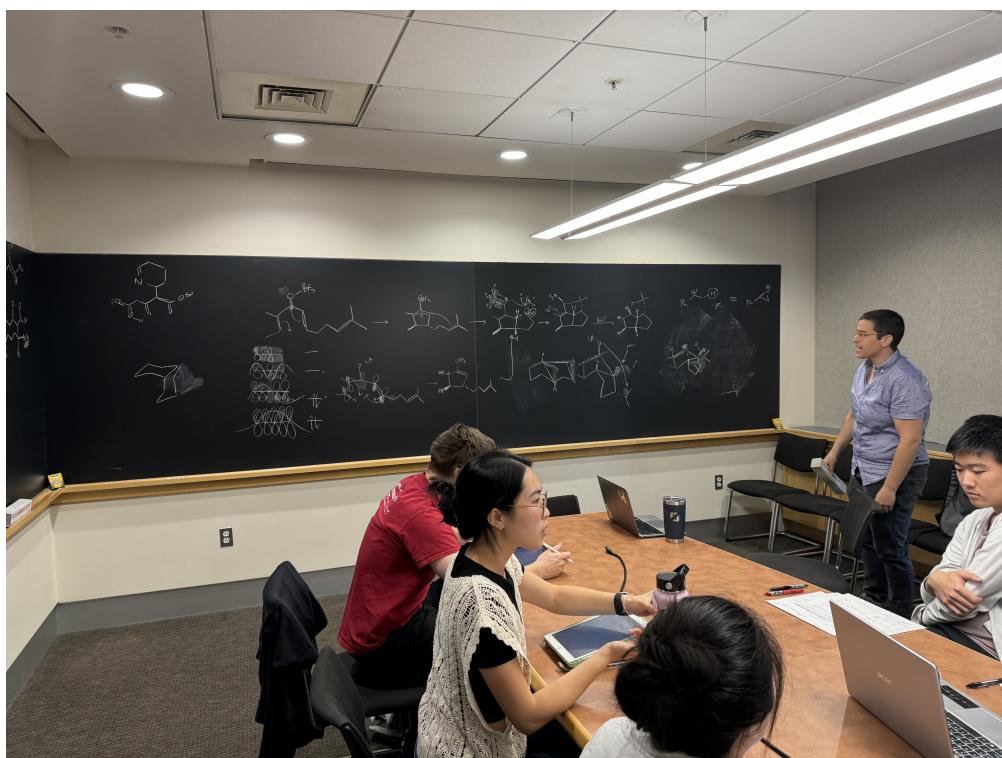


Figure 1.4: Wendlandt PSet 1, Q4 solution.

- We now begin discussing Problem 8.

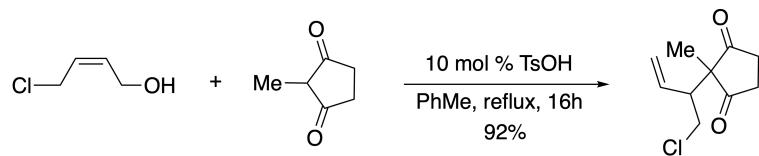


Figure 1.5: Wendlandt PSet 1, Q8.

- 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.

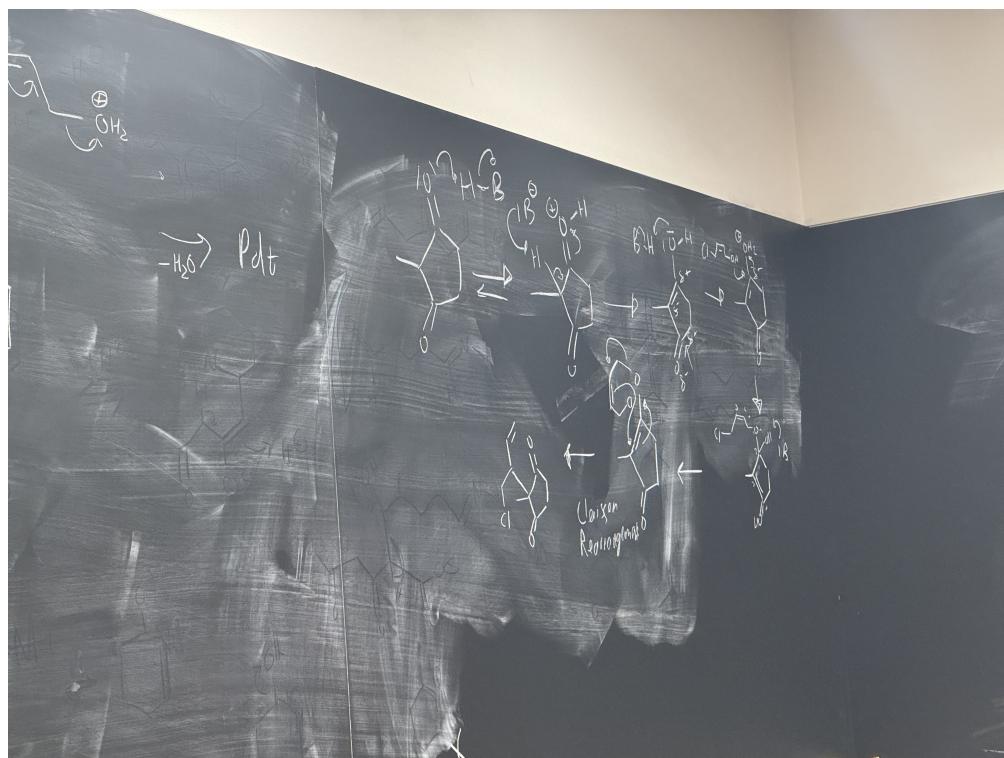


Figure 1.6: Wendlandt PSet 1, Q8 solution.

1.2 Problems 3, 5, 6, and 7

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

- We now begin discussing Problem 6.

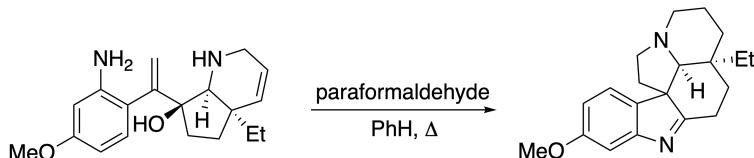
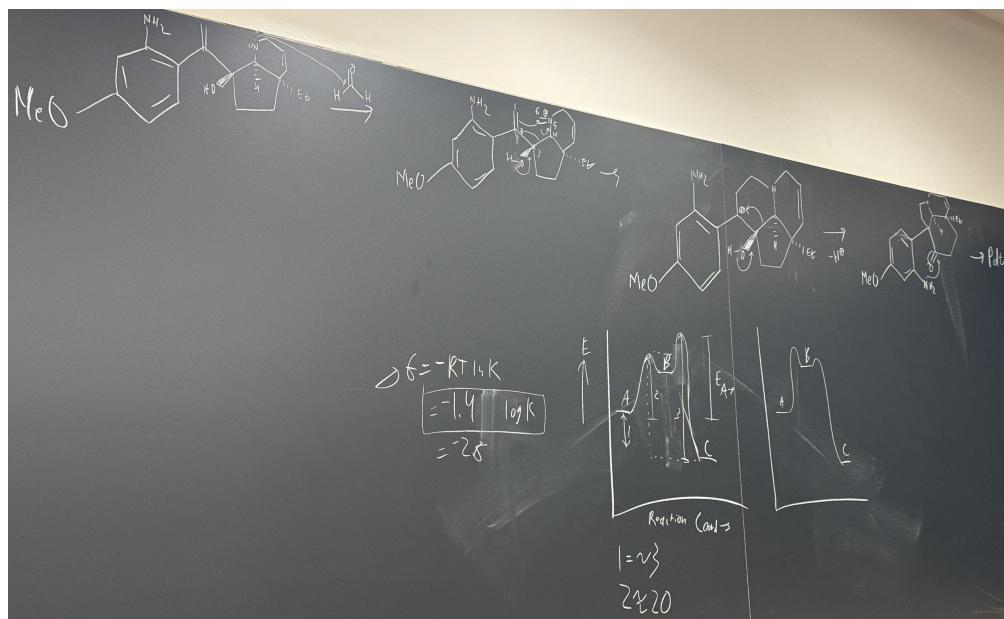


Figure 1.7: Wendlandt PSet 1, Q6.

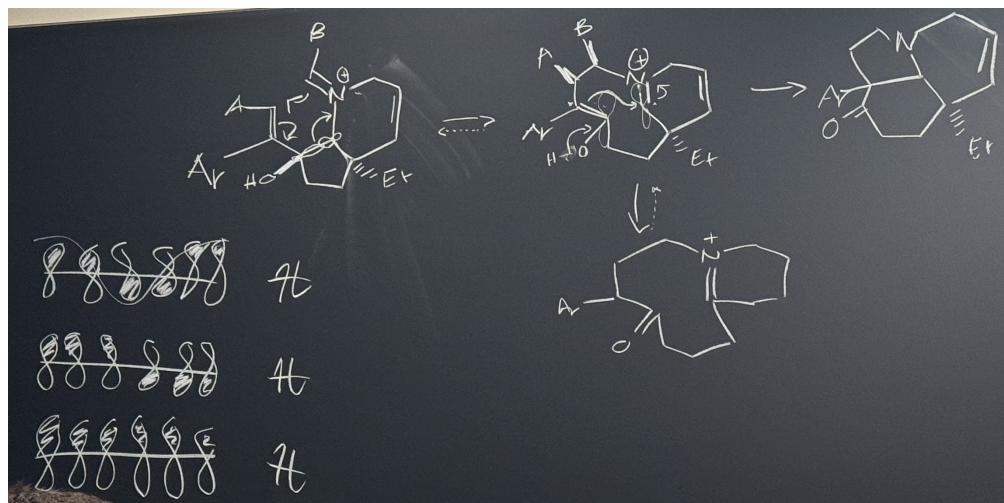
- I was the only person to have an idea for 6!
- There was a typo in the PSet.

- **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 1.8: Wendlandt PSet 1, Q6 solution.

- We now begin discussing Problem 7.

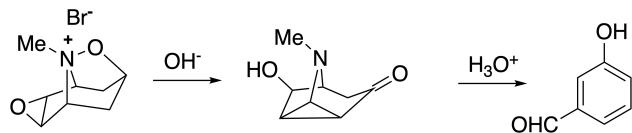


Figure 1.9: Wendlandt PSet 1, Q7.

- 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.

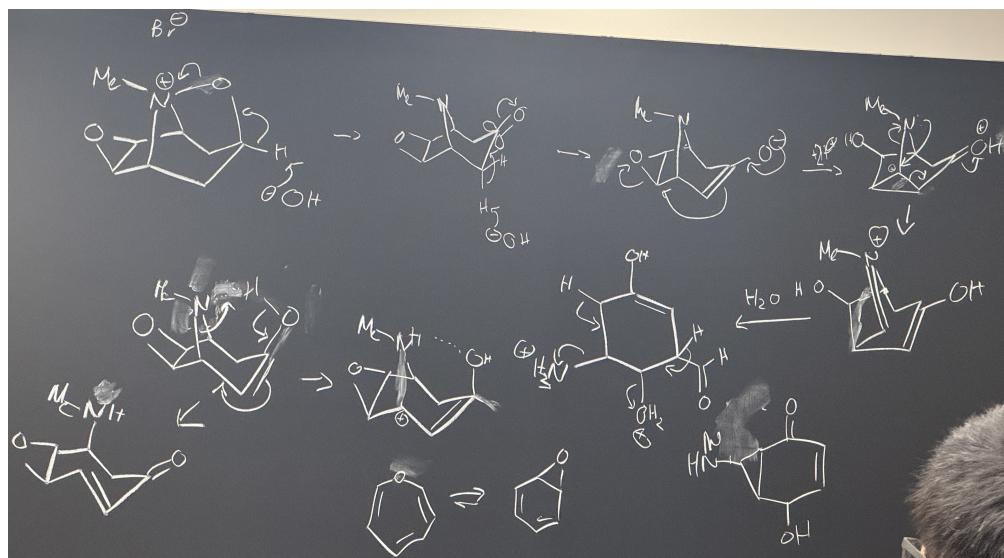


Figure 1.10: Wendlandt PSet 1, Q7 solution.

- We now begin discussing Problem 5.

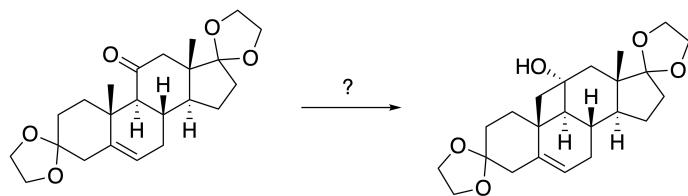


Figure 1.11: Wendlandt PSet 1, Q5.

- 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.

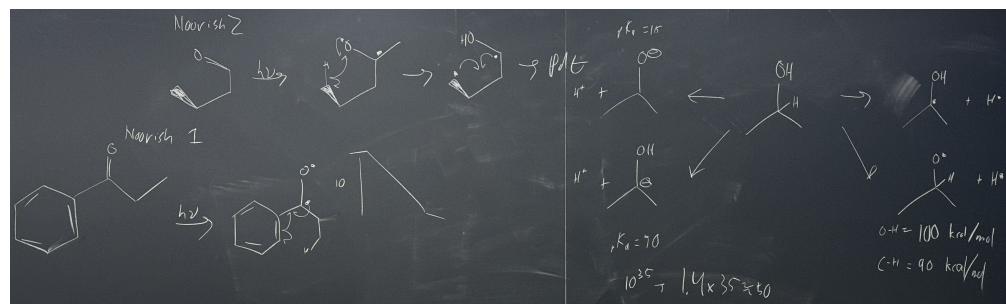


Figure 1.12: Wendlandt PSet 1, Q5 solution.

- We now begin discussing Problem 3.

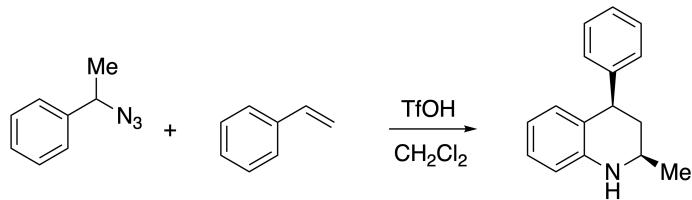


Figure 1.13: Wendlandt PSet 1, Q3.

- 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.

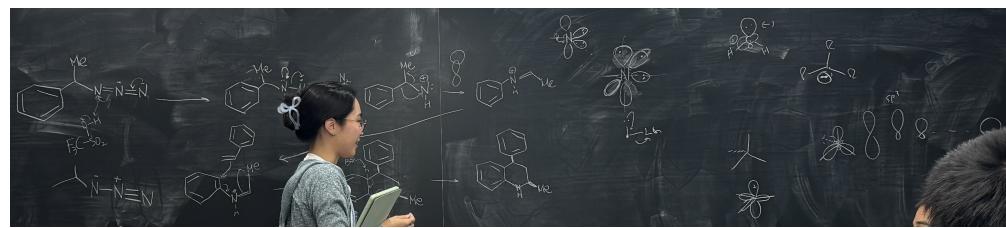


Figure 1.14: Wendlandt PSet 1, Q3 solution.

- Alison will send out PSet 2 over the weekend.

1.3 Problems 9 and 10

9/23: • PSet 2, Q1: Great place to use molecular model kits.

- We now begin discussing Problem 10.

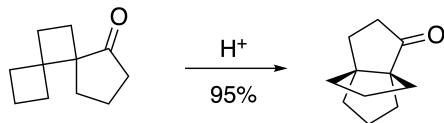


Figure 1.15: Wendlandt PSet 1, Q10.

- The final product molecule is called a **propellane** (or something like that; like a propeller).
- The first step is reversible.
 - Alison asks about the pK_a of a protonated carbonyl again.
- What would be a good acid to use?
 - An acid stronger than the pK_a of a protonated carbonyl would be great, but we don't have many of them.
 - Perhaps TsOH??
 - $pK_a = -\log K_a$.
 - Recall also $\Delta G = -RT \ln K_{eq} \approx -1.4 \log K_{eq}$.
 - Note that for a kinetically efficient process, we might not need much acid at all!
- Alison has Christina draw an energy diagram again.
- An analysis of which steps are reversible: The ones with small differences in ring strain.
 - So the product-selective steps are a bit tricky to figure out.
- The resonance-stabilized carbocation is ?? times more stable than the tertiary carbocation, which is inductively stabilized via hyperconjugation.
 - Alison has Christina draw an MO picture of hyperconjugation.
 - **Mayr electrophilicity scale**.
- Procedure for this problem.
 - Get all the connections right.
 - Think about the energy surface we're operating on (thermoneutral, downhill, uphill).
 - This should give us reversibility/irreversibility.
- Steven: It's easier to migrate a bond through-bond than through space.
 - We never have a pure, unfilled p -orbital.
 - Rather, we always have the “partial double bond” that is hyperconjugation.
 - The carbocation changes the behavior of the entire molecule, leaning bonds in.
 - This becomes a transition state structure for the hydride shift!

- TS is a 3c-2e transition state structure. This is a **nonclassical** carbocation that's much more realistic; we'll see this in 5.53. Indeed, we should *not* think of carbocations as localized but very much as delocalized regions of positive charge in the local chemical environment.
- “In the right molecule, anything can happen.” But through-space stabilization of a carbocation is much harder.
- Steven: Is there a such thing as a hydroxide shift?
 - We can't really do that in one step... but we can do it through an epoxide formation and subsequent ring opening!
- David: Is there a preference for a hydride shift or a methyl shift?
 - In both cases, we'll make the same tertiary carbocation.
 - We need to think about both sterics and electronics.
 - Electronically, C–C bonds are more electron-rich.
 - But a methyl group is also bulkier.
 - Thus, all else being equal (as in the example), both shifts are reasonable.
- This reaction is 95% yield due to the thermodynamic driving force, but a lot of energy went into making the initial high-energy structure.
- Terpene cyclizations are very hard to do without enzymes, because we have a big endergonic step to start and then lots of little downhill steps.
- Frank: With respect to the acid, ...
 - Cross-coupling pre-Buchwald ligands buys you out of a low-energy, pre-equilibrium state.
- Altogether, the full solution to PSet 1, Q10 is on the next page.

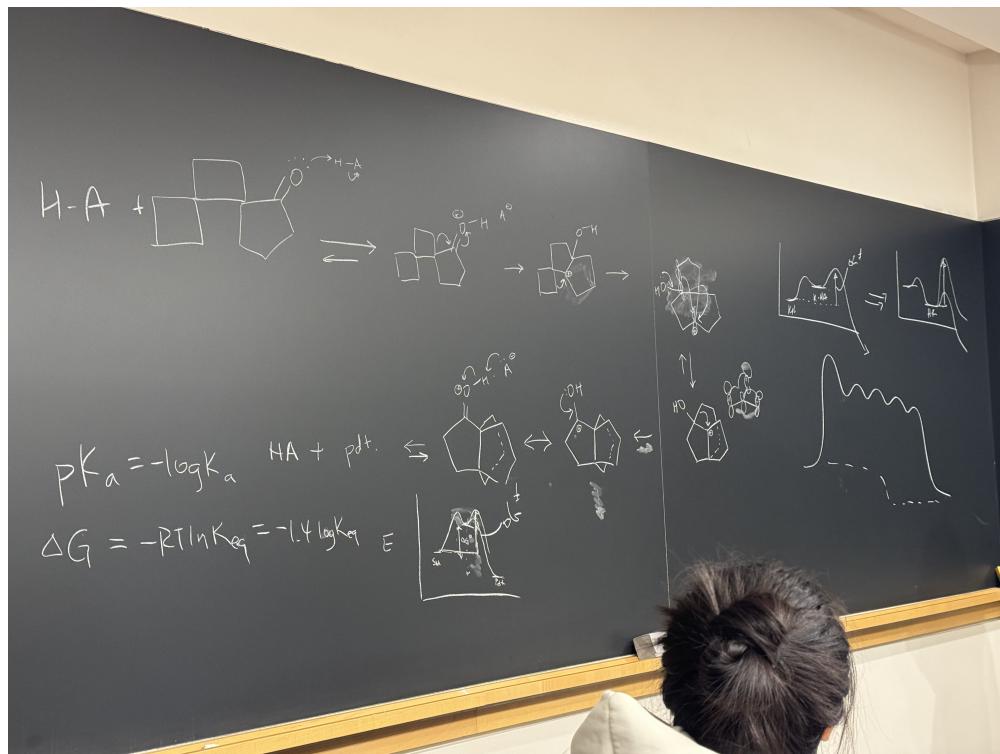


Figure 1.16: Wendlandt PSet 1, Q10 solution.

- We now begin discussing Problem 9.

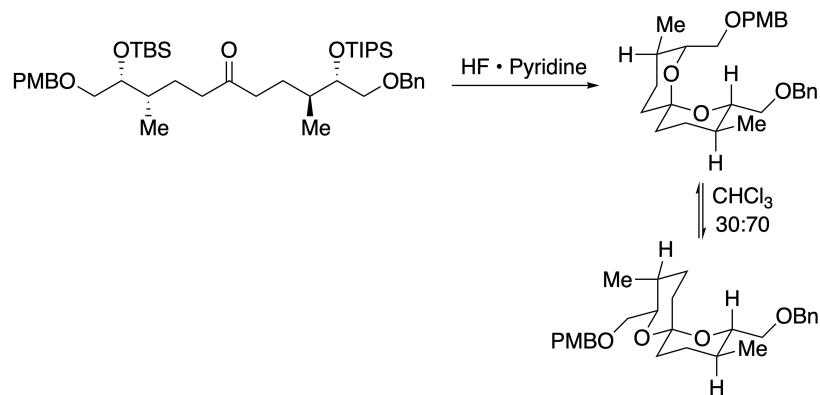


Figure 1.17: Wendlandt PSet 1, Q9.

- First step is deprotection: We lose TBS before we'll lose TIPS. Here's why.
- Consider some common protecting groups: **TMS**, **TES**, **TBS**, **TIPS**, and **TBDPS**.

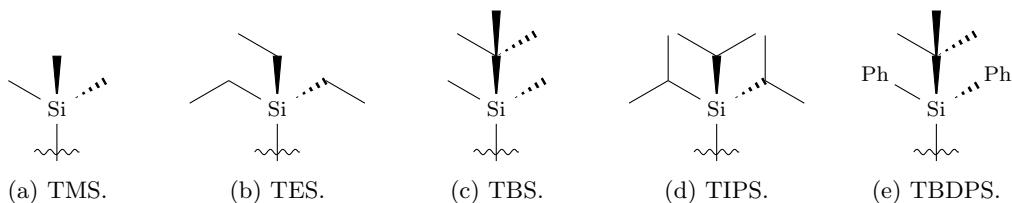


Figure 1.18: Silyl protecting groups.

- Trimethylsilane.** Denoted by **TMS**. Given by Figure 1.18a.
- Triethylsilane.** Denoted by **TES**. Given by Figure 1.18b.
- ^tButyldimethylsilane.** Denoted by **TBS**. Given by Figure 1.18c.
- Triisopropylsilane.** Denoted by **TIPS**. Given by Figure 1.18d.
- ^tButyldiphenylsilane.** Denoted by **TBDPS**. Given by Figure 1.18e.
- Relative stability against hydrolysis in acidic media.
 - TMS : TES : TBS : TIPS : TBDPS is 1 : 64 : 2000 : 700 000 : 5 000 000.
- TBDPS was developed for carbohydrate chemistry, because they needed something that wouldn't fall off!
- We get to the product as expected.
- Now let's rationalize the ratio.
 - The second product is doubly anomeric.
 - Substituents want to be equatorial, as well.
 - With axial OPMB, two H's point right at each other. And they are locked into space this way due to the *spiro-ketal*.
 - We also have to consider solvent effects.

- CHCl₃ has a relatively high **dielectric** (~ 4), and hence is relatively nonpolar.
- Look up the **dielectric effect** in chemistry!!
- Solvent dipole and molecular dipole matters in PSet 2, Q1, too!
- Indeed, chloroform is a polar molecule but a nonpolar *solvent* because it is not miscible with water and has a low dielectric constant. However, it is polar compared to many other organic solvents!
- Sterics only becomes a problem when things are “literally right on top of each other.” *picture; H₂ PE surface.*
- Bond angles matter more in most molecules!
- You get a lot more out of bringing things close together until you *really* pay.
- Takeaway: Bringing two things together is very often stabilizing (dipolar/quadrupolar interactions, LDFs, etc.). We generally get this wrong.
- Altogether, the full solution to PSet 1, Q9 is on the next page.



Figure 1.19: Wendlandt PSet 1, Q9 solution.

- We now pick up last time's discussion on nitrenes, from Problem 3 (Figure 1.13).
- **Povarov reaction.**
- Think about arrow pushing in terms of which electrons are moving from which orbital to which other orbital.
 - In the rearrangement step, electrons leave from the Ar–C bond and go into the nitrogen's empty, positively charged *p*-orbital.
 - They don't go into the N–H σ^* orbital because that kind of S_N2 attack would kick out H⁻.
 - There's also another option we can rule out.
 - Then electrons leave from the nitrogen lone pair and move into a new π -bond.
- Why does the aryl group migrate instead of the methyl group?
 - Because it forms a resonance-stabilized carbocation??
 - Specifically, we get a **phenonium ion** that stabilizes the positive charge through delocalization.
- Alison “numbers the shit” out of structures she's working on; there's no shame in it.
- Jasmin *really* can't think on her feet.
- [4 + 2] cycloaddition in the end.
- Aside: Suffixes.
 - Three examples.
 - -ium: Cation.
 - -yl: Radical.
 - -ide: Anion.
 - So “phenyl” technically means the phenyl radial.
 - This also explains the difference between “hydroxyl” and “hydroxide”

1.4 Problem 2

9/25:

- Starting with Jasmin's azide one again.
- Normal vs. **inverse electron-demand Diels-Alder**.
 - This reaction is an inverse electron-demand Diels-Alder because the HOMO of the diene is so stabilized that the electrons from the dienophile HOMO will donate into the LUMO of the diene.
 - The diene HOMO is dropped so much because of the electron withdrawing nitrogen in the conjugated system.
 - The dienophile is electron rich because it's styrene, and that's pretty electron rich.
- A concerted Diels-Alder would break aromaticity, and you'd have steric clash to the desired product, so perhaps that's disfavored. Though, I think Alison's DA stereochemistry might be backwards...
- **Twist-boat** (transition state diagram): ??
- DA regiochemistry is defined by the **orbital coefficient**, i.e., the δ^+ and δ^- .
- To a first approximation, a reasonably stable cation followed by a Friedel-Crafts type end to aromaticity is probably more defensible than a DA that breaks aromaticity.
- We now begin discussing Problem 2.

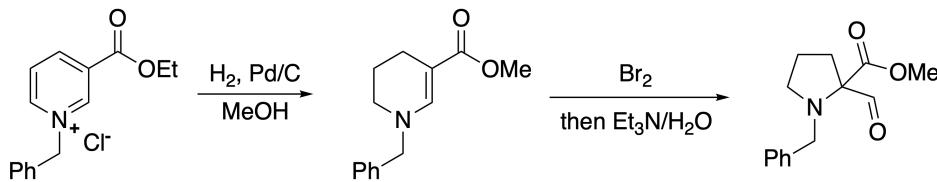


Figure 1.20: Wendlandt PSet 1, Q2.

- First step: The hydrogenation.
 - It's not that you have insufficient kinetic access to reduce the product; it's that you have a very deactivated pyridinium, and the product is actually more stable since it's so highly conjugated.
 - The pyridinium is **cross-conjugated**, as well.
 - We'll also have transesterification.
- The product is a racemate, so we can track stereochemistry through the mechanism but assign it arbitrarily. In other words, just be consistent, and then understand that the product will contain both enantiomers.
- Bromonium ion is broken by the lone pair from the nearby nitrogen. Then water adds in to form the hemiaminal.
- Hydrolysis of the hemiaminal yields the aldehyde.
- Then an S_N2 or S_N1 attack can close the 5-membered ring.
 - Alternatively, consider an intramolecular, through-bond C–N migration.
 - Leaving groups α to carbonyl groups are exceptionally good electrophiles for S_N2.
 - We can rationalize this via orbitals.
 - One idea: Donation from the C=O π -orbital to the C–Br σ^* orbital weakens that bond.
 - Another idea: Consider the transition state. The **A value** of methyl, ethyl, and isopropyl are all quite similar. Bromine is much smaller (0.83) vs. ester (1.73), so this 1 kcal difference in free energy gives us a 10 : 1 preference for equatorial ester. The reaction can only go with equatorial bromine, though.
- **Curtin-Hammett kinetic scenario.**
- **A value:** An empirical measure of how much a substituent on a cyclohexane likes to be axial or equatorial.
 - Essentially, this is a net measure of a whole bunch of different effects that cause the free energy difference between the two ring conformers.
- Altogether, the full solution to PSet 1, Q2 is on the next page.

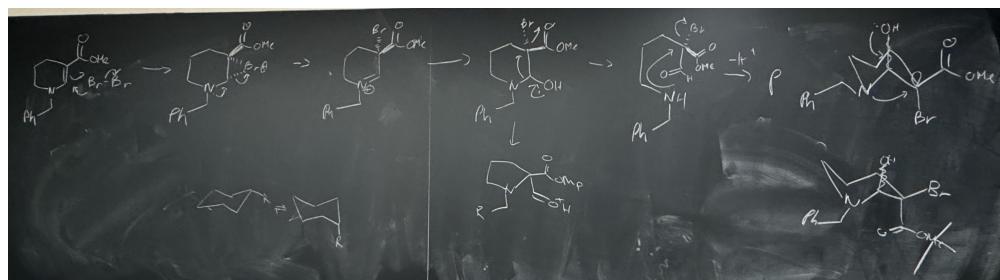


Figure 1.21: Wendlandt PSet 1, Q2 solution.

- Alison's PSets are way more open-ended than Mo's because she doesn't like arrow-pushing mechanisms.