

Problem Set 3

Cyclic Intermediates

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

9/13: • We begin with Problem 3.

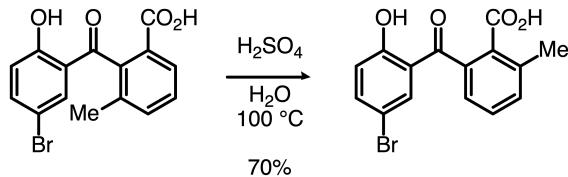


Figure 3.1: Movassaghi PSet 3, Q3.

- 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.

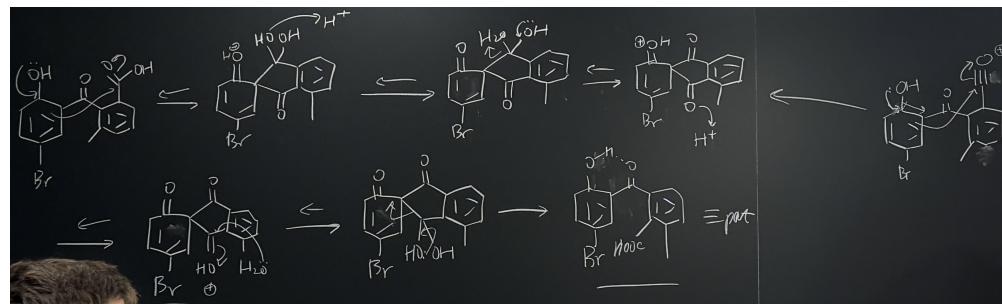


Figure 3.2: Movassaghi PSet 3, Q3 solution.

- We now begin discussing Problem 1.

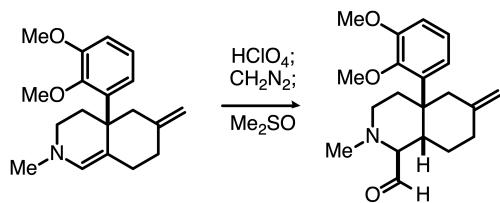


Figure 3.3: Movassaghi PSet 3, Q1.

- 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 \rightarrow 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.

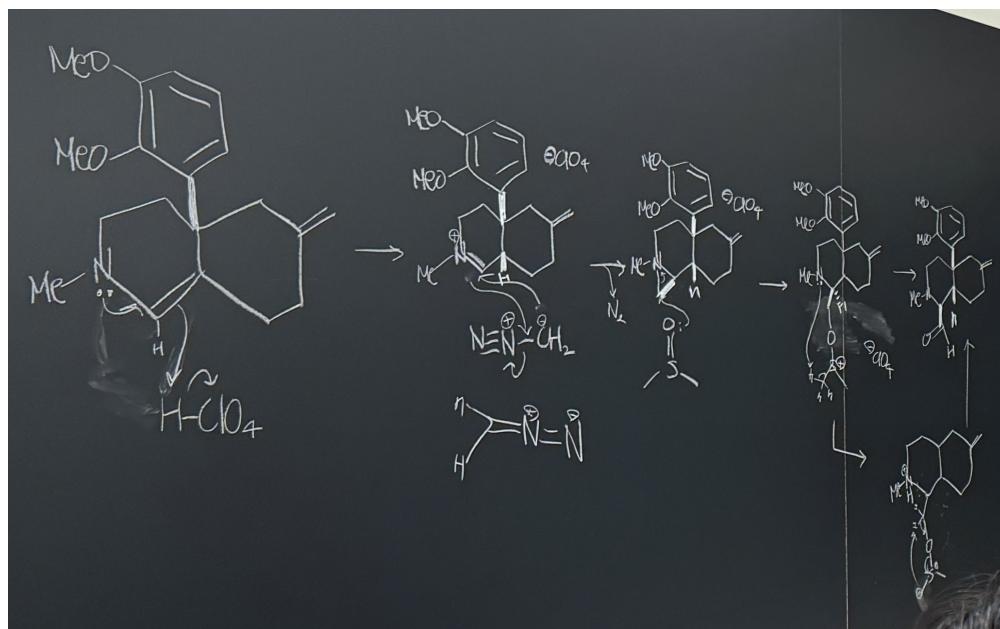


Figure 3.4: Movassaghi PSet 3, Q1 solution.

- We now begin discussing Problem 4.

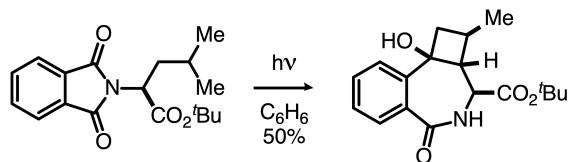


Figure 3.5: Movassaghi PSet 3, Q4.

- 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.

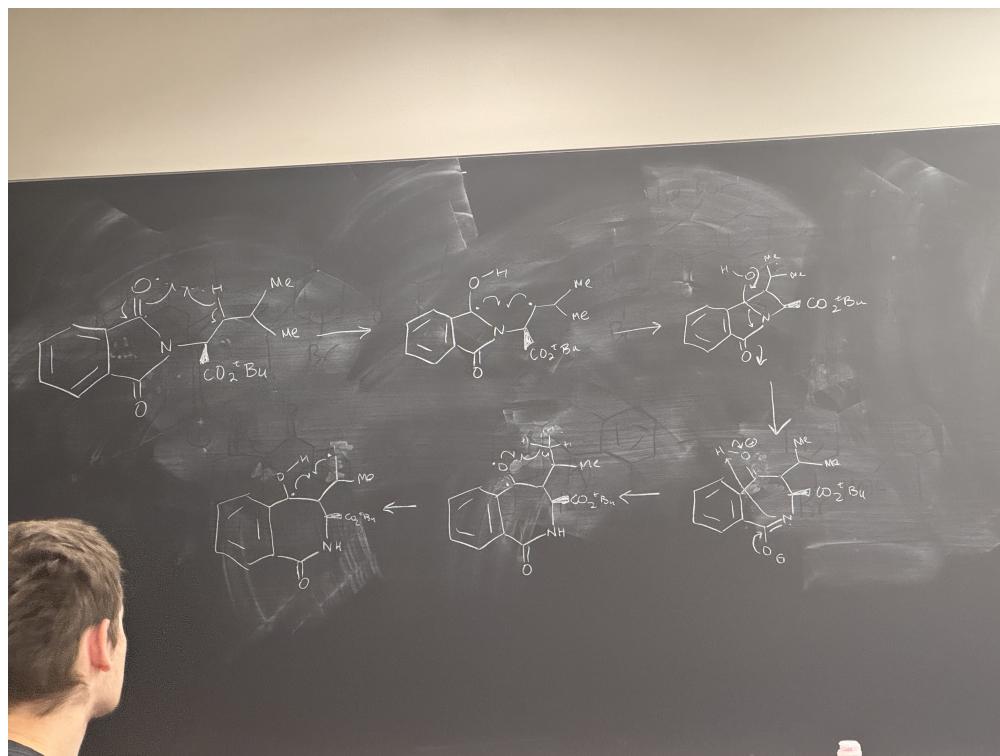


Figure 3.6: Movassaghi PSet 3, Q4 solution.

- We now begin discussing Problem 2.

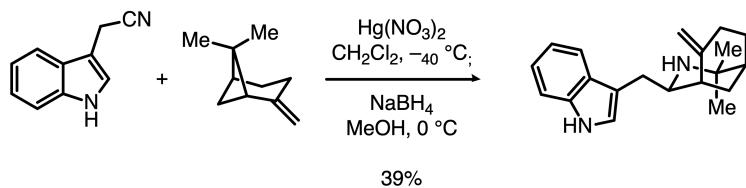


Figure 3.7: Movassaghi PSet 3, Q2.

- 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.

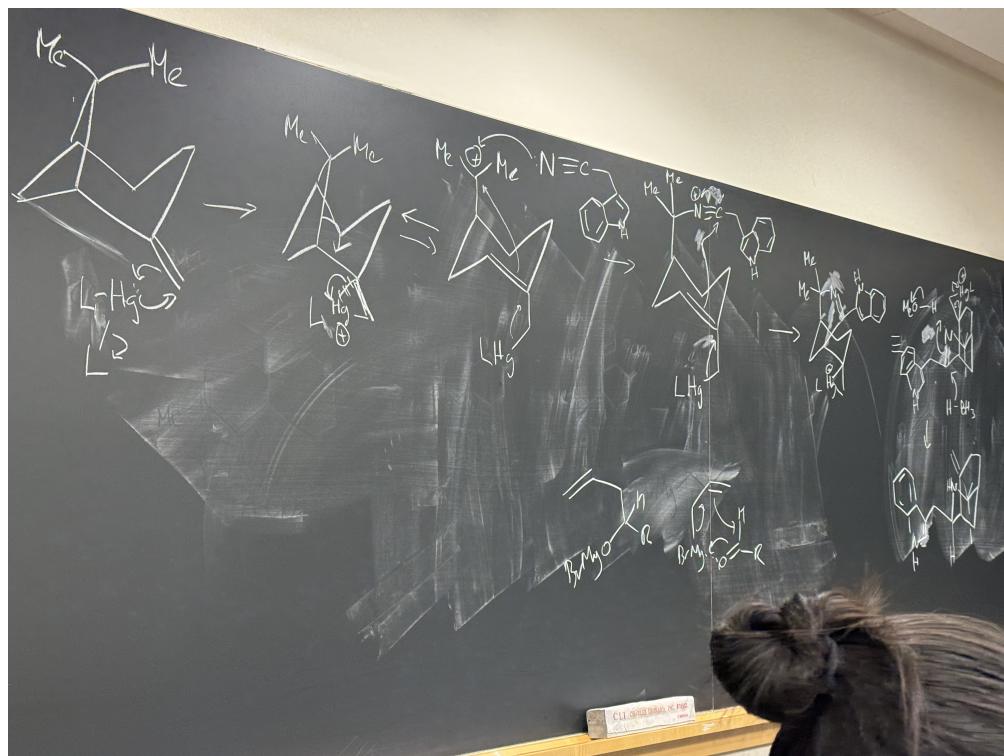


Figure 3.8: Movassaghi PSet 3, Q2 solution.

- We now begin discussing Problem 5.

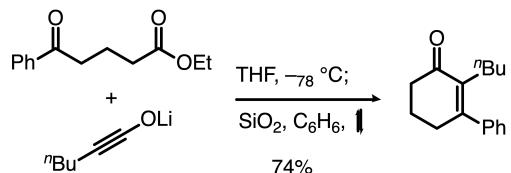


Figure 3.9: Movassaghi PSet 3, Q5.

- 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.

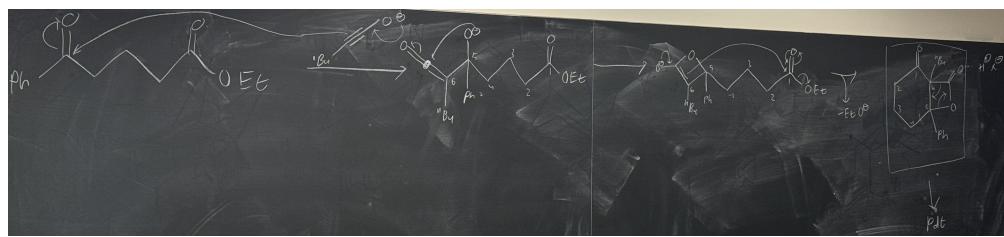


Figure 3.10: Movassaghi PSet 3, Q5 solution.

- We now begin discussing Problem 6.

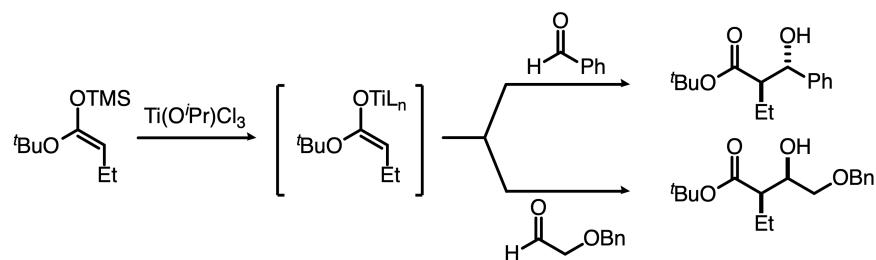


Figure 3.11: Movassaghi PSet 3, Q6.

- 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.

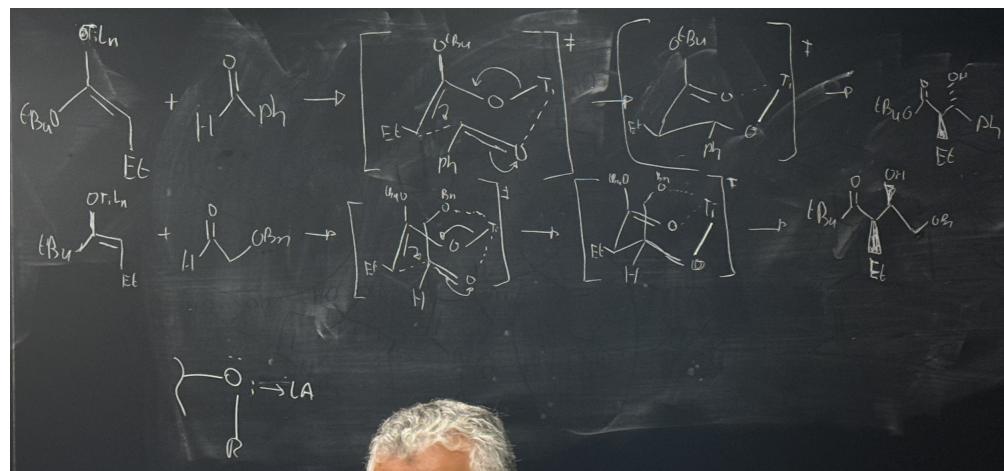


Figure 3.12: Movassaghi PSet 3, Q6 solution.

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