CEM 850 Final Exam Review

December 15, 2020

This exam consists of 6 pages. Please make certain that your exam has all of the necessary pages. Total points possible for this exam are 150. In answering your questions, please write legibly and draw all structures clearly.

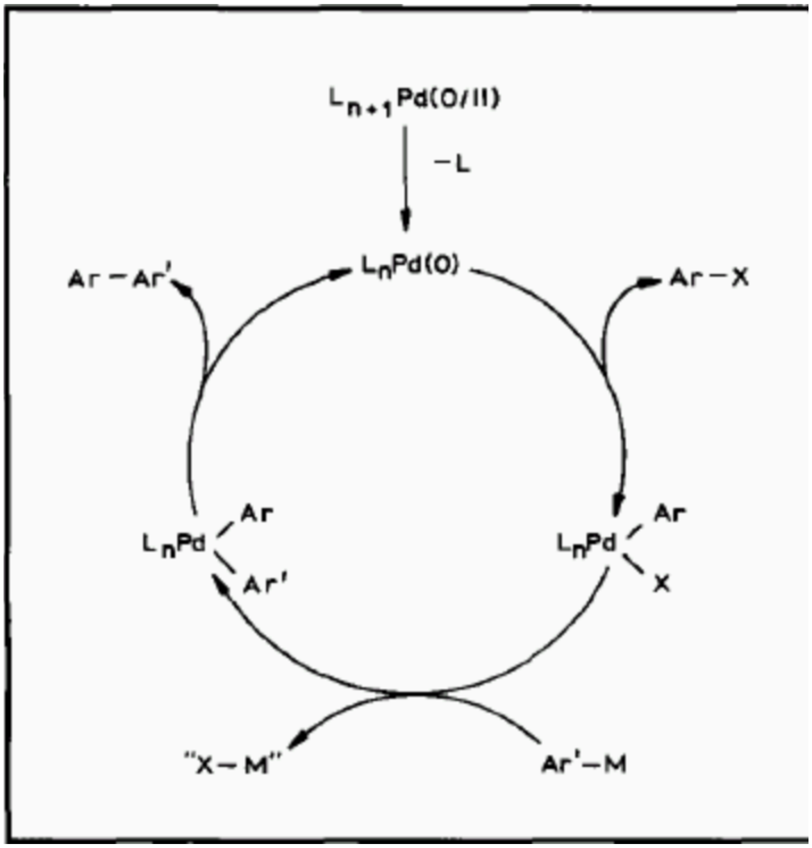
You are not to use any notes or outside resources when taking this exam.

You may send me a PDF of your answers that has been scanned or created from ChemDraw. You may also send me the original ChemDraw. I will not except any other image formats.

Good luck.

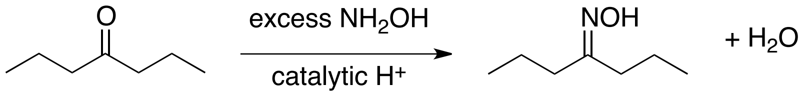
I. Pd-catalyzed cross-coupling reactions often involve a catalytic cycle that includes oxidative addition, trans-metallation, and reductive elimination steps. Illustrate a catalytic cycle involving those three steps for the generic cross-coupling reaction shown below. (9 pts)

$$\text{R–X} + \text{R'–M} \xrightarrow{\text{catalytic Pd(0)}} \text{R–R'} + \text{MX}$$



II. Throughout the semester, we saw examples of amines reacting with carbonyl compounds. Provide <u>all</u> products for each of the four examples shown below and provide complete arrow (electron) pushing mechanisms that explain your answer. (24 pts)

1.



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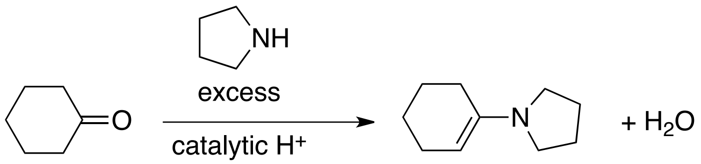

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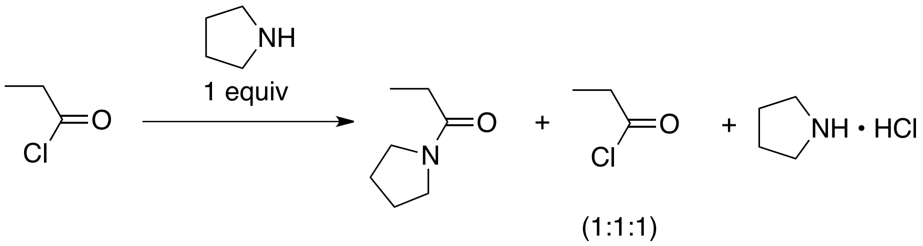

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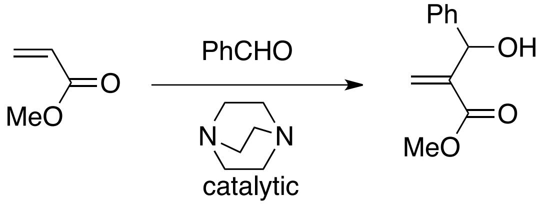
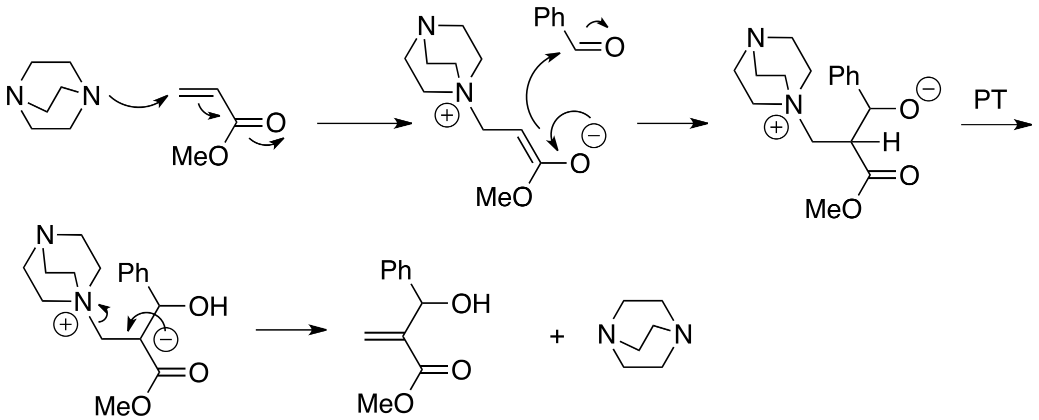
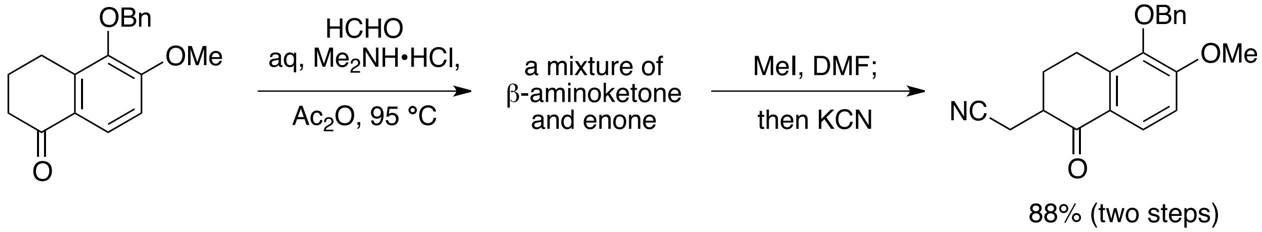
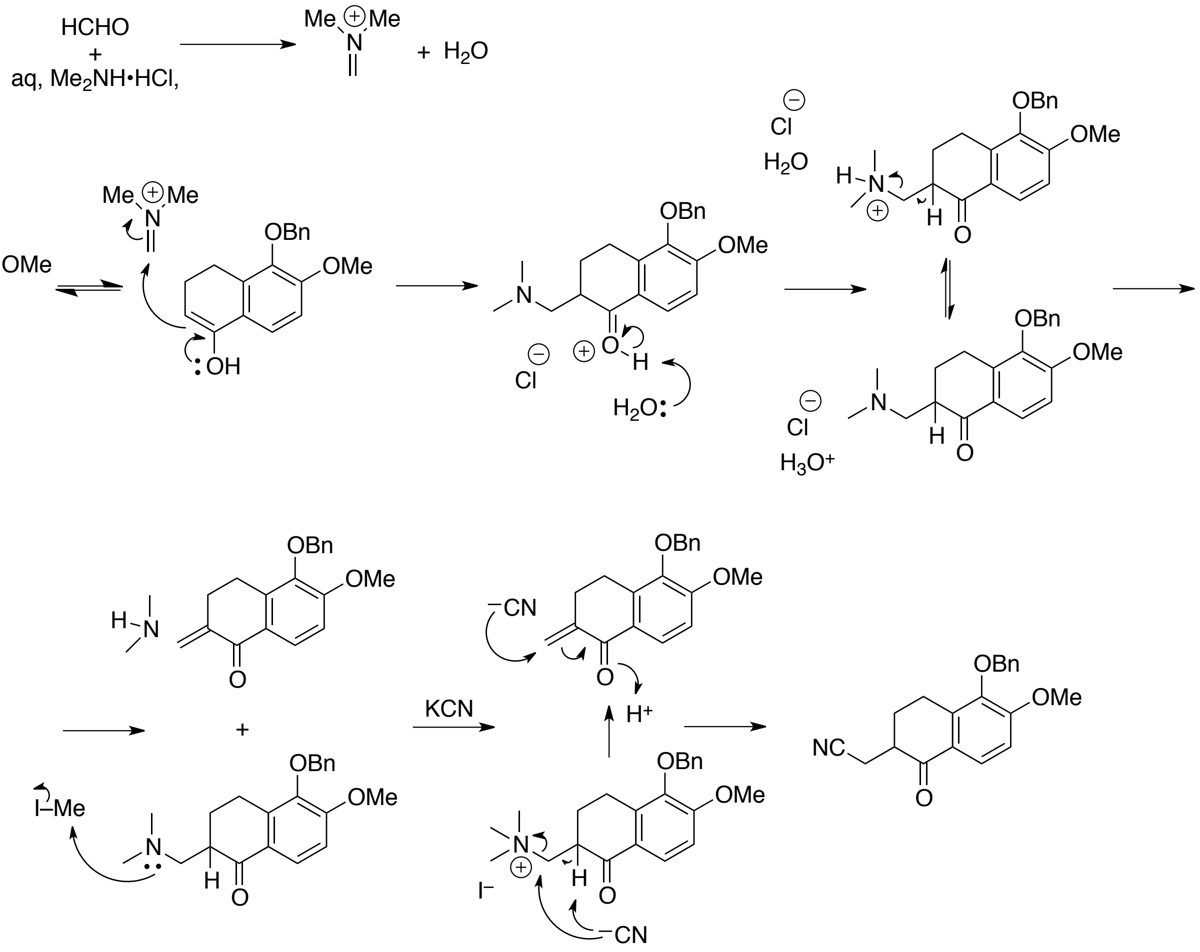


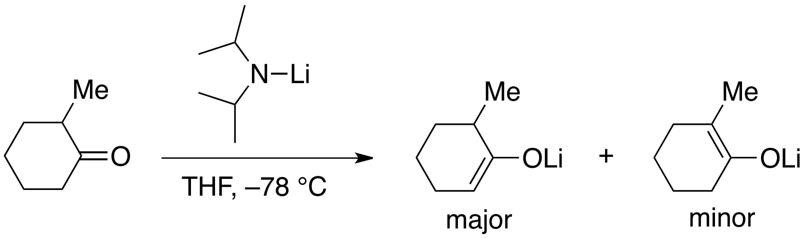


III. Provide a complete arrow (electron) pushing mechanism for the sequence shown below. (10 pts)

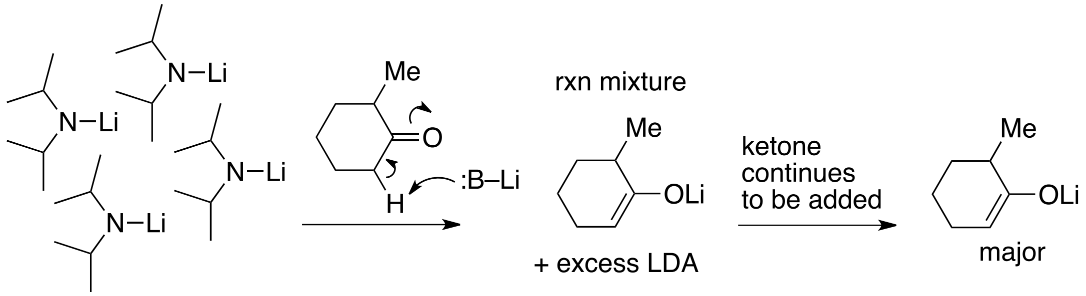




IV. The reaction of 2-methyl cyclohexanone with lithium diisopropylamide (LDA) at –78 °C can generate the less substituted (kinetic) lithium enolate preferentially over the more substituted (thermodynamic) lithium enolate. To assure the highest levels of selectivity it is best to add the ketone to an LDA solution as opposed to adding the LDA to a solution of ketone. Provide a detailed arrow (electron) pushing mechanism that explains this operational observation. (6 pts)

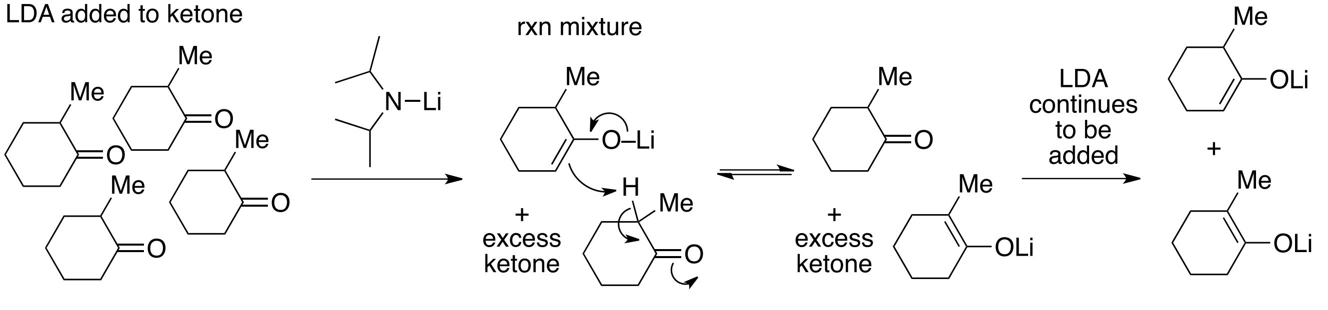


Ketone added to LDA



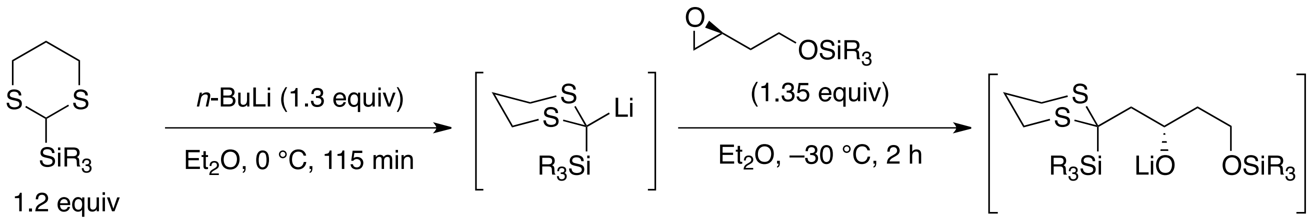
As ketone is added to the reaction it "sees" an excess of LDA. Kinetic deprotonation occurs and is irreversible. Thus the kinetic enolate predominates.

LDA added to ketone

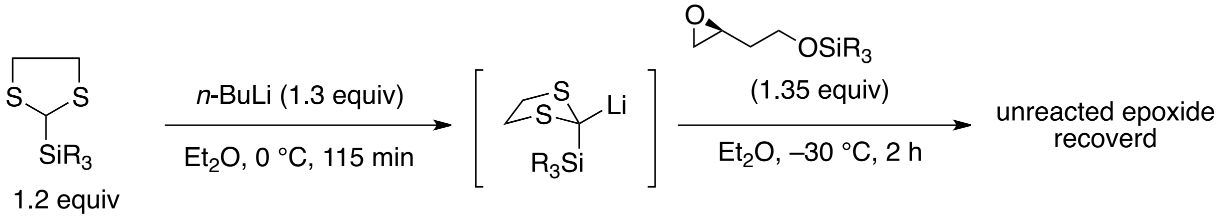


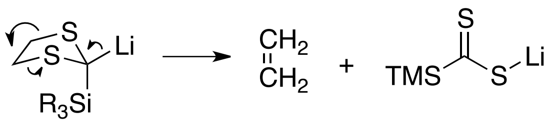
As LDA is added to the reaction it "sees" an excess of ketone. Kinetic deprotonation occurs, however the kinetic enolate can behave as a base and deprotonate some of the excess ketone. This sets up an equlibrium affording more of the thermodynamic enolate in the final mixture.

V. Our last homework assignment involved the reaction sequence shown below.

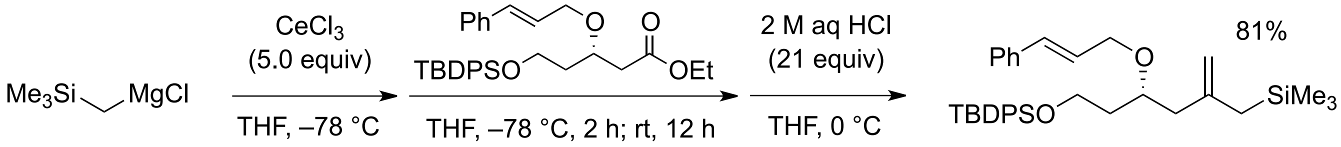


The starting dithiane undergoes deprotonation with n-BuLi in step one, the product of which then reacts with the epoxide in step two. Were one to start with the corresponding silyl-dithiolane the desired ring opening of the epoxide does not occur. Provide a detailed arrow (electron) pushing mechanism that explains why. (6 pts)



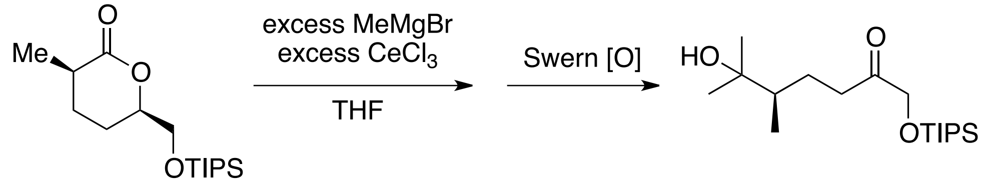


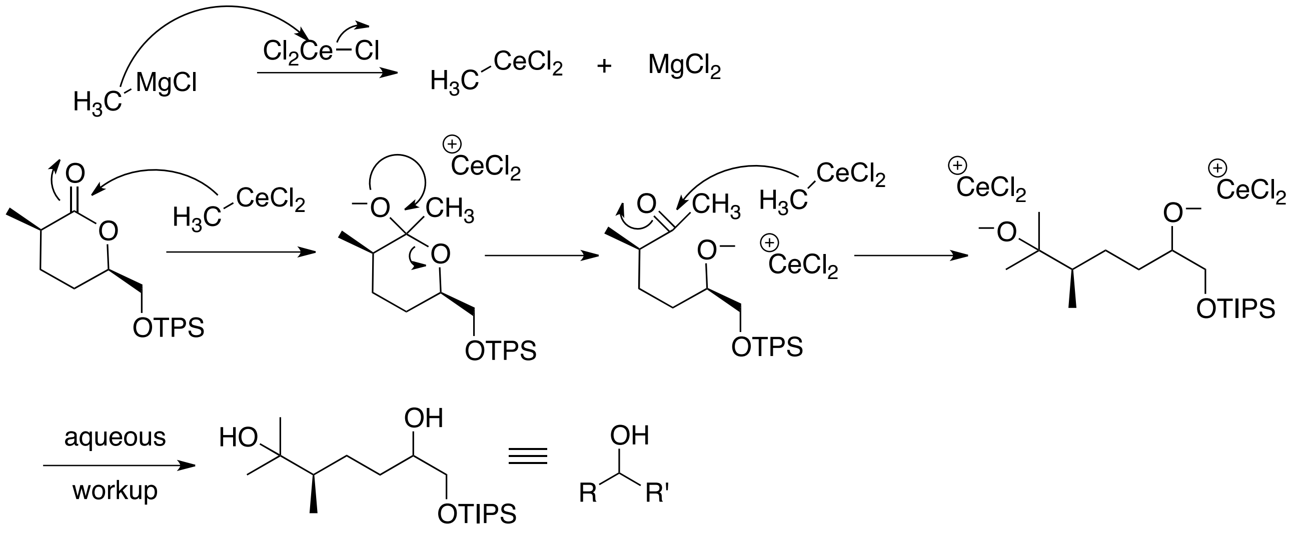
VI. In class, we saw an example where an organocerium reagent was prepared from a Grignard reagent and used as a nucleophilic addition to an ester.



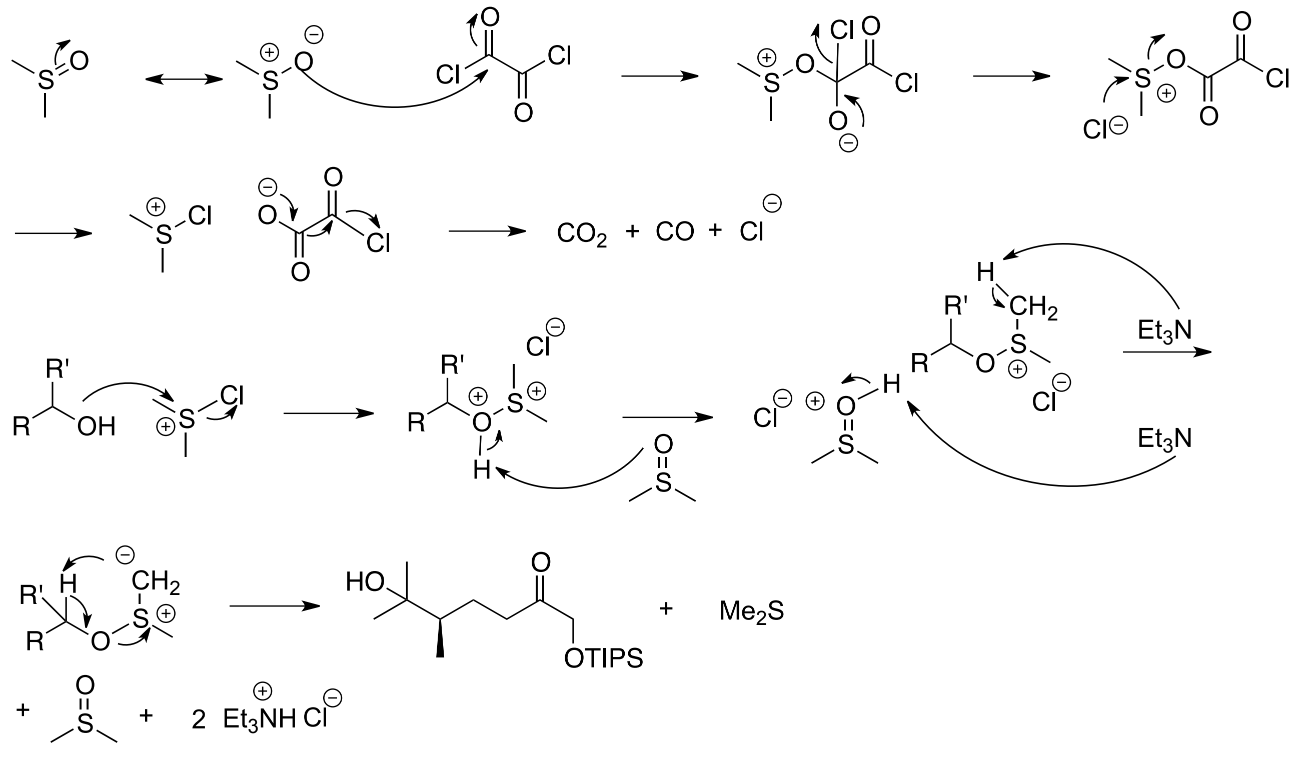
What advantage can organocerium reagents hold over organolithium and/or Grignard reagents? (3 pts) **They are less basic and therefor less likey to deprotonate carbonly substrates.**

VII. Provide a complete arrow (electron) pushing mechanism for the sequence shown below. (10 pts)

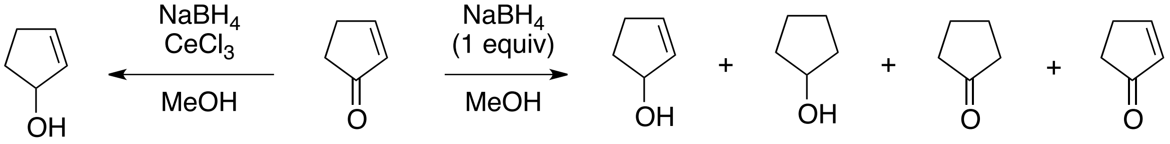




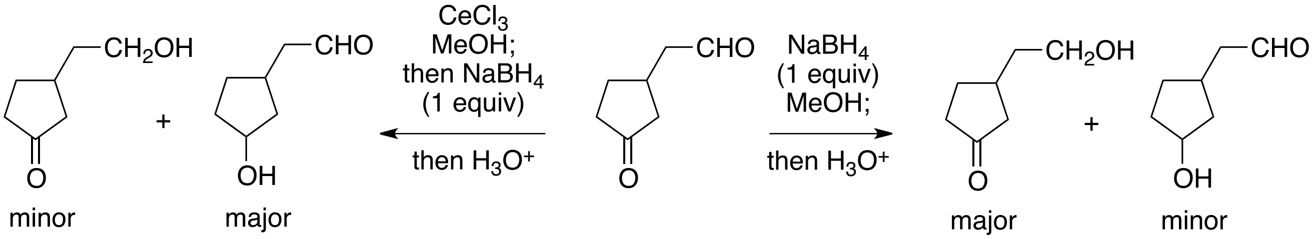
Swern



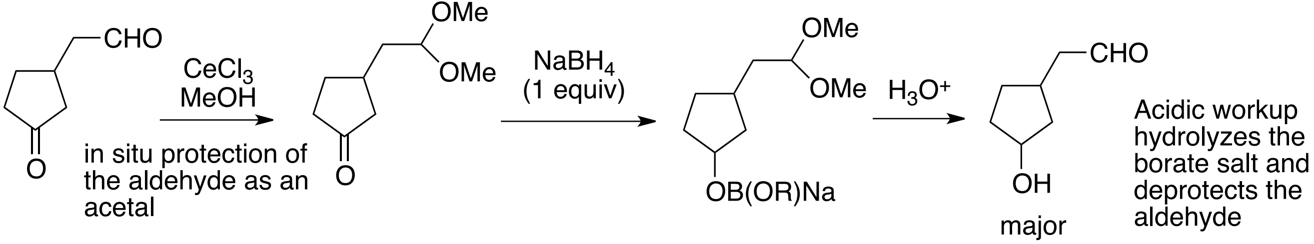
VIII. In class, we saw how $NaBH_4$ of of enones can proceed in a 1,2- or 1,4-fashion. However, in the presence of $CeCl_3$, $NaBH_4$ reductions of enone tend to be highly 1,2-selective.



The presence of $CeCl_3$ can also alter the selectivity of ketone vs. aldehyde reductions. Typically, aldehydes are more reactive than ketones. Thus, while the selectivity is often low, reductions of compunds bearing both a ketone and an aldehyde will proceed with the aldehyde being preferncially reduced.



In contrast, if $CeCl_3$ is added to the process, the major product *after acidic workup* is that in which the ketone has been reduced. Provide an explanation for this seeming preferential reduction of the ketone in the presence of the aldehyde. Note: I am not asking for an arrow pushing mechanism, but you may want to think about intermediates that may form in the presence of $CeCl_3$. (6 pts)

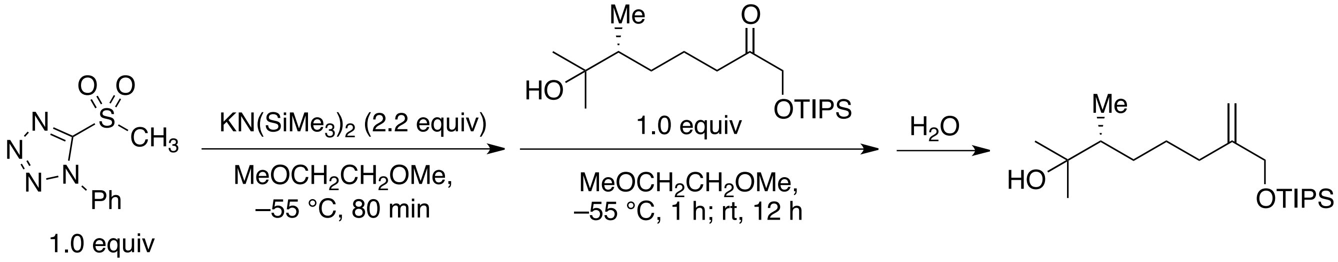


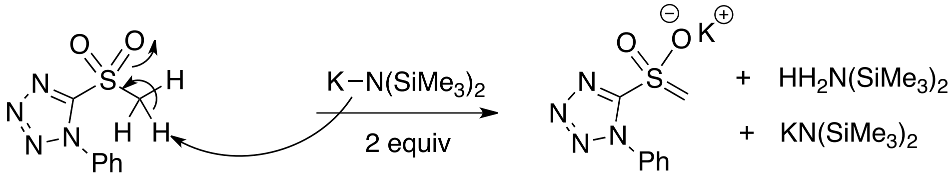
$CeCl_3$ is a Lewis acid

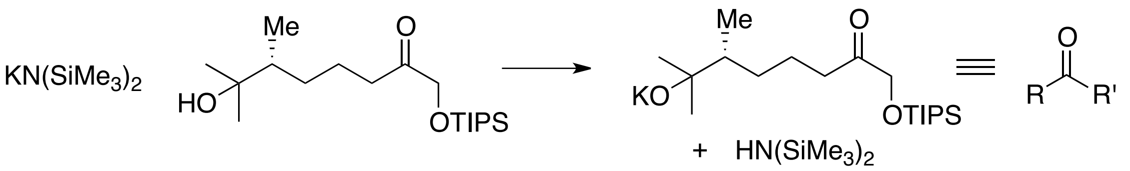
in situ protection of the aldehyde as an acetal

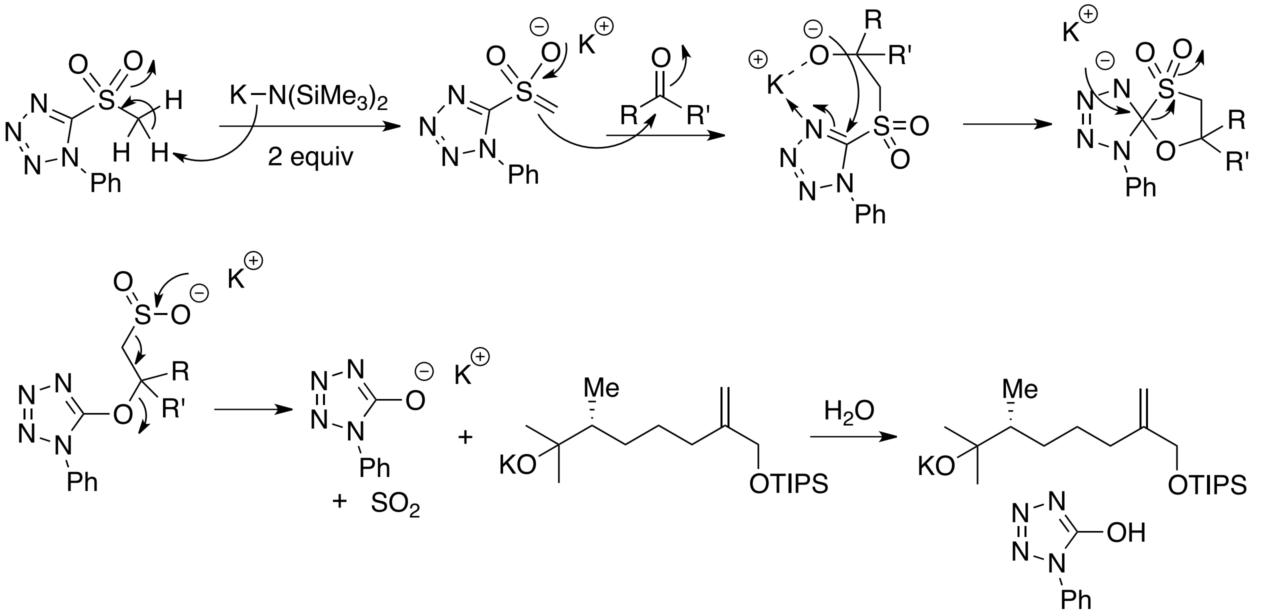
Acidic workup hydrolyzes the borate salt and deprotects the aldehyde

IX. Provide a complete arrow (electron) pushing mechanism for the sequence shown below. (6 pts)

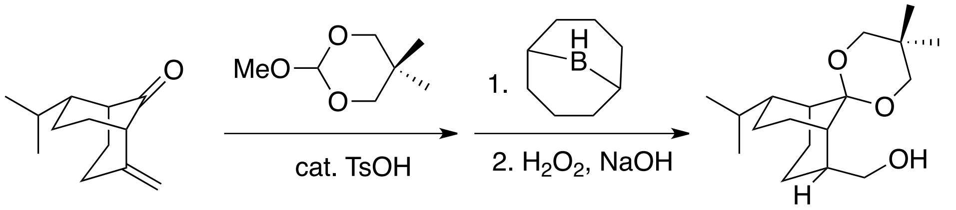


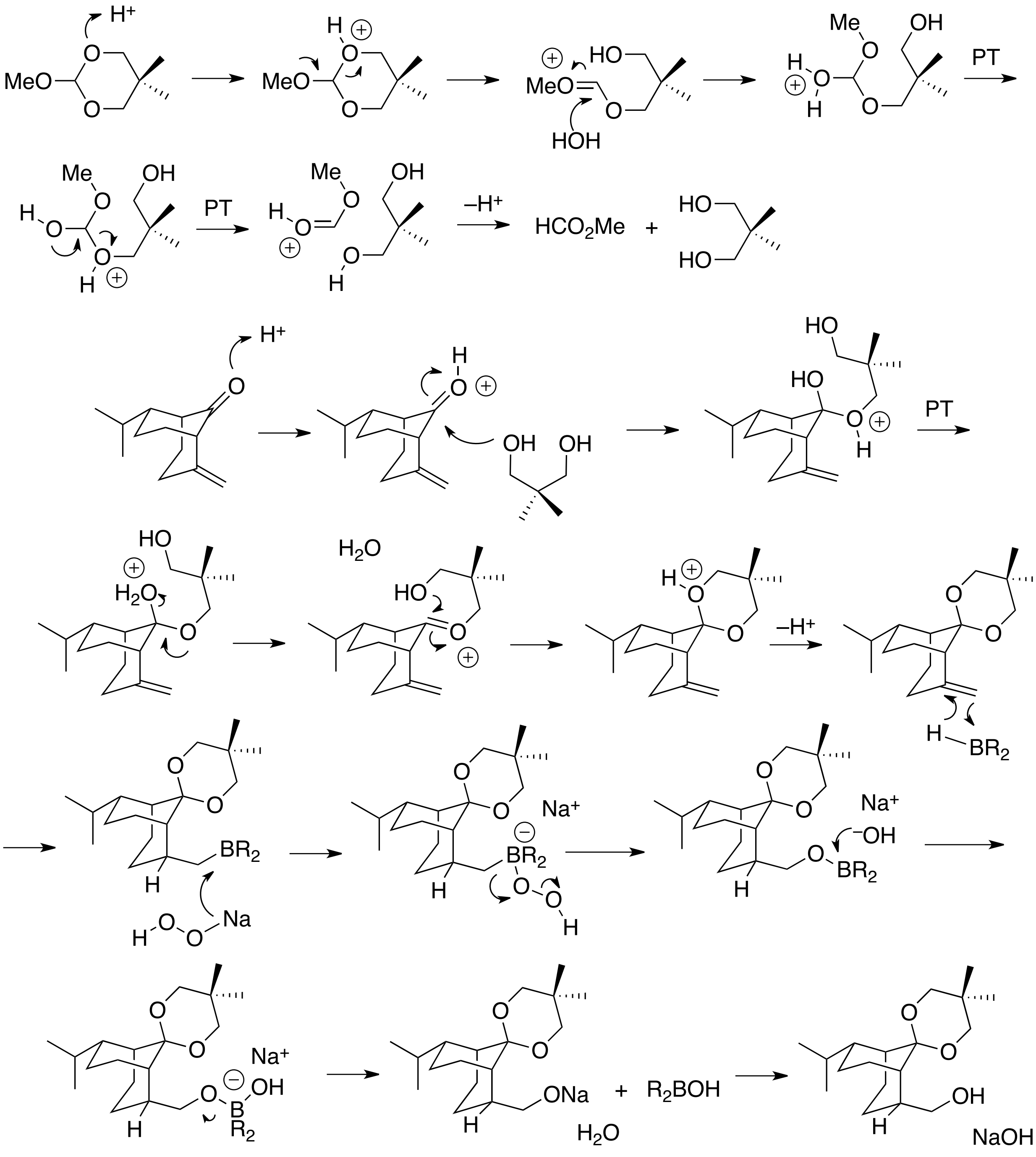




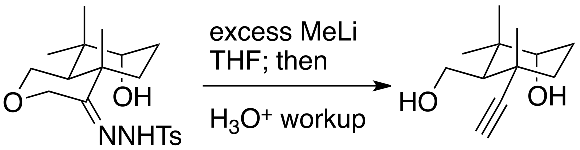


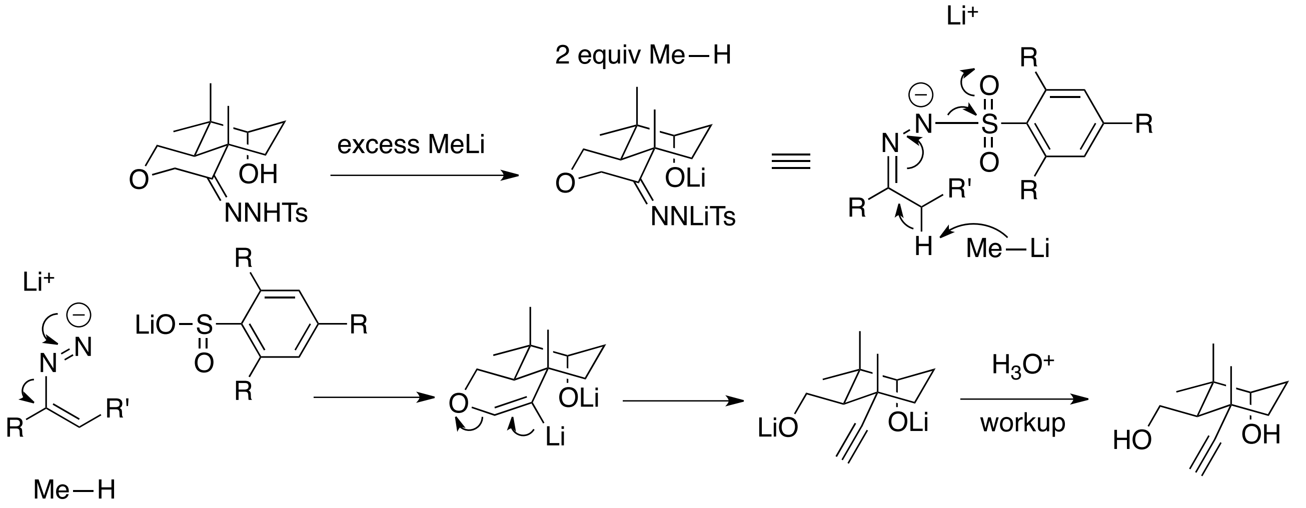
X. Provide a complete arrow (electron) pushing mechanism for the sequence shown below. (8 pts)



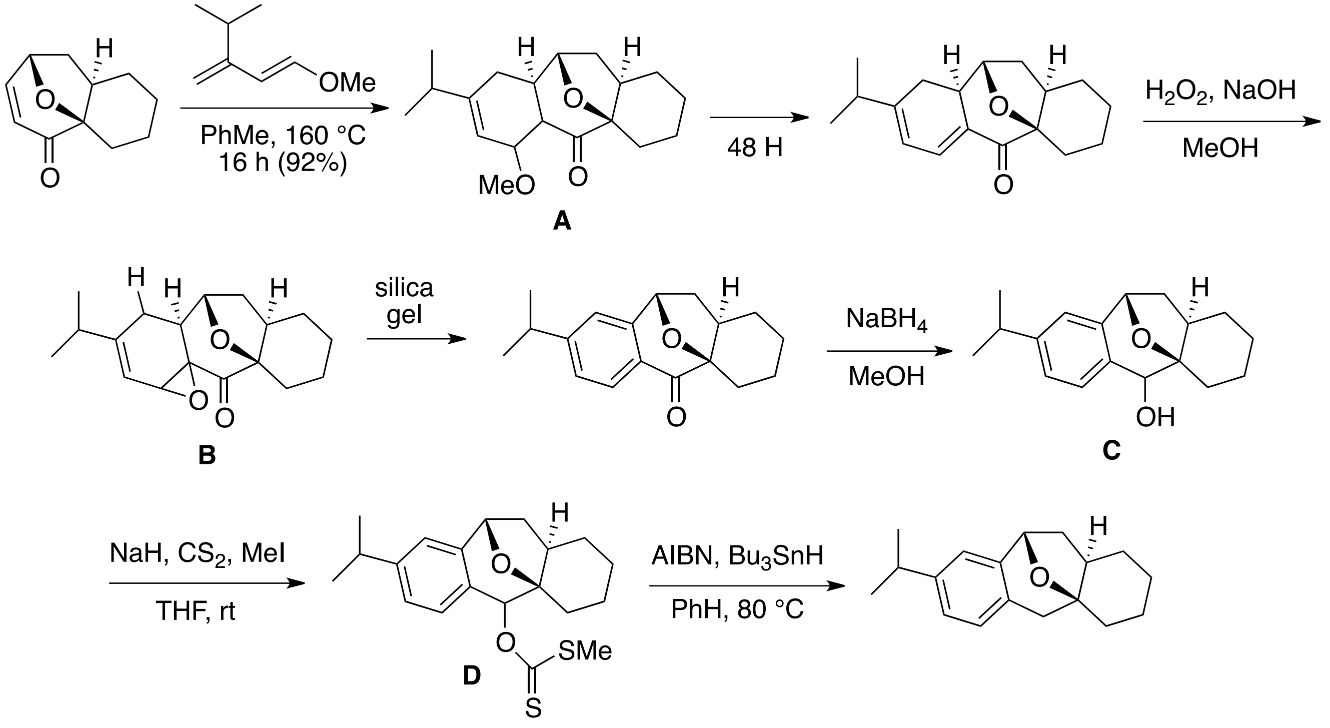


XI. Provide a complete arrow (electron) pushing mechanism for the transformation shown below. (6 pts)

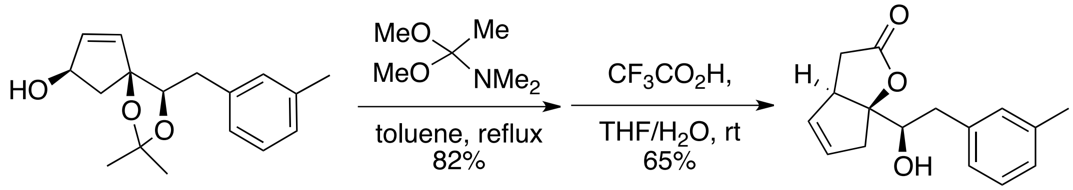


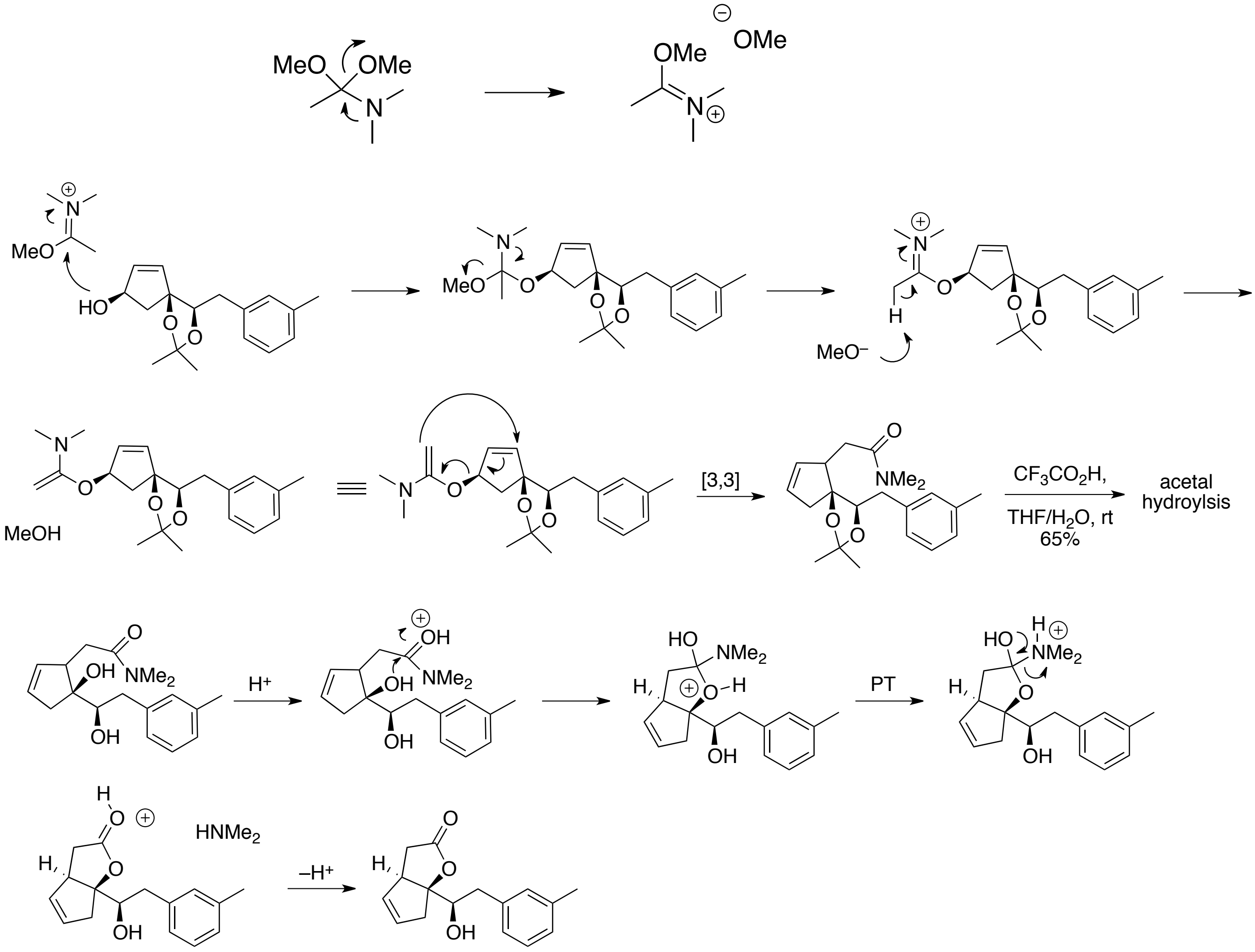


XII. Using your mechanistic knowledge provide the stuctures of intermediat products **A**–**D**. Note: I am not asking for arrow pushing mechanisms (12 pts)

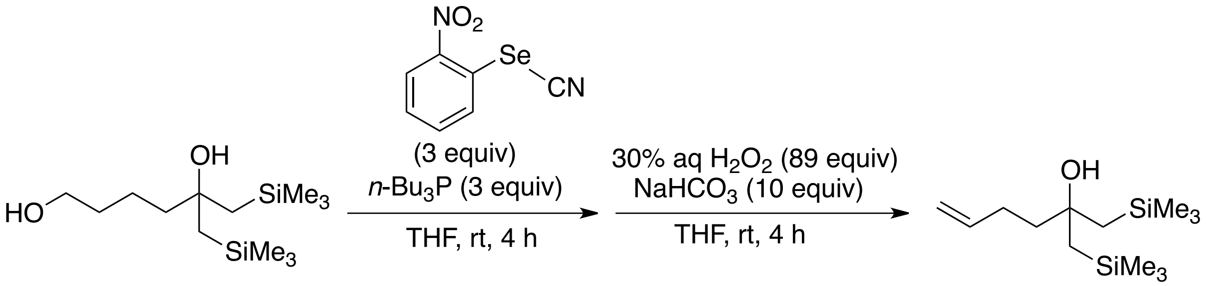


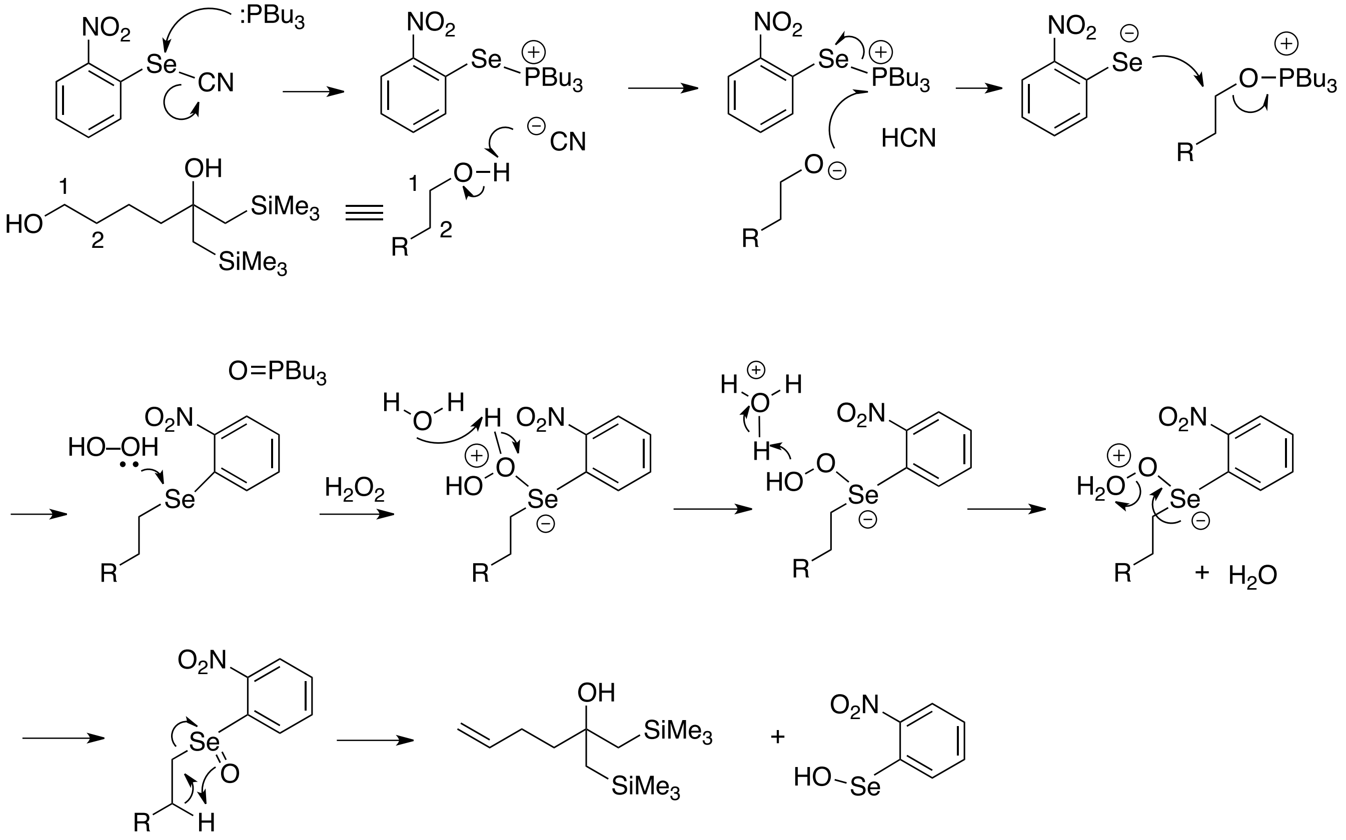
XIII. Provide a complete arrow (electron) pushing mechanism for the sequence shown below. (10 pts)



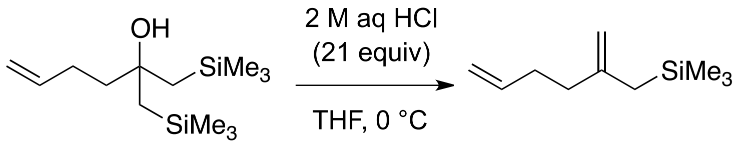


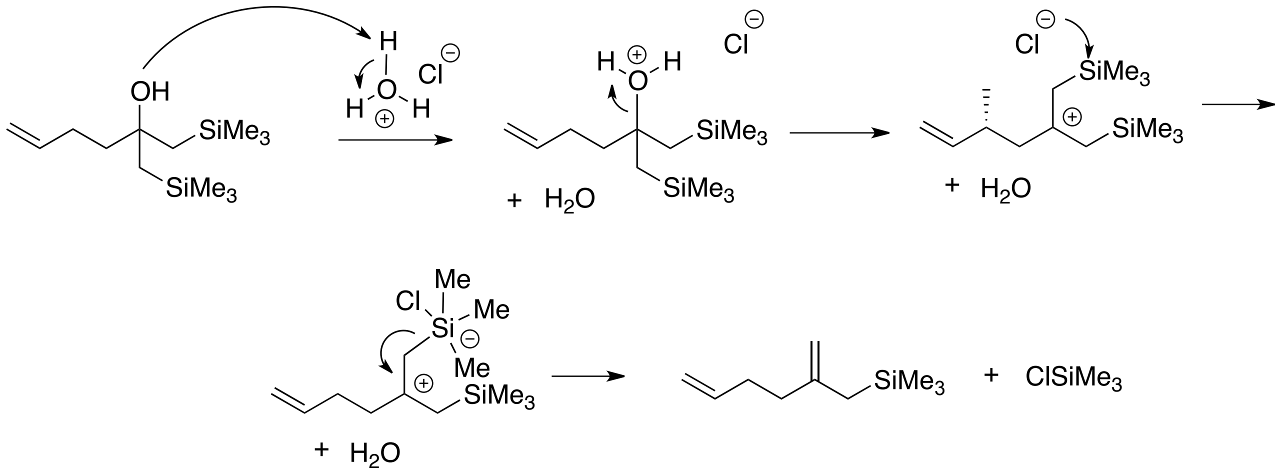
XIV. Provide a complete arrow (electron) pushing mechanism for the sequence shown below. (10 pts)



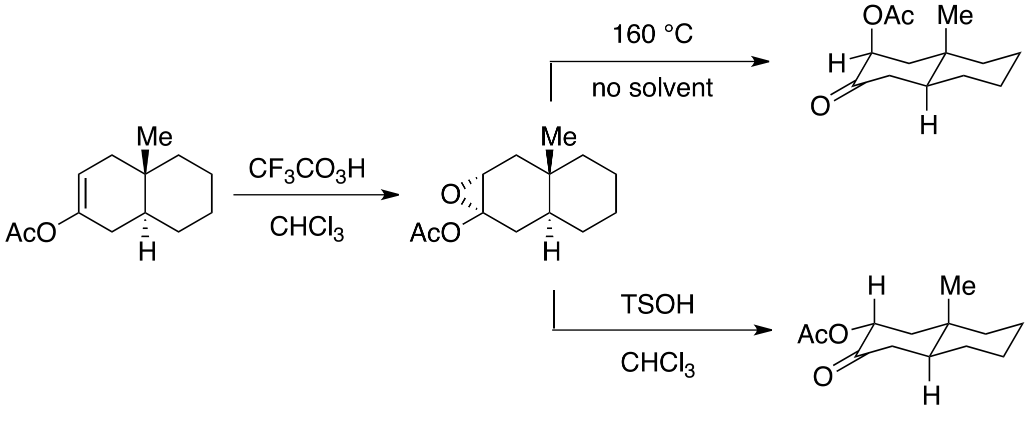


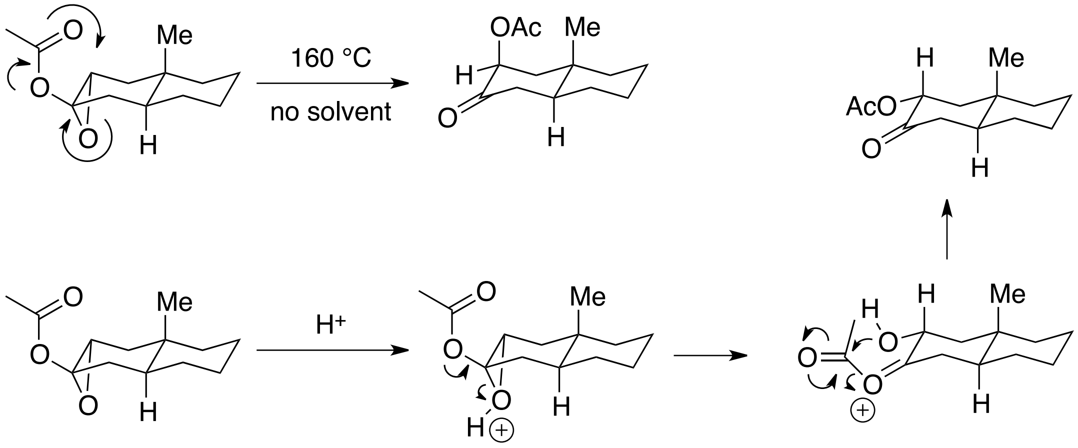
XV. Provide a complete arrow (electron) pushing mechanism for the transformation shown below. (6 pts)





XVI. Provide a complete arrow (electron) pushing mechanism for the transformations shown below. (18 pts)





Bonus Question: Pfizer's COVID vaccine is being manufactured at their Portage, MI facility. That facility was originally part of the Upjohn company. Over seventy years ago, Pfizer and Upjohn were aggressively looking to develop practical syntheses of cortisone and cortisol. (Merck's cortisone synthesis was 36 steps.) Both companies ultimately discovered biocatalytic approaches that relied on 11-deoxycortisol. Upjohn's original supply of 11-deoxycortisol came from the Glidden company, who in 1953 granted Pfizer exclusive license to their 11-deoxycortisol patents. Who was the Glidden chemist that invented their synthetic route to 11-deoxycortisol? (2 pts)

(a) Carl Djerassi
(b) Percy Julian
(c) Herbert Murray
(d) Durey Peterson
(e) Arie Luyendyk