Organic Chemistry Peer Tutoring Department
University of California, Irvine
Rachel Bauer (rdbauer@uci.edu)
Sebastian Zolog (szolog@uci.edu)

Chem 51C
Professor King
https://sites.uci.edu/ochemtutors/

Midterm 1 Review Packet Key

Objectives

Chapter 16 (18)

- Electrophilic aromatic substitution
  - Bromination, niration, sulfonation, Friedel Crafts alkylation, Friedel Crafts acylation
  - Understand the mechanisms and products for the three steps
    - Make electrophile
    - Resonance stable carbocation (must draw all possible structures)
    - Regenerate aromatic ring via E1
  - Substituent effects
    - Ring activating and deactivating trends
    - How substituents affect whether product is ortho, meta, or para
    - Predict major product when multiple substituents are on the ring
  - Steric effects
  - Nitration of aniline derivatives

Chapter 17 (20)

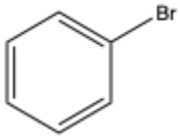
- Irreversible Reactions involving Carbonyl Compounds
  - Differentiate between type 1 and type 2 carbonyl compounds and their differing reactivity with various reagents.
    - Reduction of carbonyl compounds with $NaBH_4$, $LiAlH_4$, and DIBAL-H
    - Oxidation of carbonyl compounds with PCC and CrO_3, H_2SO_4, and H_2O reagents.
  - Understand how to prepare different organometallic reagents and utilize them in synthesis of novel compounds
    - Grignard reagents, Organolithium reagents, and Organocuprate reagents
    - Differentiate between which organometallic reagent to use in reactions involving alpha,beta-unsaturated aldehydes and ketones
    - Understand the concept behind why protecting groups are sometimes necessary in reactions involving organometallic reagents

Chapter 18 (21)

- Reversible Reactions involving Type 1 Carbonyl Compounds
  - Hydrates and Acetal formation mechanism in the forward direction

Problem Set

1. For each of the following substituted benzenes: [1] C_6H_5Br [2] C_6H_5CN [3] $C_6H_5OCOCH_3$ (18.46)



Example drawing! Draw the rest before answering the questions.

   a. Does the substituent donate or withdraw electron density by an inductive effect?

[1] Br withdraws electron density [2] CN withdraws electron density [3] $OCOCH_3$ withdraws
Each of the substituents are more electronegative than benzene, so they withdraw via inductive effects.

   b. Does the substituent donate or withdraw electron density by a resonance effect?

[1] Br donates electron density [2] CN withdraws electron density [3] $OCOCH_3$ donates
To determine whether the substituent donates or withdraws electron density via resonance, look at lone pairs. Lone pairs directly attached to the benzene ring are donating, while something like CN without lone pairs is withdrawing.

   c. On balance, does the substituent make a benzene ring more or less electron rich than benzene itself?

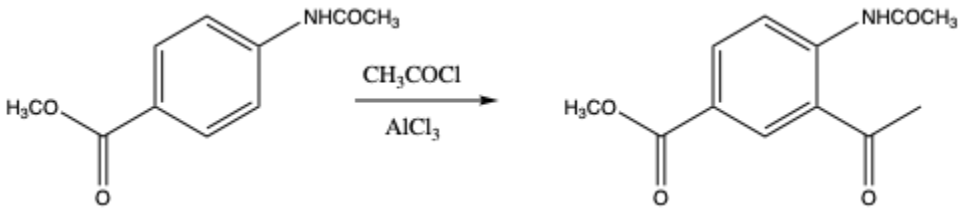
[1] Less [2] Less [3] More
To determine if the substituent makes benzene more or less electron rich, we have to weigh both the inductive and resonance effects. CN is definitely less as it withdraws via inductive and resonance effects. The other two withdraw via inductive effects, but donate via resonance. Br has a very strong inductive effect, but weak resonance effect so overall it makes benzene less electron rich. The ester, however, has a strong resonance effect that makes benzene more electron rich, even though it is slightly withdrawing via inductive effects.

   d. Does the substituent activate or deactivate the benzene ring in electrophilic aromatic substitution?

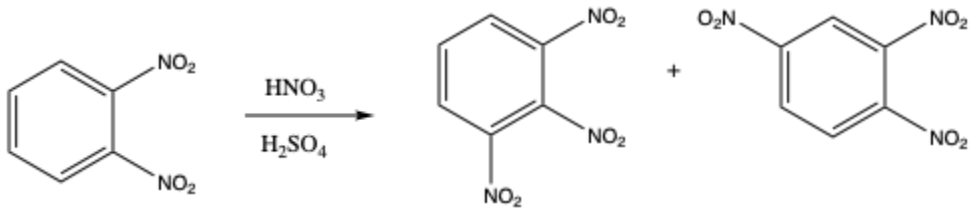
[1] Deactivate [2] Deactivate [3] Activate
Electron withdrawing substituents deactivate the ring, while electron donating activates the ring. So, our answers from part c will answer this question.

2. Draw the products of each reaction. (18.38 3rd ed)

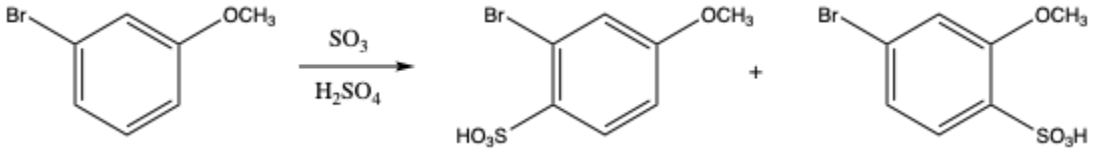
   a.



b.



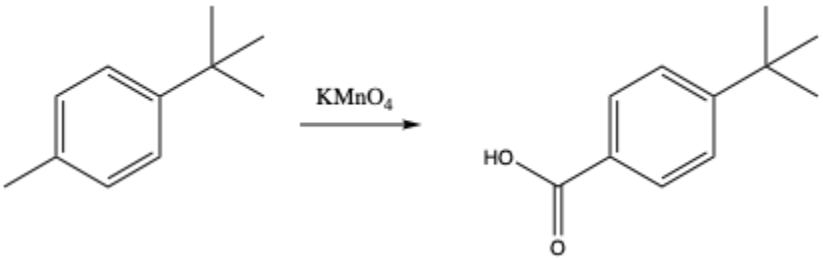
c.



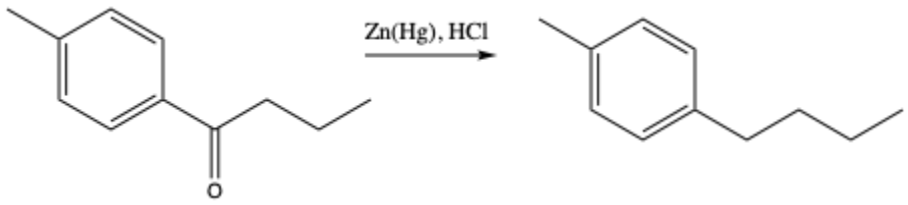
To approach these problems, we have to look at whether the group is activating or deactivating, and an ortho, para director versus a meta director. For a, our amide is electron donating, due to the lone pairs, making it ring activating, while the ester is electron withdrawing and deactivating to the ring, so Friedel Crafts acylation will occur ortho to the amide and meta to the ester. For b, both nitro groups are deactivating meta directors so depending on which direction we go, there are two possible products that could be formed where the new nitro group is meta to one nitro and ortho or para to the other. The second product would be the major product due to less steric hindrance. For c, both groups are ortho, para directing, but the methoxy group is strongly activating so our sulfate will go ortho and para to that group.

3. Draw the products of each reaction. (18.41 3rd ed)

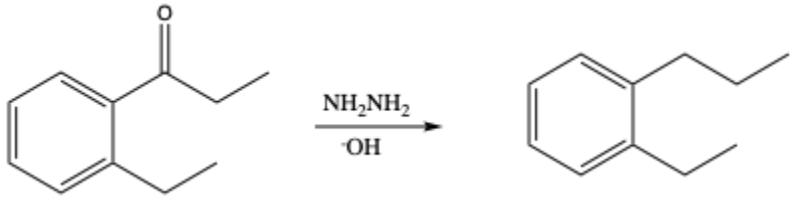
a.



b.

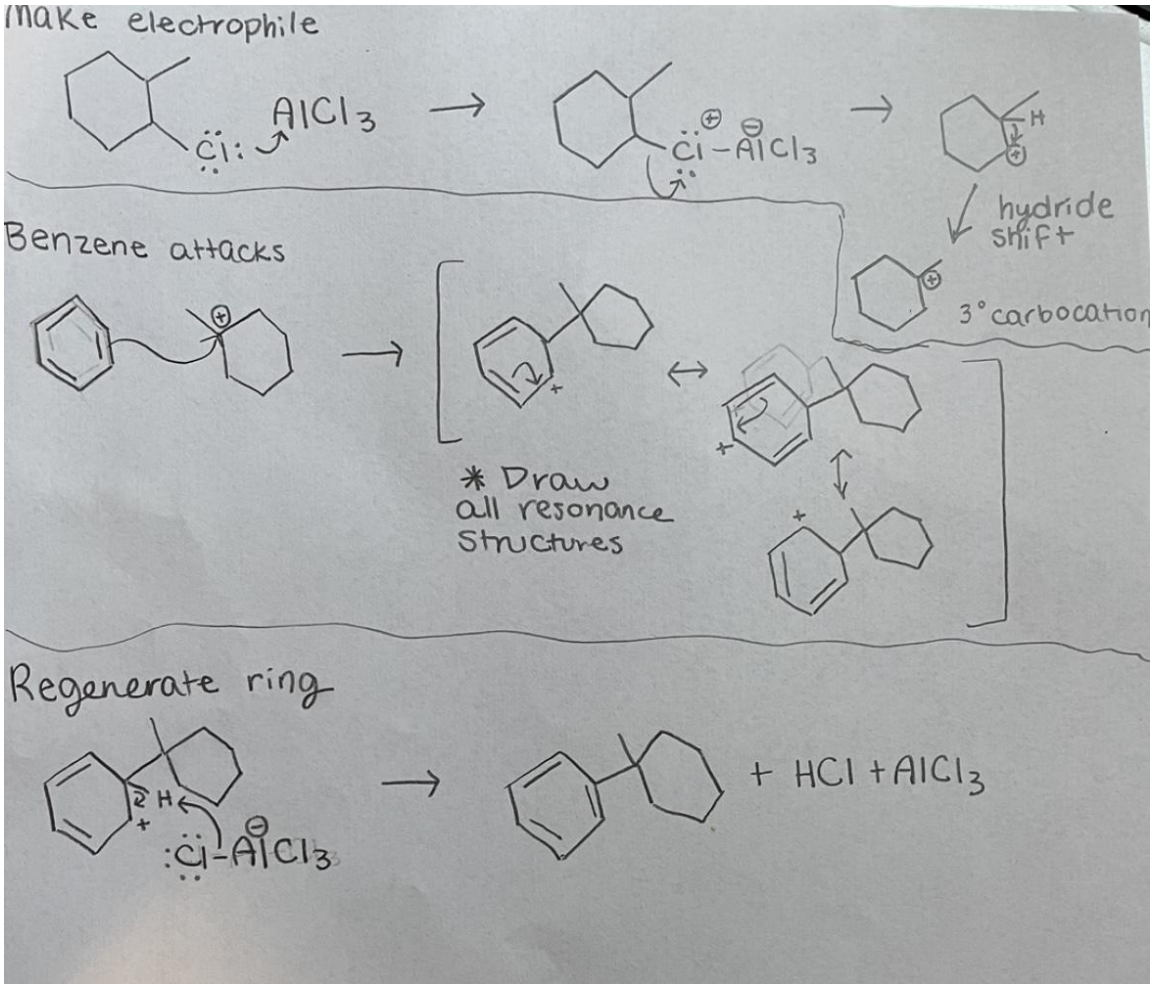


c.



$KMnO_4$ turns alkyl groups into carboxylic acids, as long as there is at least one benzylic hydrogen on the starting carbon of the alkyl chain. So for part a, the tert butyl group will not become a carboxylic acid because there are no hydrogens. Zn (Hg) and HCl reduces carbonyl so the ketone in part b will be replaced with 2 hydrogens. Similarly, NH_2NH_2 reduces carbonyls as well as nitro groups, so choosing the right reducing agent in synthesis is important.

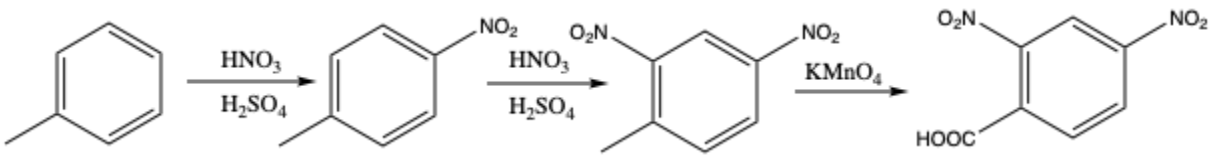
4. Draw a stepwise mechanism for the following reaction. (18.52 3rd ed)



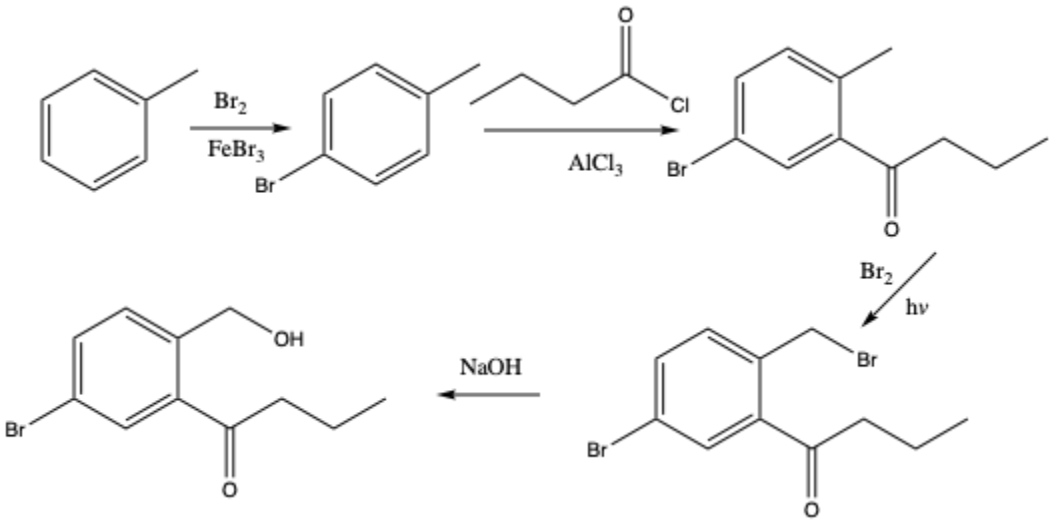
There are 3 steps to any electrophilic aromatic substitution reaction: making the electrophile, generating a resonance stabilized carbocation which benzene then attacks, and regenerating the ring. On the exam, you must draw all resonance structures to get all points. In this case there are 3, but there could be more if a substituents like OH was present on the original ring.

5. Synthesize each compound from toluene ($C_6H_5CH_3$) and any other organic or inorganic reagents. (18.64 3rd Ed)

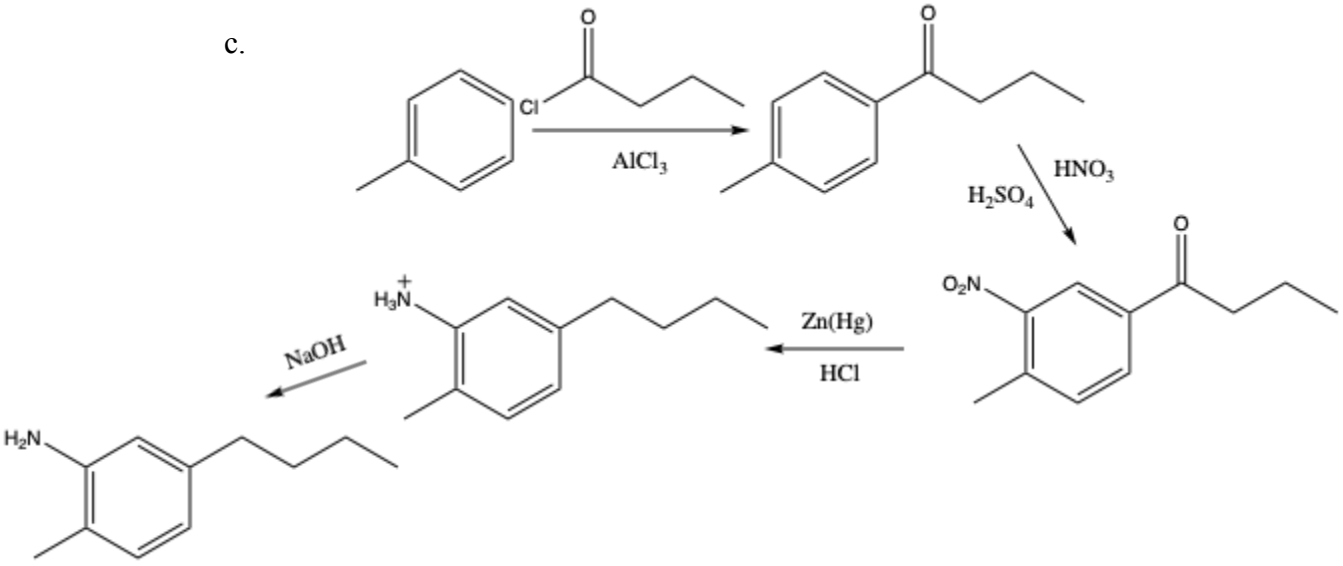
a.



b.

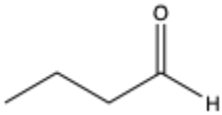


c.



For these synthesis problems, it's important that the steps are carried out in the proper order in order to get substituents in the correct place. For a, we are simply nitrating twice and then oxidizing the methyl group into a carboxylic acid. WE must nitrate before oxidizing to get the nitro group para and ortho to the carboxylic acid, as the methyl group is activating. For b, we want to brominate first to get that para to the methyl, then use Friedel Crafts Acylation to get our carbonyl on the ring, and finally use bromination from 51B to add the Bromine to our methyl which we can use simple SN2 to concert to the OH. For part c, we want to use Friedel Crafts Acylation rather than alkylation, otherwise there would be rearrangement. Then we can nitrate to get the nitro group in the correct spot. We can reduce both the ketone and nitro at the same time with Zn(Hg) and HCl.

6. Which compound in each pair is more reactive towards nucleophilic attack. (20.4 3rd Ed)



Example Drawn! Draw the rest before answering the questions.

a. $CH_3CH_2CH_2CHO$ or $CH_3CH_2CH_2COCH_3$

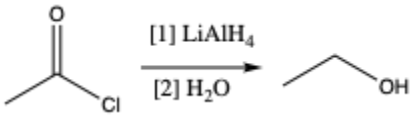
b. $CH_3CH_2COCH_3$ or $CH_3CH(CH_3)COCH_2CH_3$

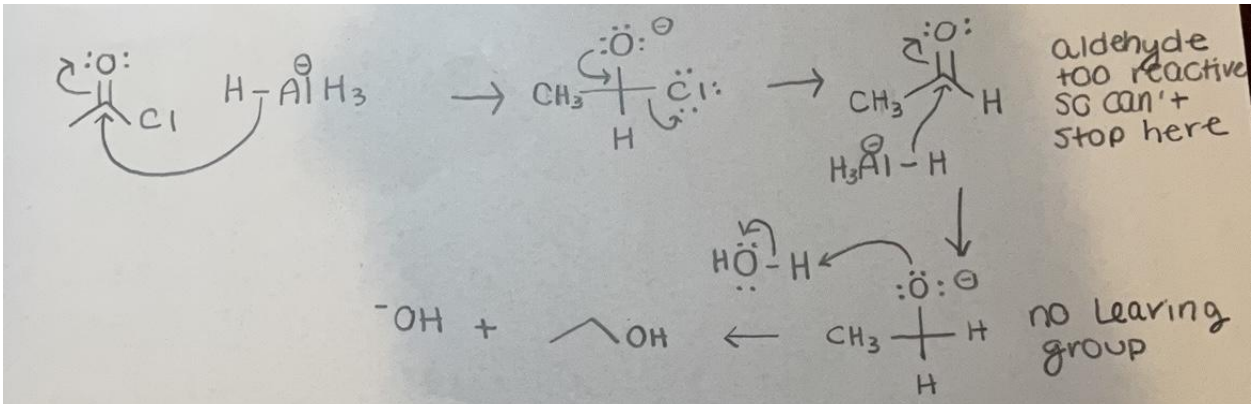
c. CH_3CH_2COCl or CH_3COOCH_3

d. CH_3COOCH_3 or $CH_3CONHCH_3$

To determine which carbonyl is more reactive/electrophilic we look at inductive and resonance effects. Inductive effects withdraw electrons from the carbonyl carbon, making it more reactive, while resonance effects donate electrons making it less reactive. Looking at these two effects we can predict which compounds will be more reactive to nucleophilic attack. We can also think about this in terms of leaving groups. A better leaving group will be more reactive for type 2 carbonyls, which explains c and d. An aldehyde is always more reactive than a ketone as a ketone has two electron donating groups that stabilize it more than an aldehyde which only has one. This helps explain part a. For part b, the ketone with less sterics will be more reactive.

7. Draw a stepwise mechanism for the following reaction. (20.11 3rd ed)

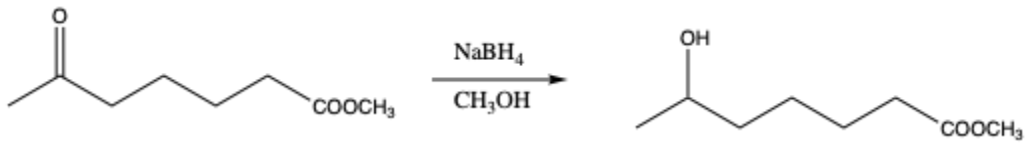




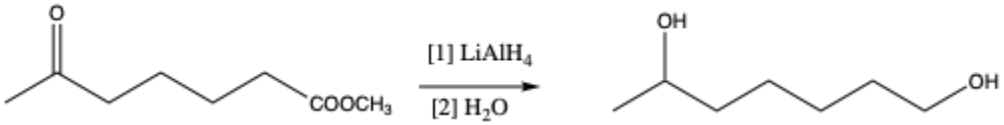
$LiAlH_4$ is a reducing agent for both type 1 and type 2 carbonyls. It reduces both to alcohols. An acid chloride is a type 2 carbonyl because it has a leaving group. This means after the first addition, an elimination occurs, resulting in an aldehyde. Because lithium aluminum hydride is so strong, the aldehyde cannot be reduced here, so another addition occurs, resulting in a primary alcohol.

8. Draw the products of each reduction reaction (20.49 3rd ed)

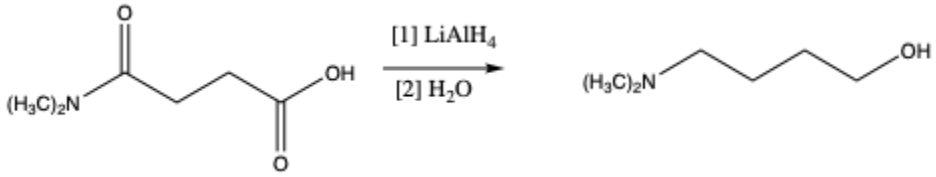
a.



b.

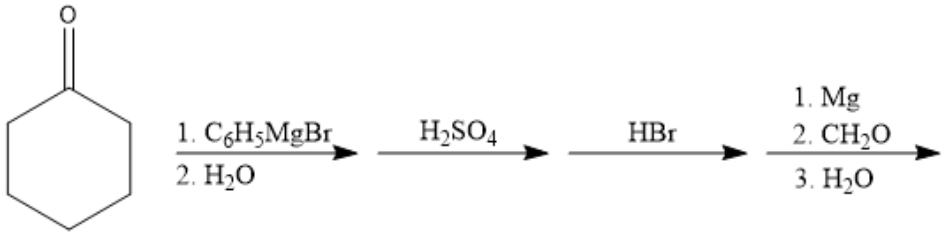


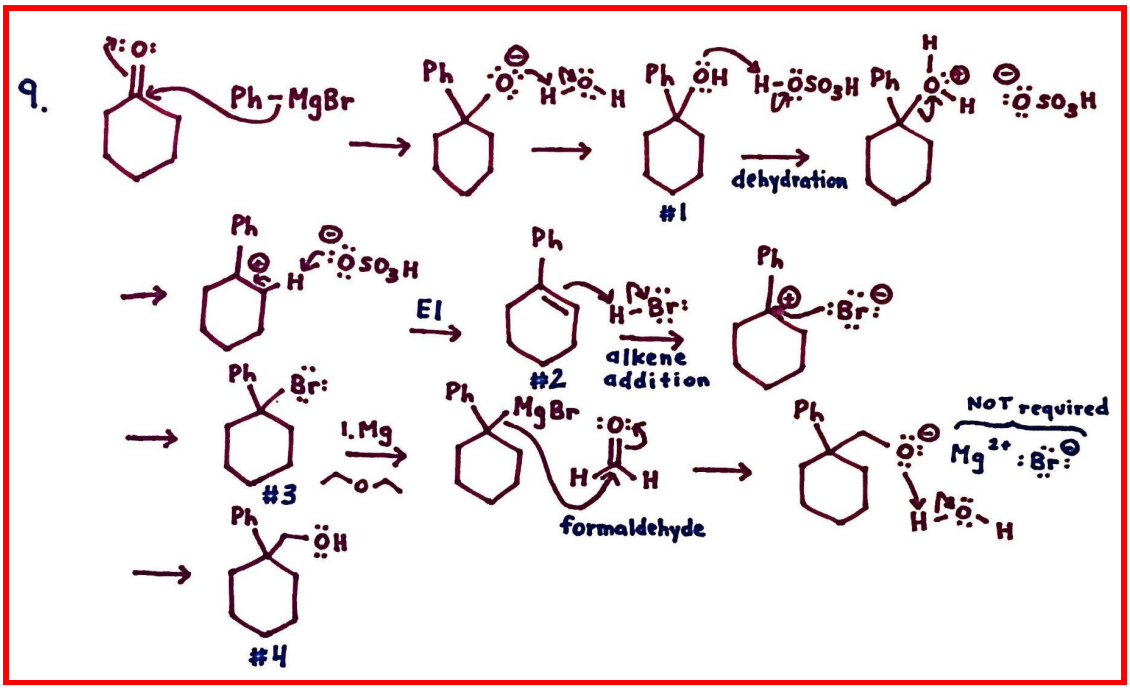
c.



Sodium borohydride only reduces aldehydes and ketones to alcohols, while lithium aluminum hydride can also reduce type 2 carbonyls, like esters, carboxylic acids, and amides. Note that an amide is reduced to an amine. It is important to understand the mechanisms of these reactions rather than just memorizing the products.

9. Identify each intermediate and the final product in the following reaction scheme. (20.49, ABEG pathway only)

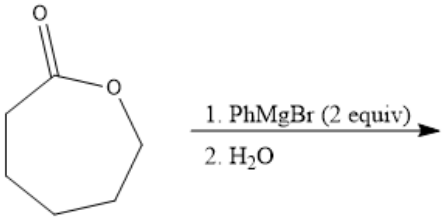


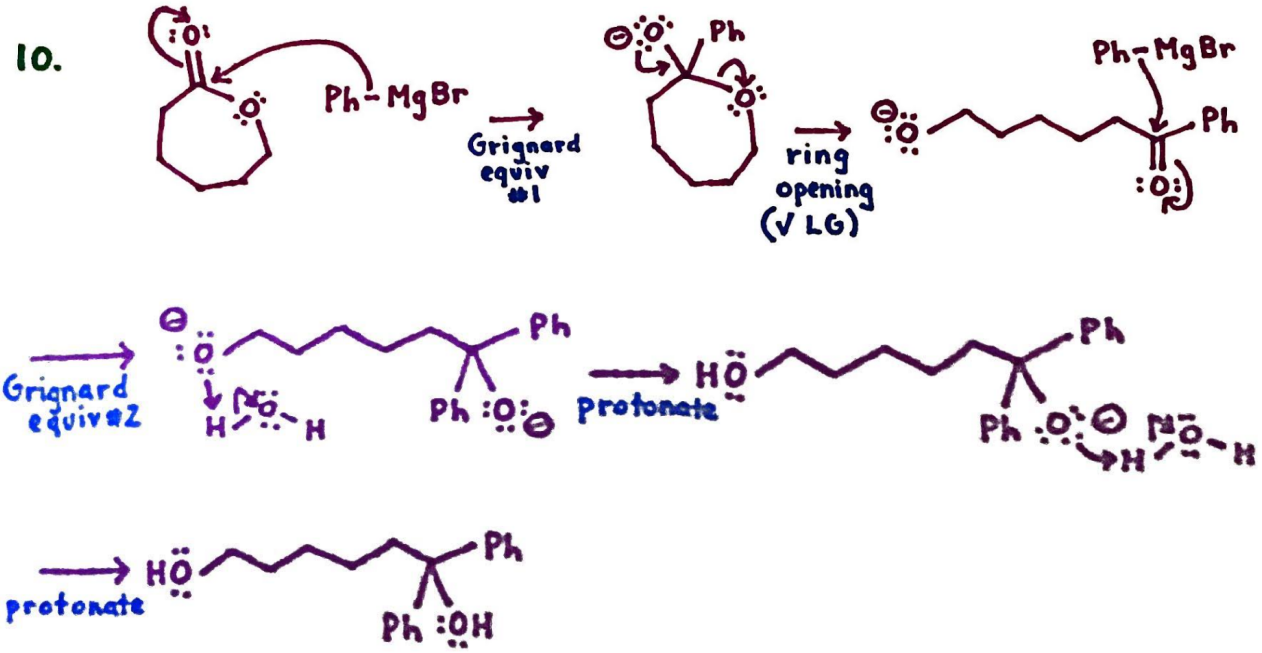


Note that the formation of product #2 is not entirely necessary, mainly because HBr can be used directly after the alcohol (product #1) to yield the tertiary alkyl halide (product #3). Recall that using PBr_3 and pyridine on a tertiary alcohol WILL NOT WORK due to its mechanism's S_N2 exclusivity. Alternative approaches consist of making a -OToS ([1] TsCl, pyr.) or directly adding HBr. Likewise, to promote dehydration, concentrated H_2SO_4 with heat should be used and is implied above.

The mechanism for each reaction was shown (despite not being required) to facilitate understanding reactions rather than memorizing them.

10. Predict the product and draw a detailed, stepwise mechanism for the following reaction. (Discussion WS 3.4 2021)





The Grignard reagent acts as a strong nucleophile that will initially attack the electrophilic ester carbon. Then, since the adjacent -OR group is a good leaving group, a **ring opening** occurs, and a ketone is formed. Finally, due to the potency of Grignard reagents, the newly formed ketone undergoes another nucleophilic attack to form the preliminary final product. The protonation step will then lead to the diol product. **Note that the final protonation steps are meant to occur in two separate steps (and in no particular order).**

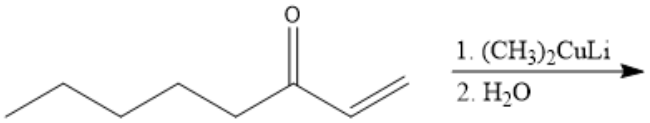
***To consider**: If this reaction were completed with only one equivalent of Grignard reagent, how would the product differ, if at all?*

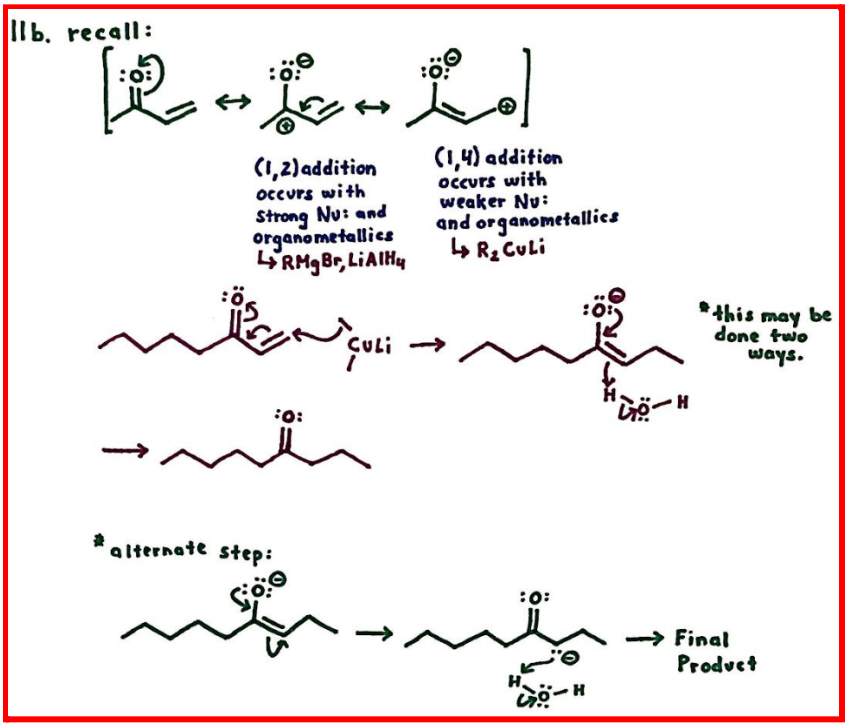
***Answer:** You would only get **50% conversion**, meaning lots of ketone product.*

*Note that Chem 51C will feature lots of reactions that open and form rings, so make sure you are comfortable doing this and always **COUNT YOUR CARBONS!***

For mechanisms, make sure all reacting atoms have lone pairs, arrows begin from areas of electron density (lone pairs, pi bonds, etc), land on areas with electron deficiency, and all bond angles are accurate (alkene substituents are 120° apart, etc).

11. Draw the product(s) of the following reactions involving organometallic reagents. (20.43 b, c)

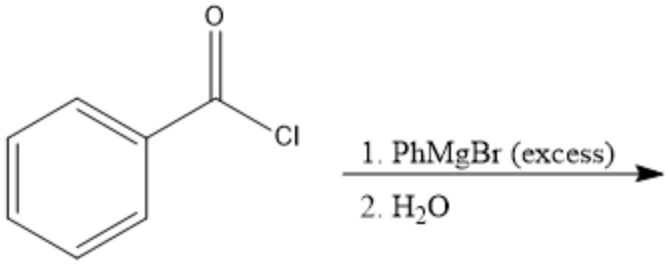
a. 

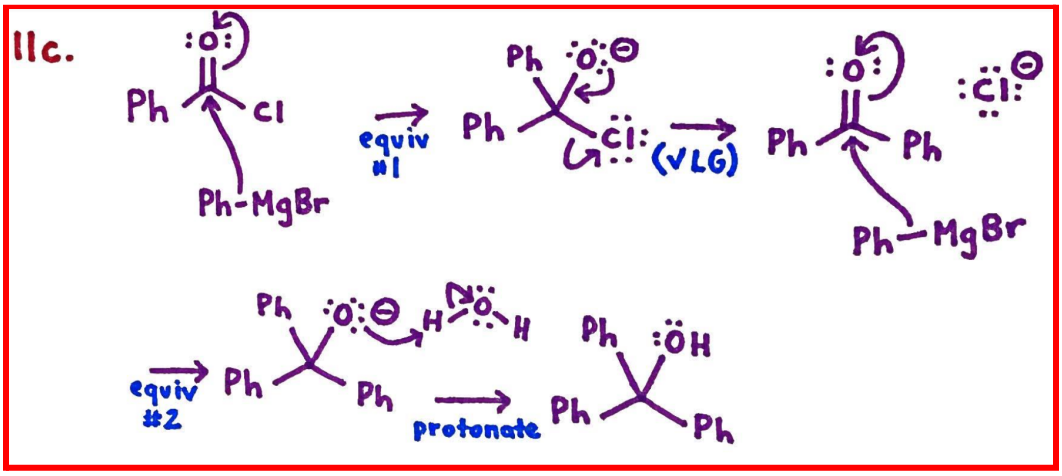


Recall that the (1,4)-kinetic product is formed when using soft organometallic reagents (such as R-CuLi) on alpha-beta unsaturated compounds. Likewise, the mechanism for protonation may be done in either of the two ways demonstrated above.

The mechanism for this reaction was shown (despite not being required) to facilitate understanding reactions rather than memorizing them.

b.



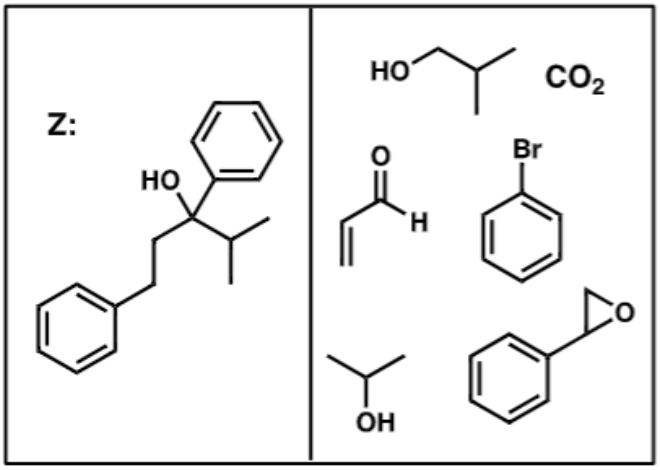


Recall that the addition of Grignard reagents to acid chlorides results in double addition to the carbonyl carbon. The protonation step is done separate from the Grignard addition due to organometallic reagents being very basic.

***To consider**: If this reaction were completed with an organocuprate instead, would the product differ from using a grignard reagent? If so, how?*

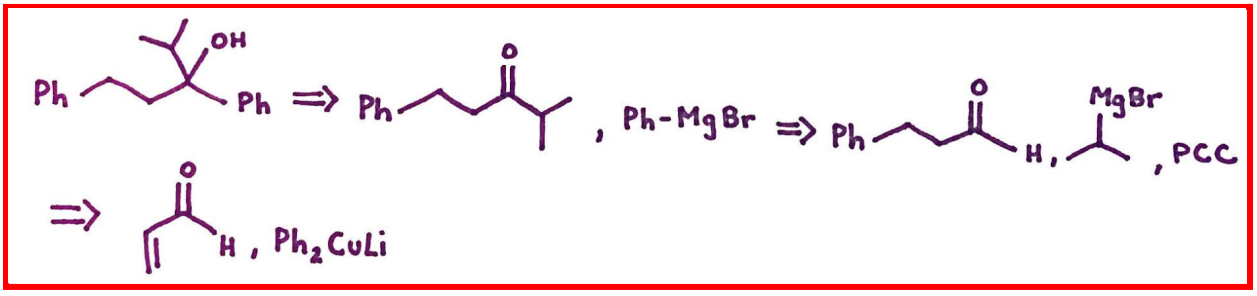
***Answer:** Recall that organocuprates can only add to epoxides, acid chlorides, and alpha-beta unsaturated compounds. In the case of acid chlorides, they only **add once** to generate a ketone.*

12. Devise a synthesis of the compound Z, using any necessary inorganic reagents, but making use of the compounds in the right-hand box as the only sources of carbon atoms. (POW WS 3.4 2021)



DISCLAIMER: Synthesis problems will 99.999% of the time have more than one solution. The pathway described below is merely one of the many possible ways to synthesize the compound presented above.

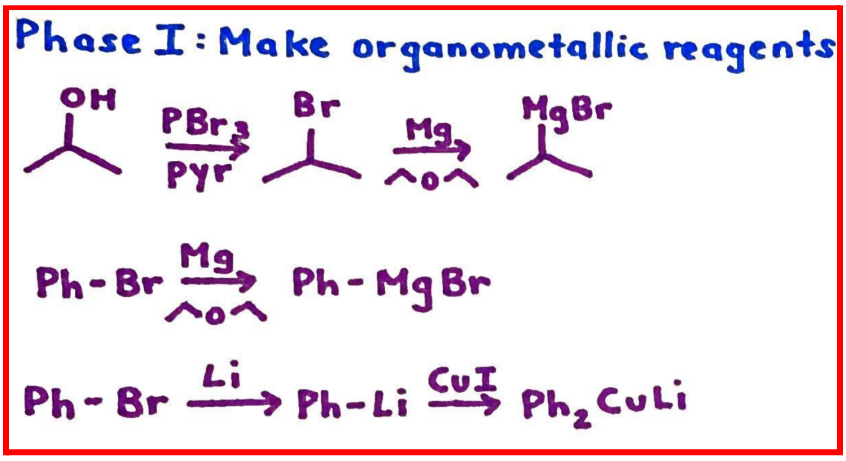
Retrosynthetic Approach

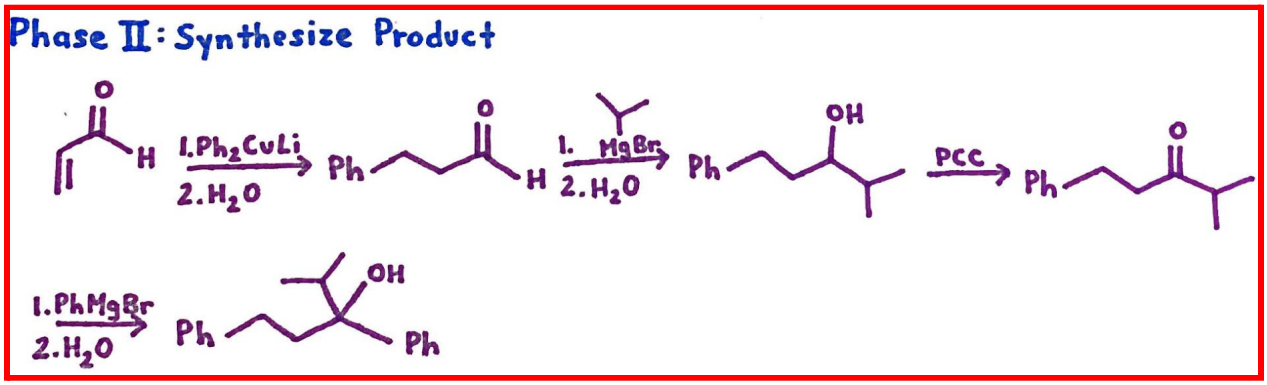


There are very many ways to synthesize the target compound in terms of which organometallic reagents to make and react with different carbonyl compounds. The pathway above highlights one such method. From the final product, the key carbon to consider is the one in which the alcohol is present. It can be implied that an organometallic reagent was used to form this alcohol from a ketone, and one such scenario is depicted as the first step of this retrosynthesis. From this ketone, it is likely that yet another organometallic reagent was used to add a separate carbon chain. Remember that addition of an organometallic reagent to a carbonyl (in this case, an aldehyde) that DOES NOT have a good leaving group will form an alkoxide that is subsequently protonated by water. Thus, to make a ketone that can undergo another addition reaction of organometallic reagent, PCC should be used. Finally, from the list of starting materials, notice

that an alpha-beta unsaturated compound can be used, together with an organocuprate, to generate the aldehyde.

Synthetic Approach

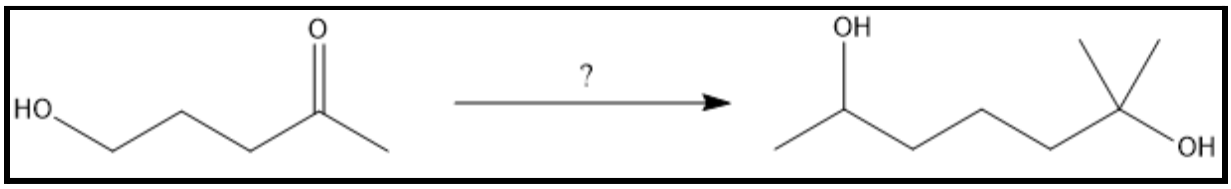




To begin synthesis of the target compound, you may start by first generating all organometallic reagents necessary. Then, use the alpha-beta unsaturated aldehyde as the starting material. Treatment with an organocuprate (generated in Phase I) will lead to addition of a Ph- group to the beta carbon. Next, add a Grignard ($(CH_3)_2CH$-MgBr) to the aldehyde in order to get the $(CH_3)_2CH$-R group present on the target product. Protonation will lead to the formation of an alcohol, which is subsequently oxidized to a ketone by PCC. Finally, to add the final Ph- group, introduce another Grignard (Ph-MgBr) followed by a protonation step.

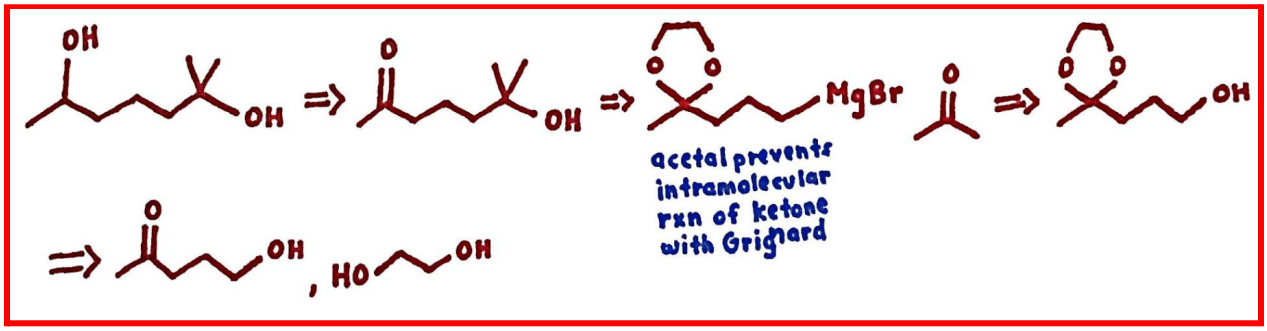
Note that, as Dr. King has mentioned in lecture, the stoichiometry and side products of organometallic reagent generation are NOT required.

13. Devise a synthesis of the following compound from the given starting material. You may only use organic alcohols having fewer than four carbons and any inorganic reagents. (21.60b)



DISCLAIMER: Synthesis problems will 99.999% of the time have more than one solution. The pathway described below is merely one of the many possible ways to synthesize the compound presented above.

Retrosynthetic Approach



The synthetic approach above details formation of the target compound by means of a "protecting group", though this is not the TBDMS-Cl group used in the previous chapter. Recall that acetal formation is reversible and can be done by adding a diol to either a ketone or aldehyde, while catalyzed by an acid. Without the acetal, the Grignard reagent used in later steps will react intermolecularly with other ketone reactants and form an undesirable product(s).

Synthetic Approach