Summary of Alcohol Syntheses, Ch. 10 (and Review of Old Ones).

1 $R{-}OH \xrightarrow{Na} R{-}ONa$

- Potassium (K) analogous.
- Key way to convert alcohol to alkoxide, reactive as S_N2 nucleophile and E2 base.

2 $R{-}OH \xrightarrow[2.\ R'\text{-}X]{1.\ Na} R{-}O{-}R'$

- Alkoxide formation-S_N2 route to ether
- The electrophile R'-X must be S_N2 reactive, preferably 1° with a good leaving group

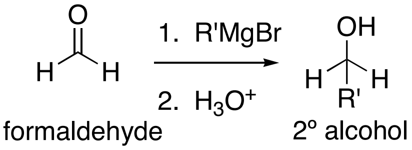
Mech?

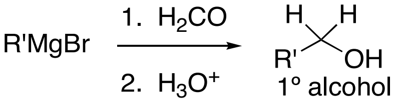
3 $R{-}Br \xrightarrow{Mg} RMgBr$

-Li is analogous for making RLi, which also act analogously.

-MgBr is spectator: $R^{\ominus}$ is key.

4

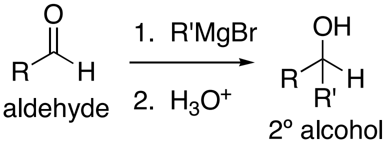


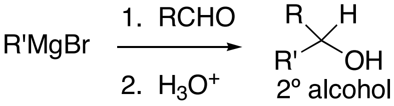


1 carbon chain extension

Mech

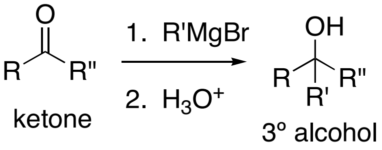
5

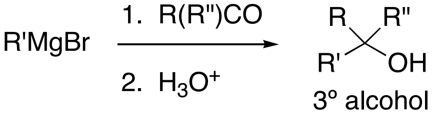




Mech

6

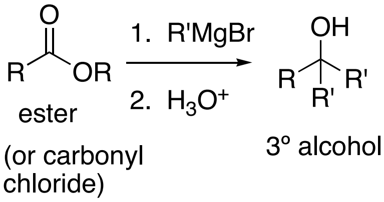


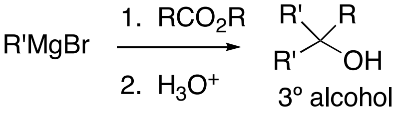


All three R groups can be different.

Mech

7

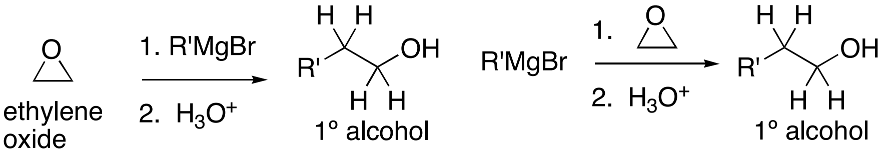




At least 2 R groups must be the same

Mech

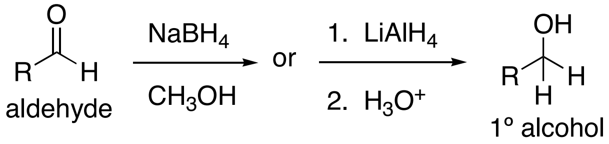
8



2-Carbon chain extension

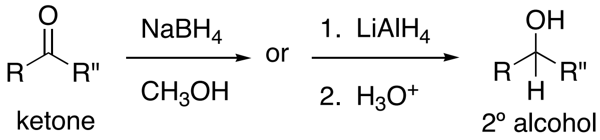
Mech

9



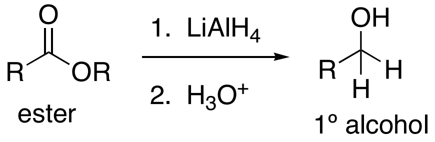
Mech

10



Mech

11

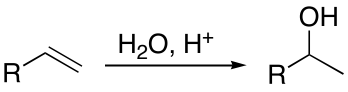


$NaBH_4$ will not react with esters

Mech

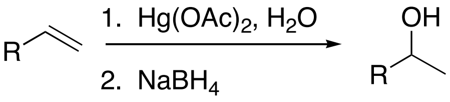
Review Routes to Alcohols

10



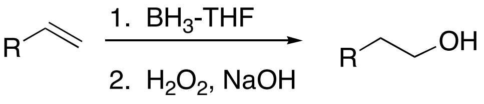
Markovnikov

11



Markovnikov

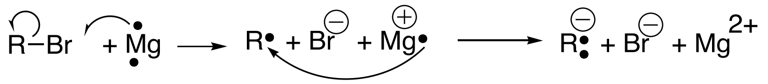
12



anti-Markovnikov

13 $R{-}X \xrightarrow{NaOH} R{-}OH$ S_N2 mech, needs 1° or 2° system and an excellent leaving group

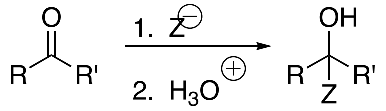
Summary of Mechanisms, Ch. 10



Not for Test

For Test:

1.

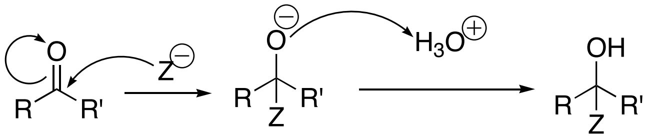


aldehyde
or ketone
or formaldehyde

$Z^{\ominus}$ may be $R^{\ominus}$ (RMgBr)

or $H^{\ominus}$ ($NaBH_4$ or $LiAlH_4$)

mech:



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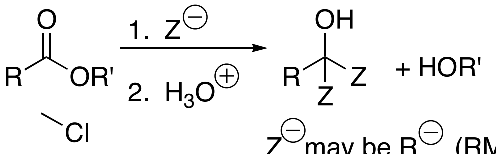
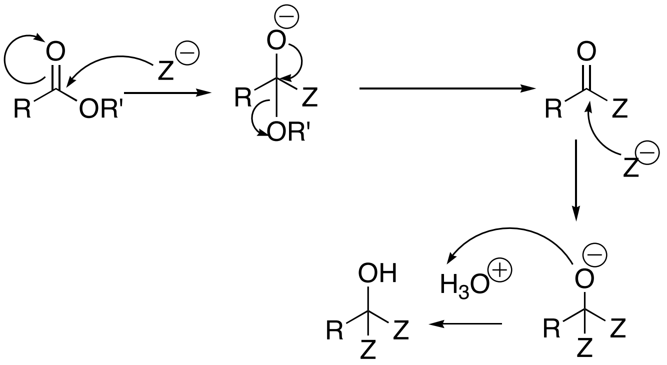


esters
or
acid chlorides

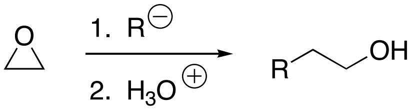
$Z^{\ominus}$ may be $R^{\ominus}$ (RMgBr)

or $H^{\ominus}$ (LiAlH4)

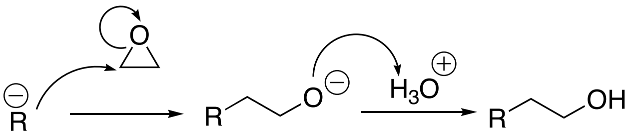
mech:



3.



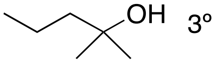
mech:

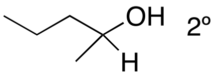


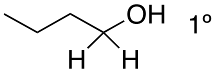
10.1,2 Intro, Classification

"**Alcohol**": OH attached to a saturated, sp^3, "alkyl" carbon

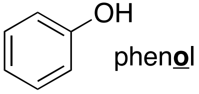
1°, 2°, 3° Alcohols: based on whether the carbon with the OH is 1°, 2°, or 3°

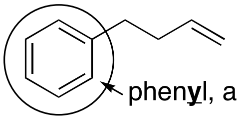






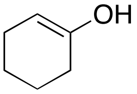
"**Phenol**": OH attached to an aromatic
-Note: phen**o**l, not phen**y**l





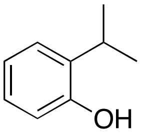
phen**y**l, as substituent

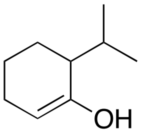
"Enol" or "vinyl alcohol": OH attached to an alkene

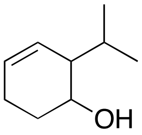


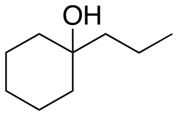
enol or vinyl alcohol

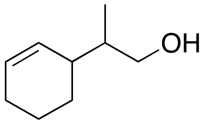
Problem: Classify each of the following either as a phenol, as a carboxylic acid, or as a 1°, 2°, 3°, or vinyl alcohol:

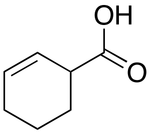








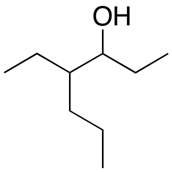


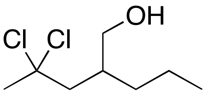


10.3 Nomenclature

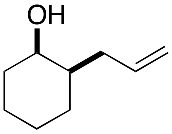
A. IUPAC, when alcohol is priority functional group and is part of the core name: x-alkan**ol**

- Choose longest carbon chain **that has the OH attached**
- Remember to number!
- The oxygen itself does not count as a number



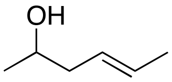


B. Cycloalkanols: The OH-carbon is automatically Number 1

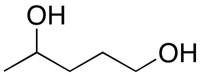


C. **x-Alken-z-ol**. When an alkene is in the main carbon chain, you need two number descriptors, one for the alkene, the second for the alcohol.

- The OH still dictates the numbering
- The OH number gets moved right before the "ol"
- The alkene number goes in front, in front of the "alken" portion
- Note: you only put the OH number right in front of the "ol" when you have an alkenol (or alkynol)



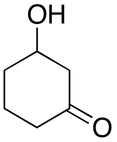
D. Diols: x,y-alkane**diol**



E. Functional Group Priority: CO_2H > C=O > OH > amine > alkene > halide

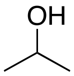
- When you have more than one functional group, the higher priority dictates the numbering
- **The higher priority is used in the "core name"**
- **The lower priority group may be forced to be named as a substituent**

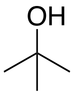
F. OH as a Substituent: "**Hydroxy**"



G. Common Names: Alkyl alcohol

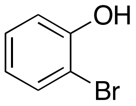
CH_3OH

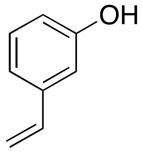


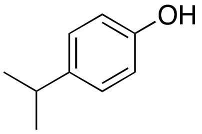


H. Substituted Phenols

- IUPAC: use numbers, with OH carbon #1
- Common:
  - **Ortho: 2-position, adjacent**
  - **Meta: 3-position, two carbons away**
  - **Para: 4 position**
- Skill: be able to use or recognize either system





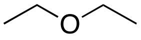


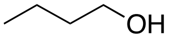
IUPAC:

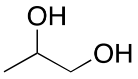
Common:

10.4 Physical Properties: Dominated by H-Bonding

BP: Match the boiling point for the following structures: 35º, 137º, 187º

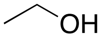




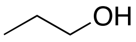


Water solubility: water solubility decreases as hydrophobic R gets longer

- In general,
  - R ≤ 4 carbons, ROH substantially water soluble
  - R ≥ 5 carbons, ROH minimal water solubility



infinite



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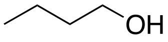
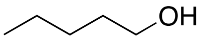
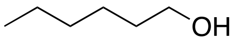


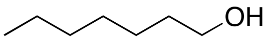
9.1g/100mL



2.7g/100mL



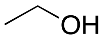
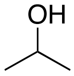
0.6g/100mL



0.1g/100mL

10.5 Commercially Important Alcohols

- Toxic: All alcohols are "toxic" if swallowed in sufficient quantities

CH_3OH		
• Cheap • Solvent • Fuel • 100 mL → death • 15 mL → blindness	• 200 mL (7 oz) → death • Least toxic alcohol • Alcoholic beverages • Fermentation • Solvent	• Rubbing alcohol • 100 mL → death • Kills germs on skin, but not absorbed

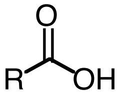
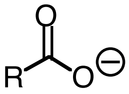
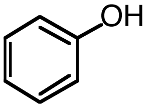
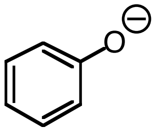
10.6 Acidity of Alcohols and Phenols

A. Alcohols are weak acids → can be ionized by stronger bases

$$ROH + B^{\ominus} \rightleftharpoons RO^{\ominus} + BH$$

- goes to the right (alkoxide) only if $RO^{\ominus}$ is more stable than $B^{\ominus}$
- ex. $^{\ominus}NH_2$, $^{\ominus}CH_3$
- ex. If a <u>less</u> stable oxygen anion can convert to a <u>more</u> stable oxygen anion

B. Acidity Table

Class	Structure	Ka	Acid Strength	Anion	Base Strength
Strong Acids	H-Cl	10^{2}		$Cl^{\ominus}$	
Carboxylic Acid		10^{-5}			
Phenol		10^{-10}			
Water	H_2O	10^{-16}		$HO^{\ominus}$	
Alcohol	ROH	10^{-18}		$RO^{\ominus}$	
Amine (N-H)	RNH_2	10^{-33}		$RNH^{\ominus}$	
Alkane (C-H)	RCH_3	10^{-50}		$RCH_2^{\ominus}$	

Notes/skills:

1. Be able to rank acidity.
2. Memorize/understand neutral OH acidity ranking: $RCO_2H > H_2O > ROH$
   - Reason: **resonance** stabilization of the **anion**
3. Predict deprotonation (acid/base) reactions
   - Any weak acid **will be** deprotonated by a **stronger base (lower** on table)
   - Any weak acid **will not be** deprotonated by a **weaker base (higher** on table)
4. Predict ether/water extraction problems
   - If an organic chemical is neutral and stays neutral, it will stay in ether layer
   - If an organic chemical is ionized (by an acid-base reaction), it will extract into the aqueous layer

Problems

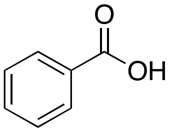
8. Draw arrow to show whether equilibrium favors products or reactants. (Why?)

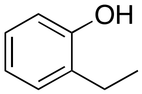
9. Which of the following will deprotonate methanol?

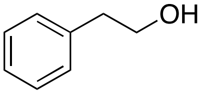
H_2O CH_3CO_2Na PhONa NaOH $NaNH_2$ CH_3MgBr

An acid (left side) will only be deprotonated by an anion/base that is **lower** on the right side

10. When the following are dissolved in ether and then treated with NaOH/water, which would extract out of the ether layer into the water layer?



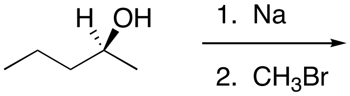




10.6B Formation of Sodium, Potassium Alkoxides; 2-Step Conversion of Alcohols into Ethers via the Alkoxides

1	$R{-}OH \xrightarrow{Na} R{-}ONa$ $R{-}OH \xrightarrow{K} R{-}OK$ $\Big\}\ R{-}O^{\ominus}$	• Potassium (K) analogous. • Key way to convert alcohol to alkoxide, reactive as S_N2 nucleophile and E2 base.
2	$R{-}OH \xrightarrow[2.\ R'\text{-}X]{1.\ Na} R{-}O{-}R'$	• Alkoxide formation-S_N2 route to ether • The electrophile R'-X must be S_N2 reactive, preferably 1° with a good leaving group

Reaction 1: Key source of nucleophilic/basic alkoxides



10.7 Synthesis of Alcohols: Review: See p. 2, from Alkyl Halides (S_N2) and Alkenes

10.8 Organometallics: RM (M = Metal) = R$^{\ominus}$ M$^{\oplus}$

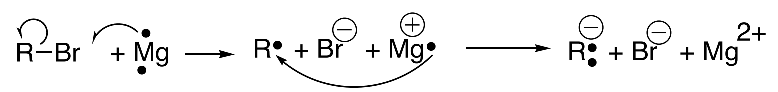
$$\mathrm{R{-}Br} \xrightarrow{\mathrm{Mg}} \underset{\text{"Grignard Reagent"}}{\mathrm{RMgBr}}$$

$$\mathrm{R{-}Br} \xrightarrow{\mathrm{2Li}} \mathrm{RLi + LiBr}$$

-Li is analogous for making RLi, which also act analogously.

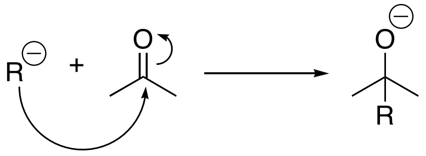
-MgBr is spectator: R$^{\ominus}$ is key.

1. We will focus on the magnesium reagents RMgBr
2. RMgBr = "Grignard Reagents" (Victor Grignard)
3. Key: This is the way to make R$^{\ominus}$, strong nucleophiles/bases
4. RMgBr are formed via redox reaction.
   - Mg gives up two electrons, is oxidized
   - Bromine is reduced to bromide anion
   - Carbon is reduced to carbanion



Not for Test

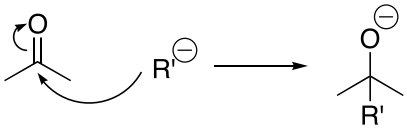
5. The formation of Grignard Reagents is completely general for all R-Halides:
   - 3°, 2°, and 1° alkyl halides all work well
   - Aryl and Vinyl halides as well as alkyl halides work well
   - RCl, RBr, and RI all work well
   - For class, we will normally use bromides, due to synthetic accessibility
6. **<u>View as carbanions: RMgBr = R$^{\ominus}$ Super Strong Bases and Nucleophiles</u>**
   - The counterion metal is a spectator
   - Stability-reactivity principle: very unstable → very reactive
   - This great reactivity is very useful (as nucleophile)
   - This great reactivity (as base) has implication for proper technical use (see following)
7. Solvent and handling: Grignard reactants RMgBr must be made, stored, and handled in special solvents under special conditions:
   - No water allowed
     - R$^{\ominus}$ + H_2O → R-H + HO$^{\ominus}$ Destroys carbanion
   - No alcohol or amines or acids allowed either, or carbanion will just deprotonate them too
   - If any chemicals with carbonyls are present, they too will react with the carbanion by nucleophile/electrophile reaction



   - Grignards and other organometallics are made in either alkane or ether solvents.
     - These don't have any acidic hydrogens that protonate carbanions.
     - These don't have any carbonyls that react with carbanions
8. Two perspectives for dealing with organometallics in general and RMgBr in particular
   - Mechanistic Thinking: R$^{\ominus}$
   - Predict-the-product thinking: R-MgBr: easier to see source and substitution product.

$$\mathrm{R{-}Br} \xrightarrow{\mathrm{Mg}} \mathrm{R{-}MgBr} \xrightarrow{\text{Electrophile}} \text{R−Electrophile}$$

10.9 Addition of RMgBr to Carbonyl Compounds: Alcohols are Produced



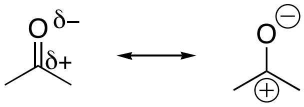
Exothermic Addition of Carbon or Hydrogen Anions:

- σ bond (made) stronger than π bond (broken)
- oxygen anion more stable than carbanion

Carbonyl is strongly electrophile

-much stronger even than a 1° alkyl iodide!

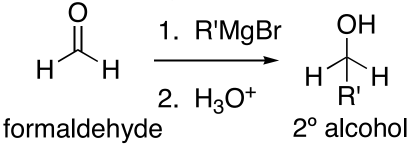
1. Breakable π bond
2. Carbonyl polarity

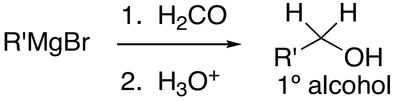


Additions of Grignard Reagents to Carbonyl Compounds

From Carbonyl's Perspective — From Grignard's Perspective

4

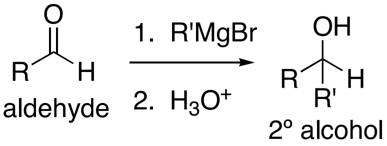


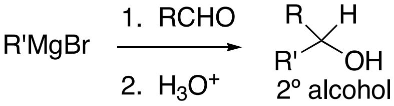


1 carbon chain extension

Mech

5





Mech

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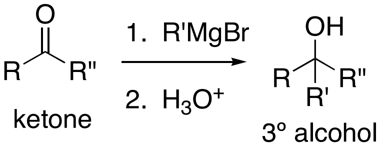
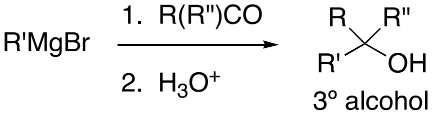
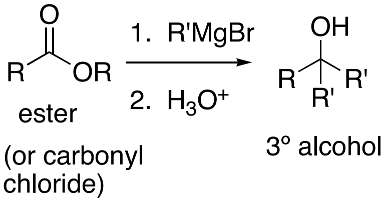


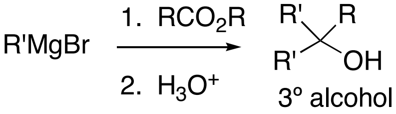


All three R groups can be different.

Mech

7





At least 2 R groups must be the same

Mech

Pattern:

1. After reaction, the original carbonyl carbon will have one and only one C-O single bond
2. For formaldehyde, aldehydes, and ketones, one R group adds (reactions 4-6)
3. For esters or carbonyl chlorides ("acid chlorides"), two R groups add
    - Replace not only the carbonyl p-bond, but also the "extra" C-O or C-Cl single bond
4. Product output:
    - Formaldehyde (2 H's) → 1° alcohol
    - Aldehyde (1 H) → 2° alcohol
    - Ketone (0 H) → 3° alcohol. No need for all 3 attachments to be the same.
    - Ester (0 H) → 3° alcohol. At least two common attachments at end.

Predicting Grignard Reaction Products

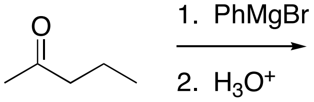
1. From carbonyl perspective:
   - The carbanion R’ adds to the carbonyl carbon
   - The carbonyl =O gets replaced by –OH
   - For formaldehyde, aldehydes, and ketones: the two attachments on the original carbonyl carbon remain attached as spectators
   - For esters or acid chlorides: the one non-heteroatom attachment on the original carbonyl carbon remain attached as spectators.
     - The “extra” heteroatom gets replaced by a second carbanion R’

2. From Grignard perspective:
   - Where R-MgBr begins, R-C-OH ends.
     - In other words, the MgBr gets replaced by the carbonyl carbon

Note: Be sure that in the product, no carbon has more than one C-O bond

Draw products from the following reactions.

1º, 2º or 3º?

1


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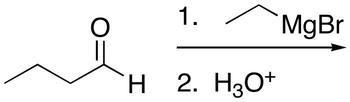

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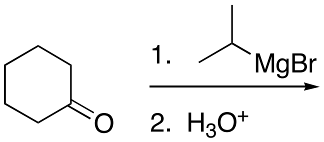

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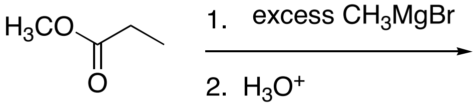

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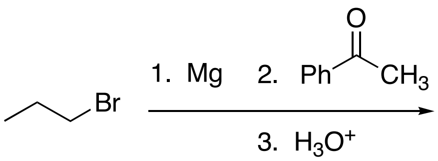

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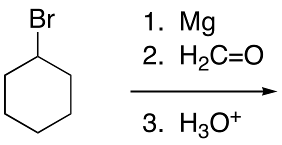
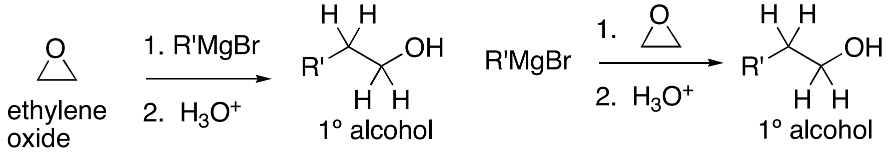


10.9E Grignard Reaction with Ethylene Oxide (Simplest Epoxide)

8



2-Carbon chain extension

Mech

Notes

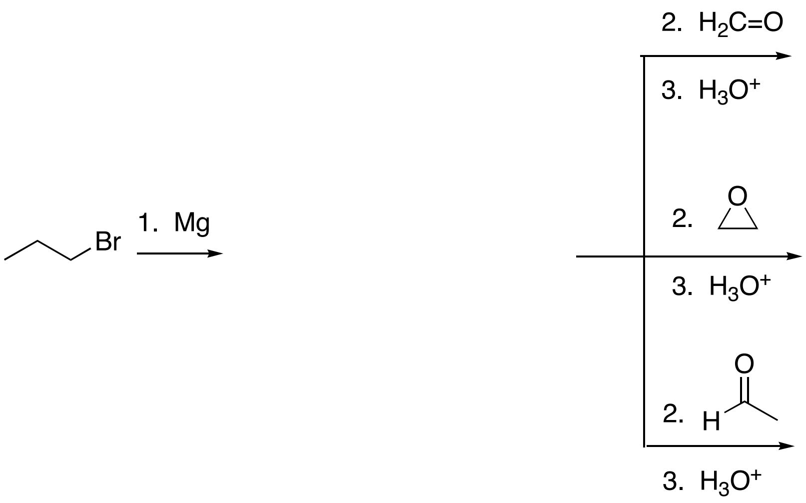
1. Results in a 1° Alcohol
2. **Predicting product: Two carbons end up in between the carbanion R' and the OH**
3. Ethylene oxide and formaldehyde are complementary Grignard acceptors leading to 1° alcohols
    - Ethylene oxide extends the carbon chain by two (relative to the original RMgBr)
    - Formaldehyde extends the carbon chain by one (relative to the original RMgBr)
4. 2-Carbon ethylene oxide and 2-carbon ethanal give different products
    - Ethylene oxide → the OH is 1° and the OH is two carbons removed from the carbanion R
    - Ethanal → the OH is 2° and the OH and carbanion R are both connected to the same carbon

Draw products from the following reactions.

1

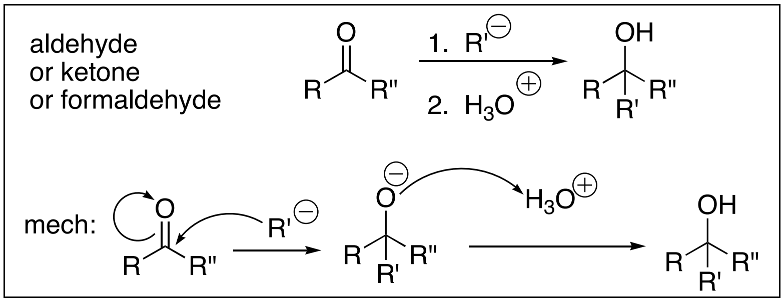
2

3



Reaction Mechanisms for Grignard Reactions

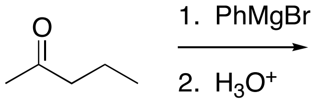
Formaldehyde, Aldehyde, or Ketone as Carbonyl Compound (Reactions 4, 5, and 6)



1. Two simple steps:
    - **a. Addition**
    - **b. Protonation**
2. Timing:
    - a. The carbanion is added first, at one step in time, under strongly anionic conditions
    - b. Later acid is added, in a second laboratory step. This provides a cationic environment
3. RMgBr = R-MgBr = $R^{\ominus}$ carbanion
    - a. The $^{\oplus}$MgBr stuff is spectator, doesn't need to be drawn in
    - b. Ignore in mechanisms
    - c. In reality, it actually does play a nontrivial role, but we'll save that for grad school!

Draw mechanisms for the following reactions:

1



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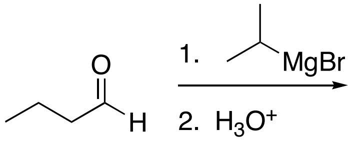
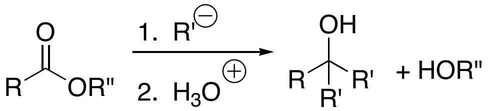
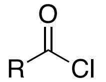


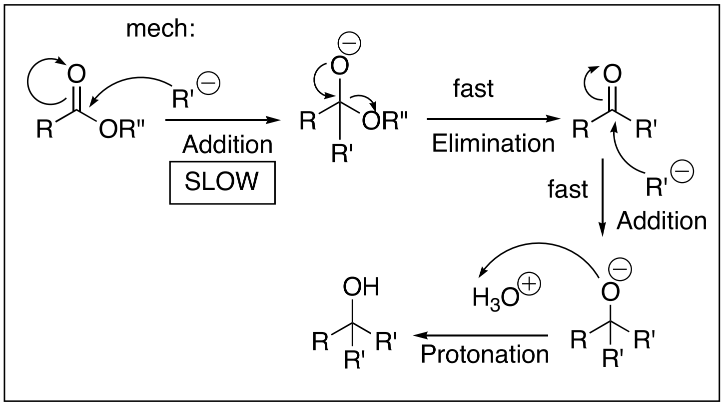
<u>Esters or Acid Chlorides: More Complex, Needs to Explain Two Additions and More Bond Breakings</u>



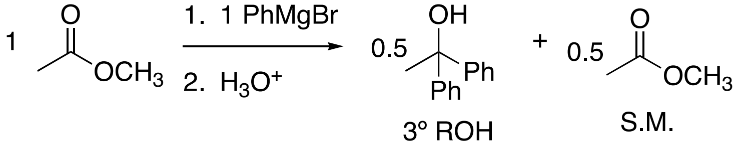
esters or
acid chlorides

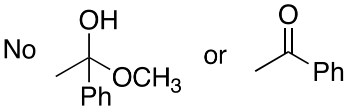


acid chlorides



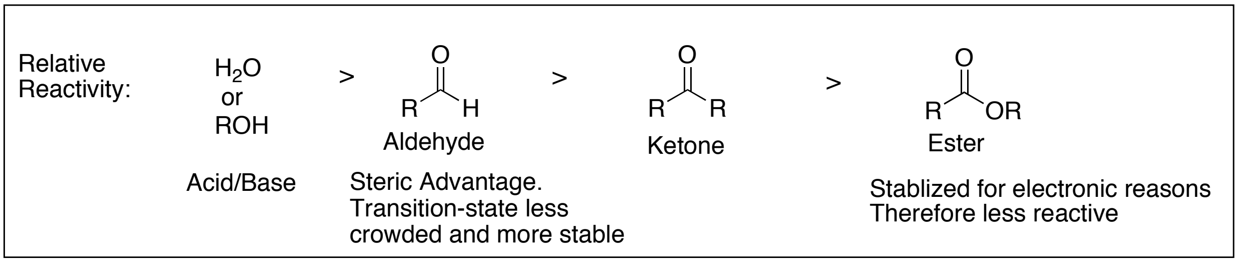
1. Four Step Mechanism:
   - a. **<u>Addition</u>**
   - b. **<u>Elimination</u>**
   - c. **<u>Addition</u>**
   - d. **<u>Protonation</u>**
2. Timing:
   - a. The carbanion is added first, at one point in time, under strongly anionic conditions
     - o The first three steps all occur under these anionic conditions
   - b. Acid is only added much later, in a second laboratory step. This gives a cationic environment.
   - c. Why don't you just protonate after the first step?
     - o There is no proton source available, and the elimination proceeds instead!
3. What if I add only one RMgBr?





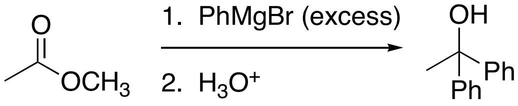
After Grignard reaction, **<u>never</u>** show any products in which a carbon has more than one oxygen

Why? Kinetics and Reactivity. **<u>MEMORIZE</u>**.



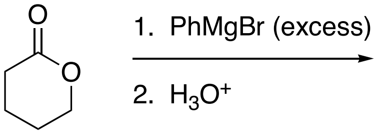
- Large differences in reactivity, with ketone > ester
- Elimination step 2 is also very fast
- Thus, under the anionic conditions, the addition is the slow step
  - o After it does happen, elimination and another addition happens bang-bang.

Draw Mechanism:

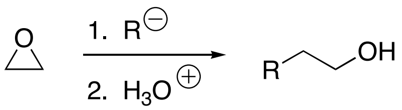


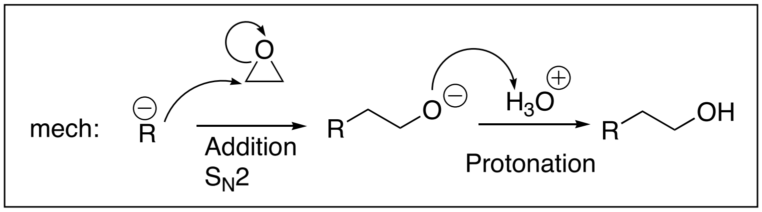
Cyclic Ester: The O-Carbonyl single bond breaks, but the other C-O single bond does **not** break
-the result is formation of a dialcohol

Draw product and mechanism for the following:

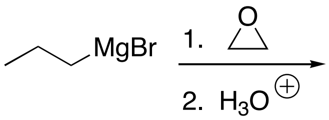


Ethylene Oxide Mechanism

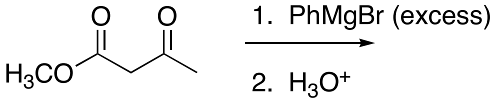




Draw product and mechanism for the following:



More Grignard Practice. Including polyfunctional Molecules: (Know relative reactivity)

1


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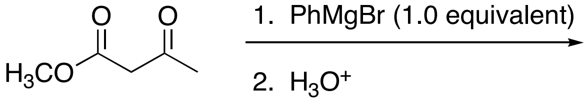

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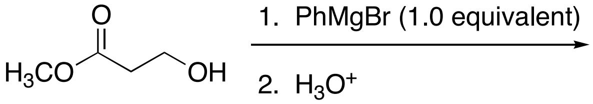

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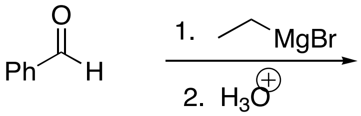

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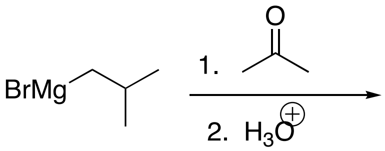

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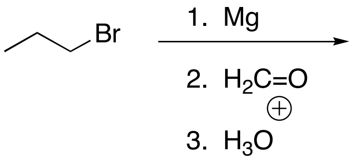

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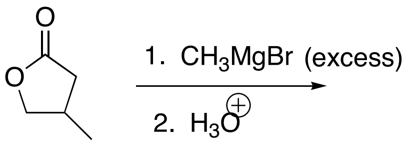

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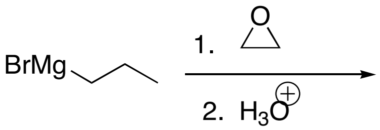
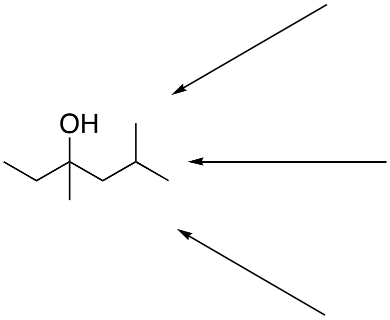
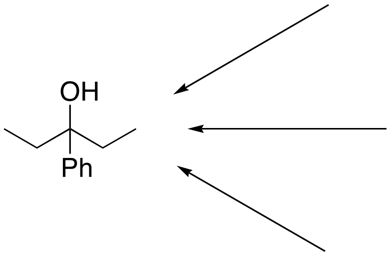


Grignards in Synthesis: Provide Precursors.

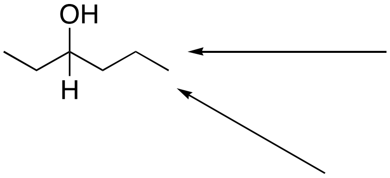
- **Think backwards from Targets to Reactants.**
- Identify possible Grignards and Grignard acceptors
- **Pattern:**
  - **3° alcohol, all three attachments different ← Ketone Precursor**
  - **3° alcohol, two (or more) of the attachments identical ← Ester**
  - **2° alcohol ← Aldehyde**
  - **1° alcohol ← Formaldehyde or ethylene oxide**



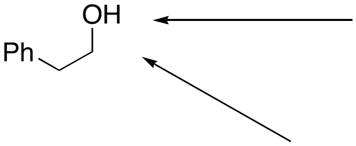
a.



b.



c.

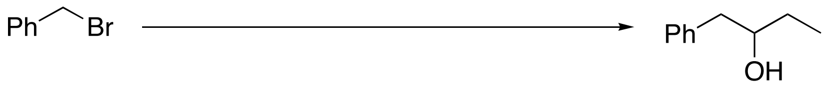


d.

<u>Provide Reagents for the Following Transformations.</u> You may use whatever reagents, including ketones or aldehydes or Grignards or esters, that you need.

- Key: Try to identify key C-C connection in the product that wasn't present to start with
- Try to identify the where the reactant carbons are in the final product
- Numbering your carbon chains is very helpful.
- Usually best to work backwards from the product

a.

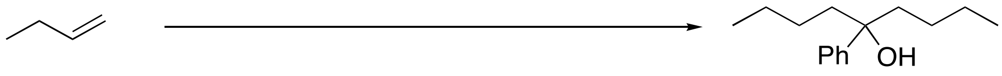


2 steps plus
H_3O^+ workup

b.

3 steps plus
H_3O^+ workup

c.



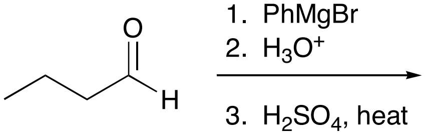
3 steps plus
H_3O^+ workup

d.

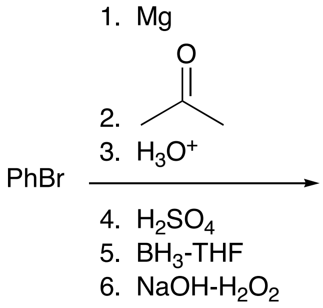
e.

Combining Grignard Reactions with Other Reactions

a.



b.

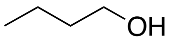


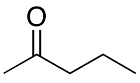
10.10 Restrictions on Grignard Reactions

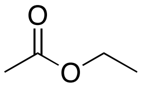
- RMgBr = R$^{\ominus}$ carbanion, highly unstable, highly reactive.
- Unstable in the presence of:
  1. OH's (get proton transfer reaction)
  2. Carbonyls (get Grignard-type nucleophilic addition)

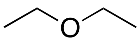
1. Solvent limitations. RMgBr cannot be formed and used in the presence of
   - H2O
   - ROH
   - Any solvent with a C=O

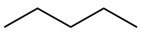
Which Solvents (if any) Would be OK for Handling RMgBr?,





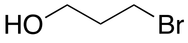


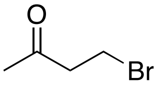


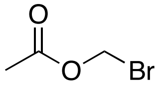


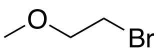
2. Substrate limitations. Any organohalide that also contains an OH or C=O bond can't be converted into a useful RMgBr, because it will self-destruct.

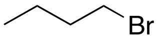
Which substrates could be converted into RMgBr, and subsequently reacted with CH_3CHO?





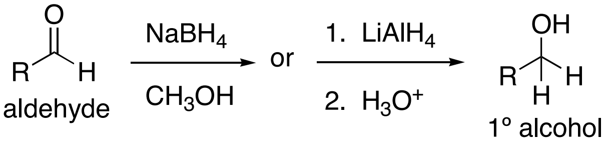


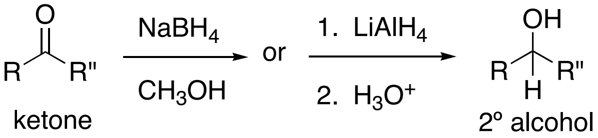


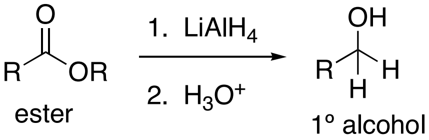


3. Atmosphere/Glassware/Storage limitations. Make, store, and use in:
   - water-free dried glassware
   - moisture-free atmosphere. (Dried air, or else under nitrogen or argon atmosphere)
   - When stored for extended periods, must have very good seals so that no air can leak in.

10.11 Alcohols by Reduction of Carbonyls: H$^{\ominus}$ Addition

9  Mech

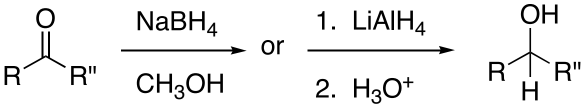
10  Mech

11  Mech

NaBH$_4$ will not react with esters

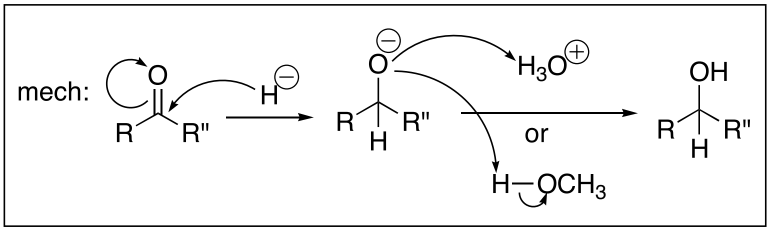
Mechanism
Aldehydes and Ketones

aldehyde
or ketone
or formaldehyde

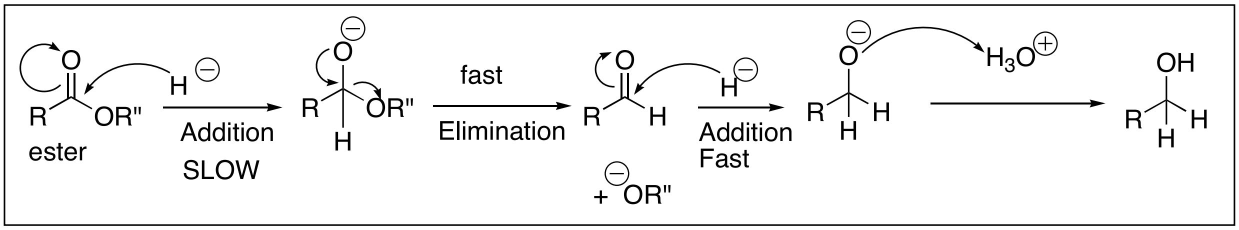


NaBH$_4$ = H$^{\ominus}$

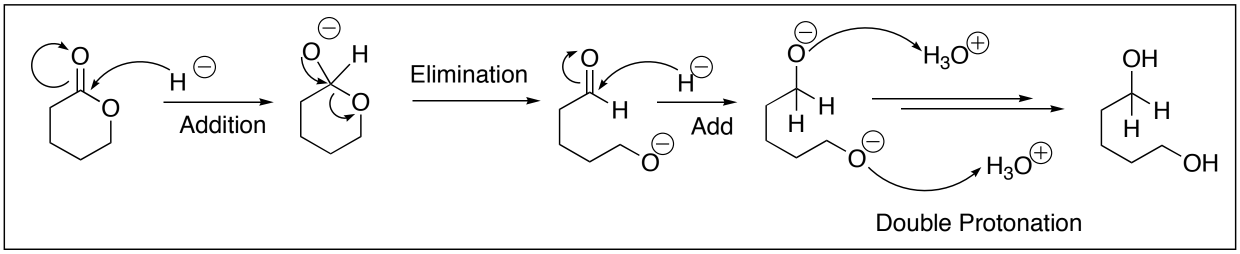
LiAlH$_4$ = H$^{\ominus}$



Esters

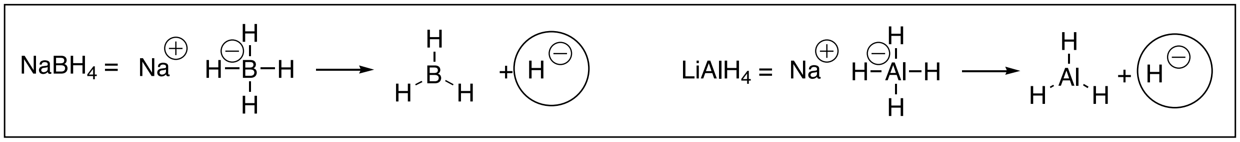


Cyclic Esters



Notes:

- Mechanisms are exactly like with Grignard reactions
- $LiAlH_4$ and $NaBH_4$ function as hydride anions $H^{\ominus}$
- For mechanisms, just draw $H^{\ominus}$ rather than trying to involve the Li and Al and Na and B…



- Boron is one row higher than aluminum, and in keeping with normal periodic patterns is more electronegative
  - Because boron is more electronegative, the $BH_4^{\ominus}$ anion is more stable, and less reactive.
    - The boron holds the $H^{\ominus}$ more tightly.
  - Aluminum being less electronegative doesn't attract and hold the $H^{\ominus}$ as well, and thus is considerably more reactive.

Reactivity

	Aldehydes	Ketones	Esters
$LiAlH_4$	Yes	Yes	Yes
$NaBH_4$	Yes	Yes	No

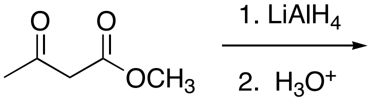
$LiAlH_4$ is much stronger, $NaBH_4$ much weaker

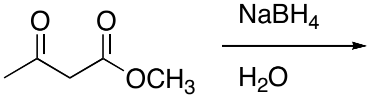
1. $LiAlH_4$ is strong enough to react with esters, $NaBH_4$ isn't
2. **Selective reduction**: if both an ester and an aldehyde/ketone are present:
   - $LiAlH_4$ reduces both
   - $NaBH_4$ selectively reduces the aldehyde/ketone but leaves the ester untouched
3. **$LiAlH_4$ is strong enough to react with and be destroyed by water or alcohol; $NaBH_4$ isn't**

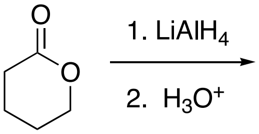
$$LiAlH_4 + H_2O \rightarrow H_2(\text{gas}) + LiOH + AlH_3 + \text{heat}$$

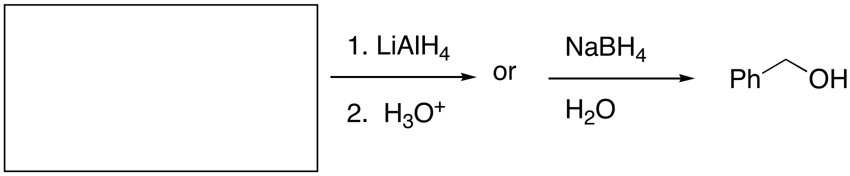
   a. As a result, $LiAlH_4$ is harder to use and store
   b. Acid has to be added in a subsequent step with the $LiAlH_4$; (thus, 2-step recipe)
   c. $NaBH_4$ can be run in alcohol solvent which serves as a proton source for protonating alkoxide
   d. Solvent restrictions, glassware must be dry, wet air must be excluded, etc.
   e. Because $NaBH_4$ is stable to water, it's easier to handle in air, easier to store, much easier to work with
   f. Default: for a simple aldehyde or ketone reduction, normally use $NaBH_4$ because it's so much easier
4. $LiAlH_4$ is strong enough to react with esters, $NaBH_4$ isn't

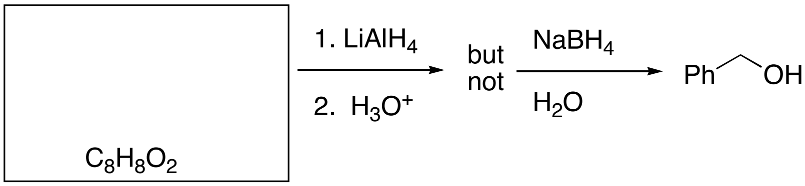
Draw the products for the following reactions.

1. 

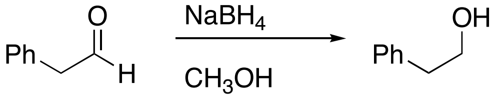
2. 

3. 

4. 

5. 

Draw the mechanism for the following reaction.

6. 

7.