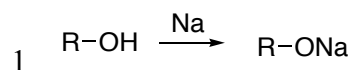
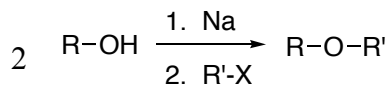
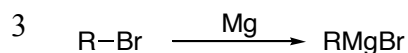


Summary of Alcohol Syntheses, Ch. 10 (and Review of Old Ones).

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



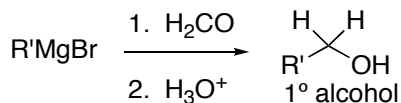
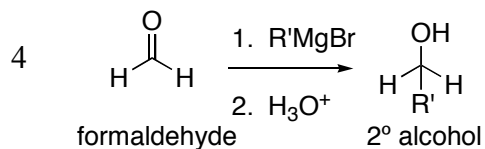
- Alkoxide formation-S_N2 route to ether
- The electrophile R'-X must be S_N2 reactive, preferably 1° with a good leaving group



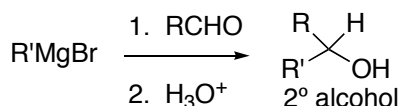
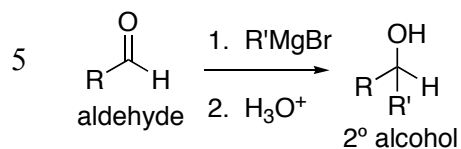
-Li is analogous for making RLi, which also act analogously.

-MgBr is spectator: R[⊖] is key.

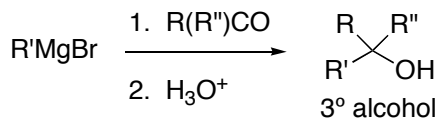
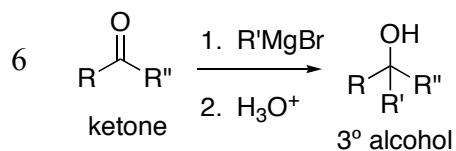
Mech?



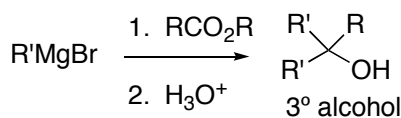
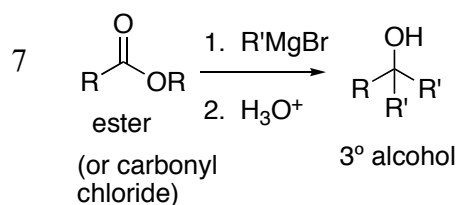
1 carbon chain extension Mech



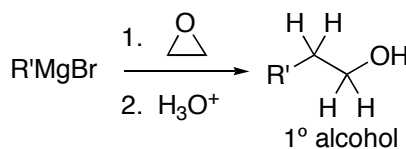
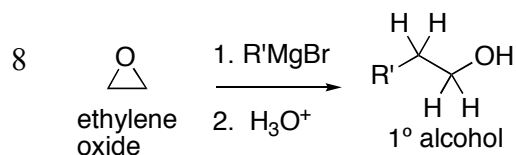
Mech



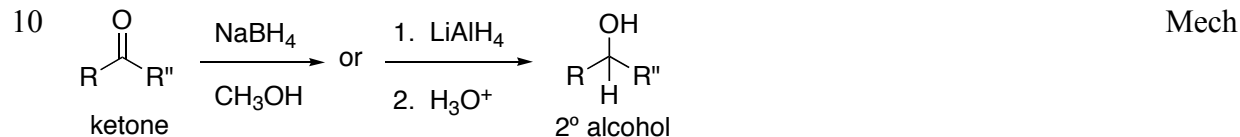
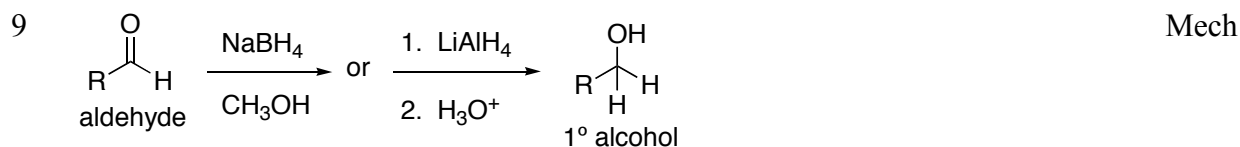
All three R groups can be different. Mech



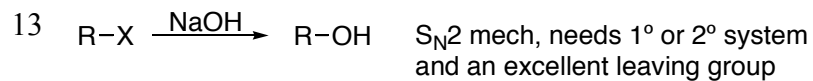
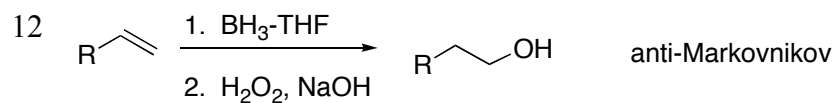
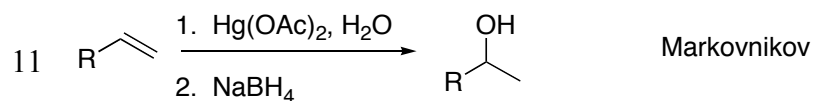
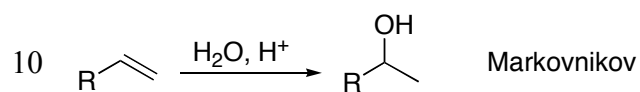
At least 2 R groups must be the same Mech

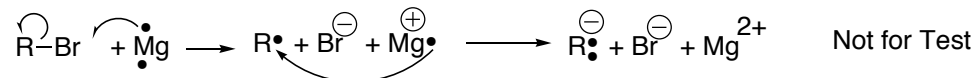


2-Carbon chain extension Mech

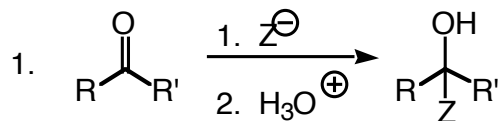
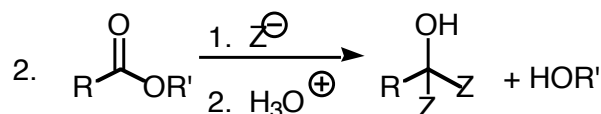
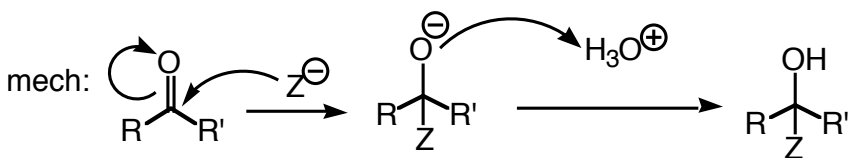



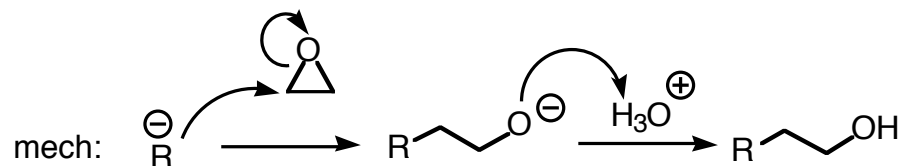
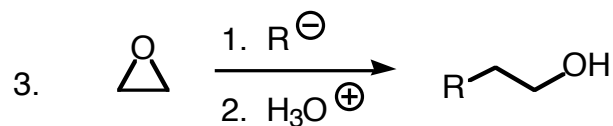
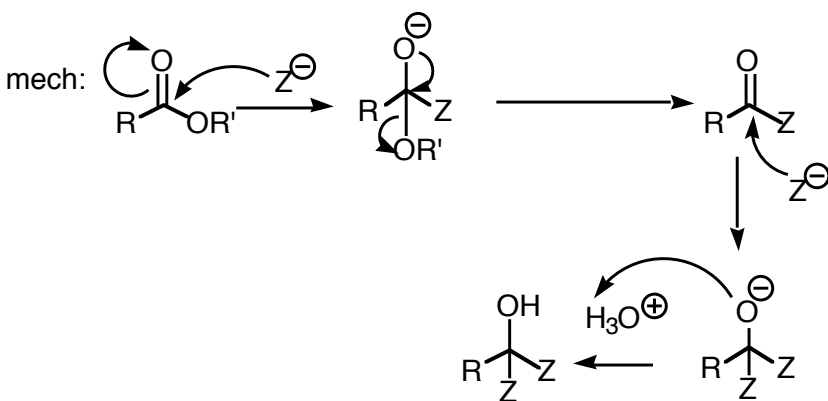
Review Routes to Alcohols



Summary of Mechanisms, Ch. 10

For Test:

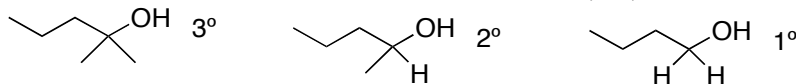
aldehyde
or ketone
or formaldehyde
 Z^\ominus may be R^\ominus (RMgBr)
or H^\ominus (NaBH₄ or LiAlH₄)


esters
or
acid chlorides

 Z^\ominus may be R^\ominus (RMgBr)
or H^\ominus (LiAlH₄)


10.1,2 Intro, Classification

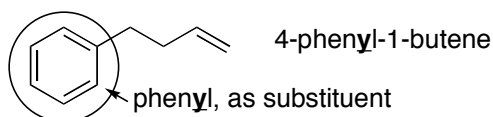
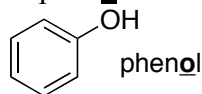
“**Alcohol**”: OH attached to a saturated, sp^3 , “alkyl” carbon

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

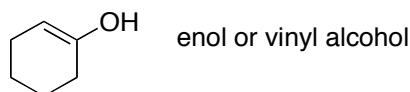


“**Phenol**”: OH attached to an aromatic

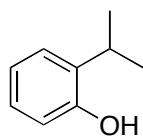
-Note: phenol, not phenyl



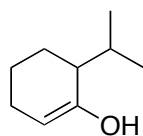
“Enol” or “vinyl alcohol”: OH attached to an alkene



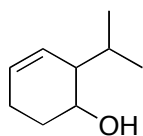
Problem: Classify each of the following either as a phenol, as a carboxylic acid, or as a 1°, 2°, 3°, or vinyl alcohol:



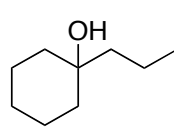
phenol



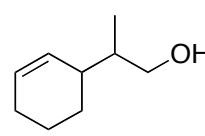
vinyl alcohol



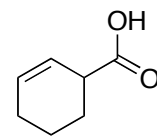
2° alcohol



3° alcohol



1° alcohol

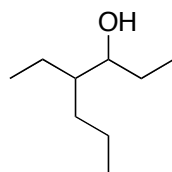


carboxylic acid

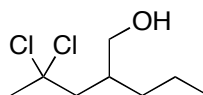
10.3 Nomenclature

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

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

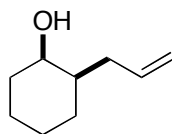


4-ethyl-3-heptanol



4,4-dichloro-2-propyl-1-pentanol

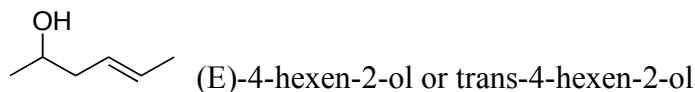
B. Cycloalkanols: The OH-carbon is automatically Number 1



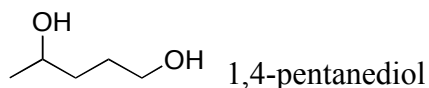
cis-2-allylcyclohexanol

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)



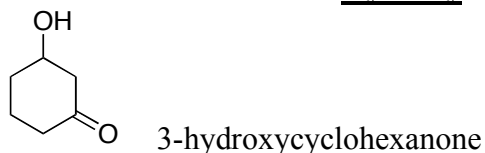
D. Diols: x,y-alkanediol



E. Functional Group Priority: $\text{CO}_2\text{H} > \text{C}=\text{O} > \text{OH} > \text{amine} > \text{alkene} > \text{halide}$

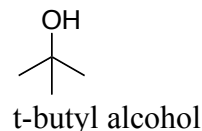
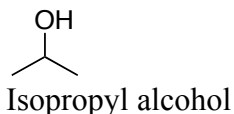
- When you have more than one functional group, the higher priority dictates the numbering
- **The higher priority is used in the “core name”**
- **The lower priority group may be forced to be named as a substituent**

F. OH as a Substituent: “**Hydroxy**”



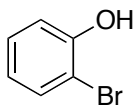
G. Common Names: Alkyl alcohol

CH_3OH
Methyl alcohol



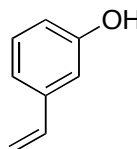
H. Substituted Phenols

- 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

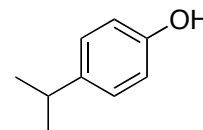


IUPAC:
Common

2-bromophenol
ortho-bromophenol or
o-bromophenol



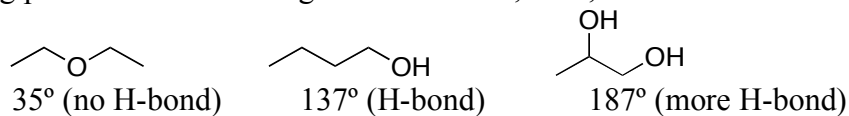
3-vinylphenol
meta-vinylphenol or
m-vinylphenol



4-isopropylphenol
para-isopropylphenol
or p-isopropylphenol

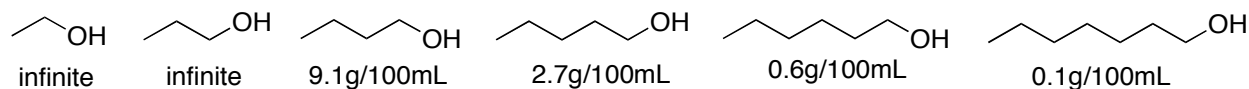
10.4 Physical Properties: Dominated by H-Bonding

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





Water solubility: water solubility decreases as hydrophobic R gets longer

- In general,
 - $R \leq 4$ carbons, ROH substantially water soluble
 - $R \geq 5$ carbons, ROH minimal water solubility



10.5 Commercially Important Alcohols

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

CH_3OH		
<ul style="list-style-type: none"> • Cheap • Solvent • Fuel • 100 mL \rightarrow death • 15 mL \rightarrow blindness 	<ul style="list-style-type: none"> • 200 mL (7 oz) \rightarrow death • Least toxic alcohol • Alcoholic beverages • Fermentation • Solvent 	<ul style="list-style-type: none"> • Rubbing alcohol • 100 mL \rightarrow death • Kills germs on skin, but not absorbed

10.6 Acidity of Alcohols and Phenols

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

- goes to the right (alkoxide) only if RO^{\ominus} is more stable than B^{\ominus}
- ex. $\ominus \text{NH}_2$, $\ominus \text{CH}_3$
- ex. If a less stable oxygen anion can convert to a more stable oxygen anion

B. Acidity Table

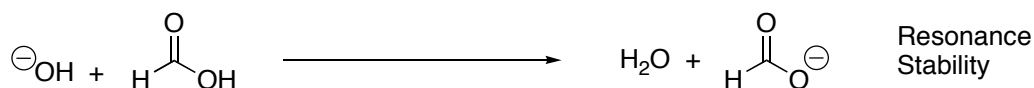
<u>Class</u>	<u>Structure</u>	<u>K_a</u>	<u>Acid Strength</u>	<u>Anion</u>	<u>Base Strength</u>
Strong Acids	H-Cl	10 ²	Most	Cl [⊖]	Least
Carboxylic Acid		10 ⁻⁵			
Phenol		10 ⁻¹⁰			
Water	H ₂ O	10 ⁻¹⁶		HO [⊖]	
Alcohol	ROH	10 ⁻¹⁸		RO [⊖]	
Amine (N-H)	RNH ₂	10 ⁻³³		RNH [⊖]	
Alkane (C-H)	RCH ₃	10 ⁻⁵⁰	Least	RCH ₂ [⊖]	Most

Notes/skills:

- Be able to rank acidity.
- Memorize/understand neutral OH acidity ranking: RCO₂H > H₂O > ROH
 - Reason: **resonance** stabilization of the **anion**
- 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)
- 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

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

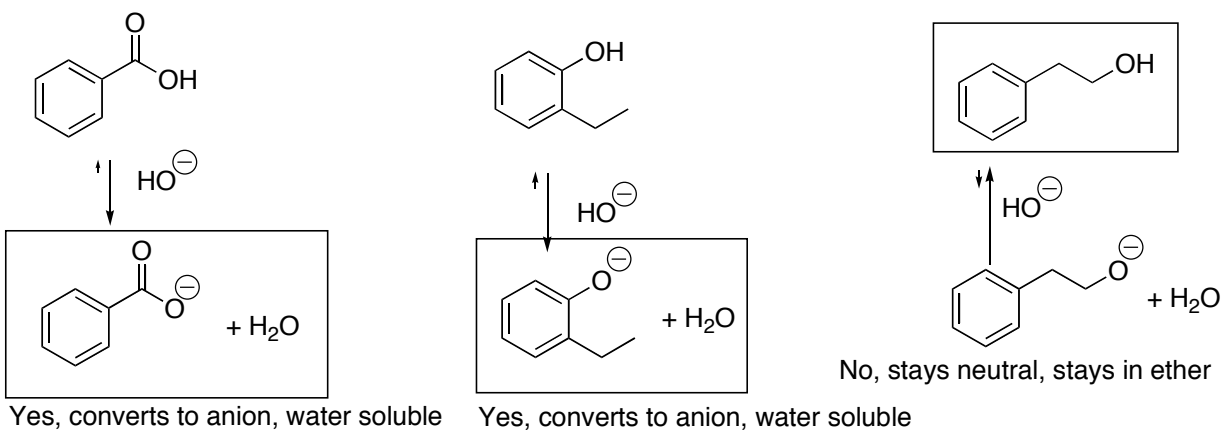


- Which of the following will deprotonate methanol?

H ₂ O	CH ₃ CO ₂ Na	PhONa	NaOH	NaNH ₂	CH ₃ MgBr
No	No	No	No	Yes	Yes

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

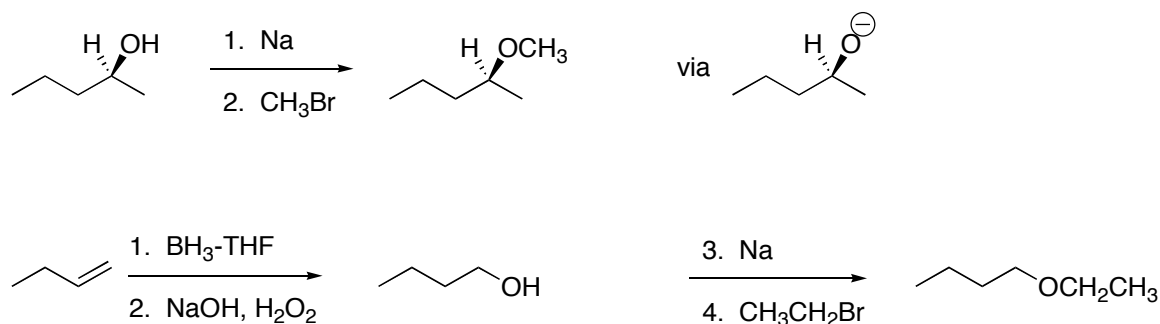
3. When the following are dissolved in ether and then treated with NaOH/water, which would extract out of the ether layer into the water layer?



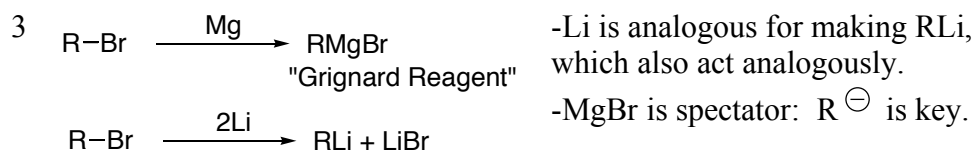
10.6B Formation of Sodium, Potassium Alkoxides; 2-Step Conversion of Alcohols into Ethers via the Alkoxides

1	$\begin{array}{l} \text{R-OH} \xrightarrow{\text{Na}} \text{R-ONa} \\ \text{R-OH} \xrightarrow{\text{K}} \text{R-OK} \end{array} \left. \vphantom{\begin{array}{l} \text{R-OH} \\ \text{R-OH} \end{array}} \right\} \text{R-O}^{\ominus}$	<ul style="list-style-type: none"> • Potassium (K) analogous. • Key way to convert alcohol to alkoxide, reactive as $\text{S}_{\text{N}}2$ nucleophile and E2 base.
2	$\text{R-OH} \xrightarrow[2. \text{R}'\text{-X}]{1. \text{Na}} \text{R-O-R}'$	<ul style="list-style-type: none"> • Alkoxide formation-$\text{S}_{\text{N}}2$ route to ether • The electrophile $\text{R}'\text{-X}$ must be $\text{S}_{\text{N}}2$ reactive, preferably 1° with a good leaving group

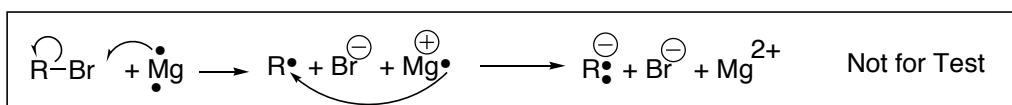
Reaction 1: Key source of nucleophilic/basic alkoxides



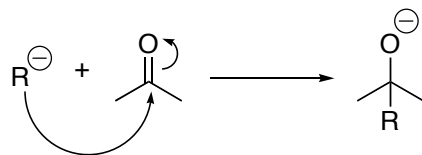
10.7 Synthesis of Alcohols: Review: See p. 2, from Alkyl Halides ($\text{S}_{\text{N}}2$) and Alkenes

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

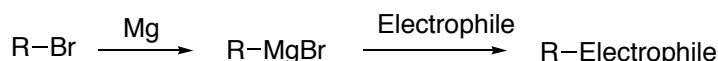
1. We will focus on the magnesium reagents $RMgBr$
2. $RMgBr$ = "Grignard Reagents" (Victor Grignard)
3. Key: This is the way to make R^{\ominus} , strong nucleophiles/bases
4. $RMgBr$ are formed via redox reaction.
 - Mg gives up two electrons, is oxidized
 - Bromine is reduced to bromide anion
 - Carbon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



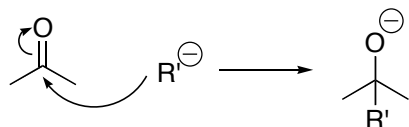
5. The formation of Grignard Reagents is completely general for all R-Halides:
 - 3°, 2°, and 1° alkyl halides all work well
 - Aryl and Vinyl halides as well as alkyl halides work well
 - RCl, RBr, and RI all work well
 - For class, we will normally use bromides, due to synthetic accessibility
6. **View as carbanions: $RMgBr = R^{\ominus}$ Super Strong Bases and Nucleophiles**
 - The counterion metal is a spectator
 - Stability-reactivity principle: very unstable \rightarrow 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
 - $R^{\ominus} + H_2O \rightarrow R-H + HO^{\ominus}$ 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.



10.9 Addition of RMgBr to Carbonyl Compounds: Alcohols are Produced



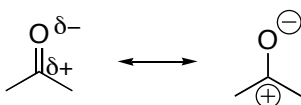
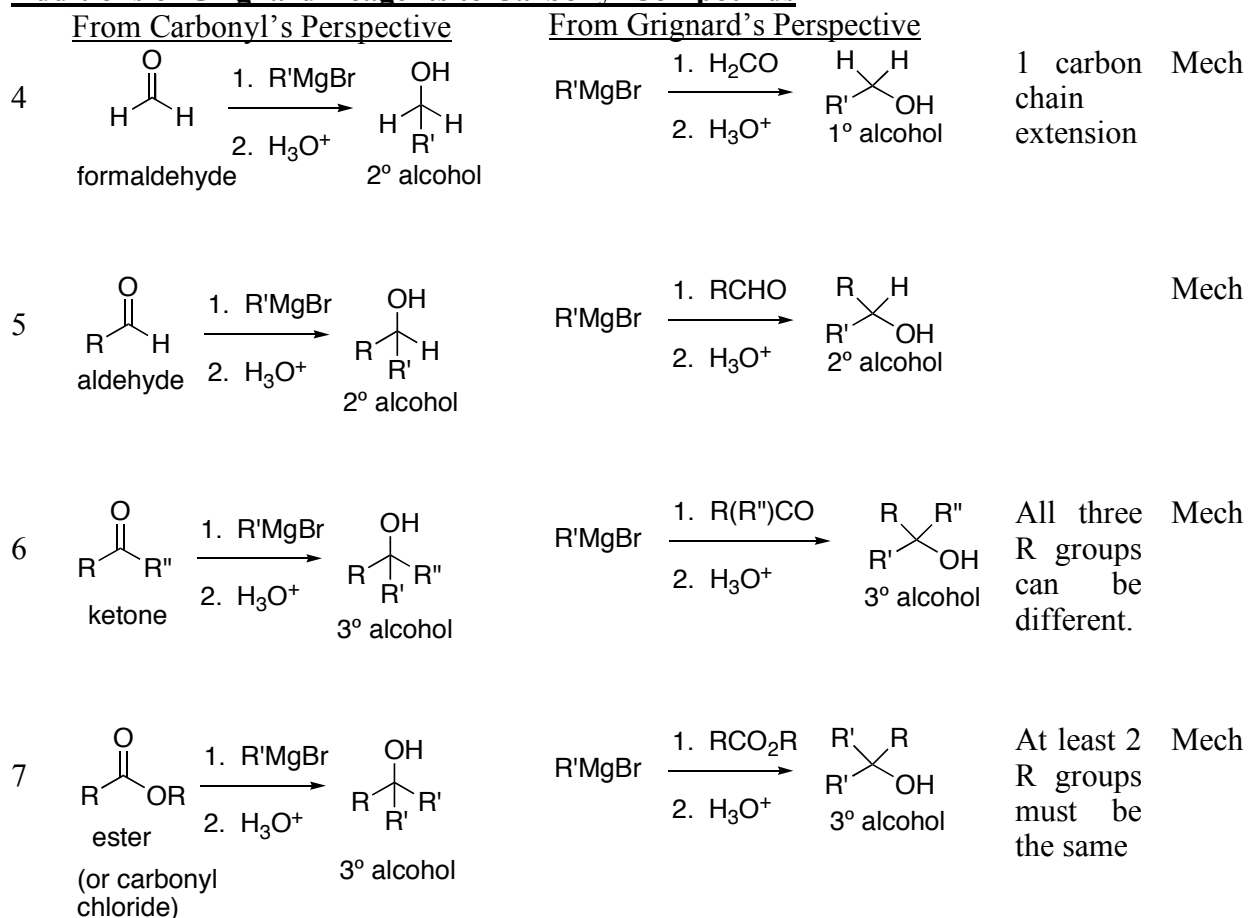
Exothermic Addition of Carbon or Hydrogen Anions:

- 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 CompoundsPattern:

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 π -bond, but also the "extra" C-O or C-Cl single bond
4. Product output:
 - Formaldehyde (2 H's) \rightarrow 1° alcohol
 - Aldehyde (1 H) \rightarrow 2° alcohol
 - Ketone (0 H) \rightarrow 3° alcohol. No need for all 3 attachments to be the same.
 - Ester (0 H) \rightarrow 3° alcohol. At least two common attachments at end.

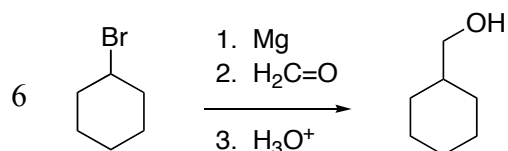
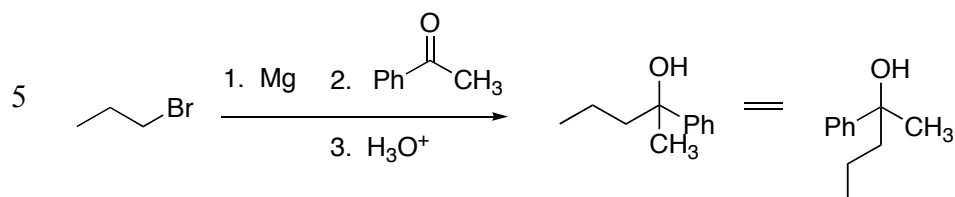
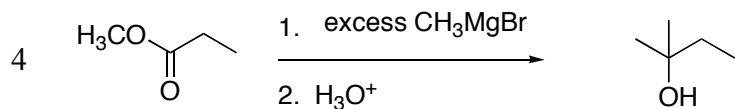
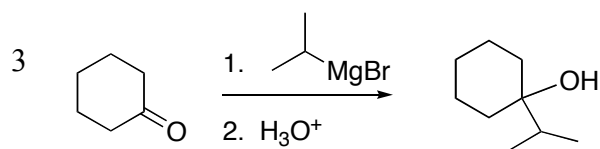
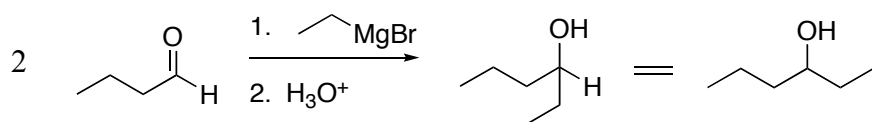
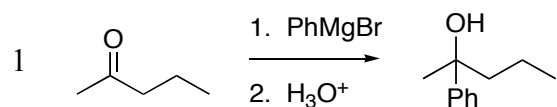
Predicting Grignard Reaction Products

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

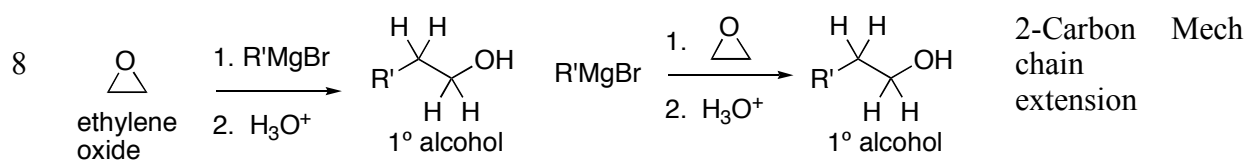
Note: Be sure that in the product, no carbon has more than one C-O bond

Draw products from the following reactions.

1°, 2° or 3°?

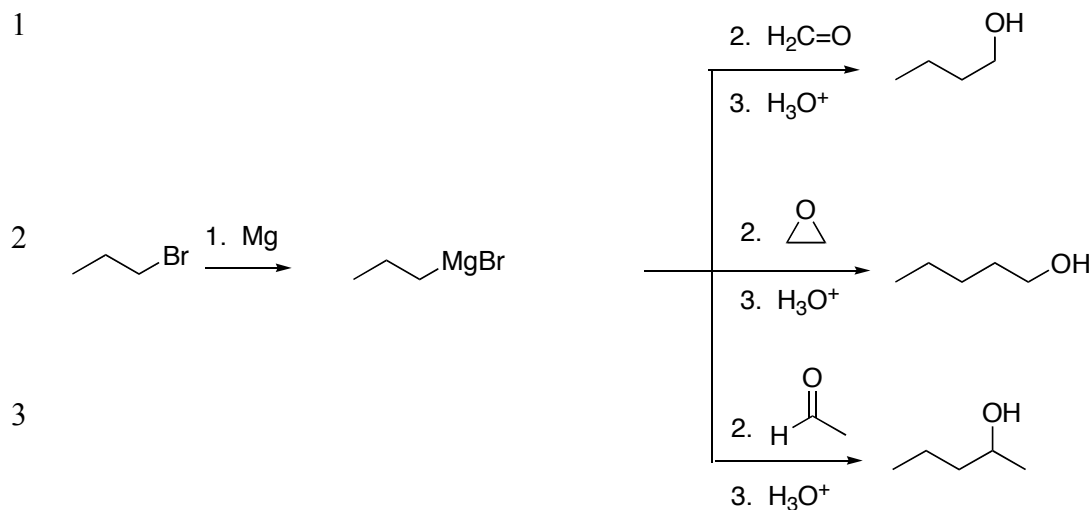


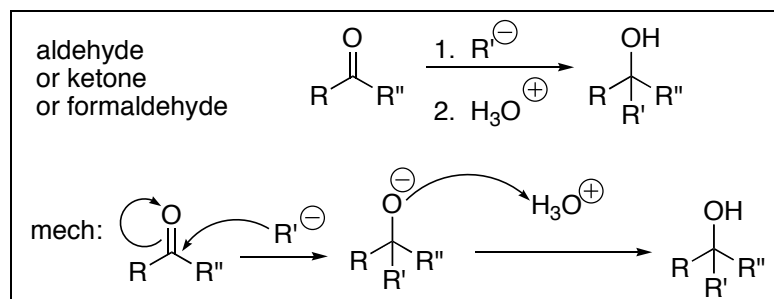
10.9E Grignard Reaction with Ethylene Oxide (Simplest Epoxide)

Notes

- Results in a 1° Alcohol
- Predicting product: Two carbons end up in between the carbanion R' and the OH**
- 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)
- 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

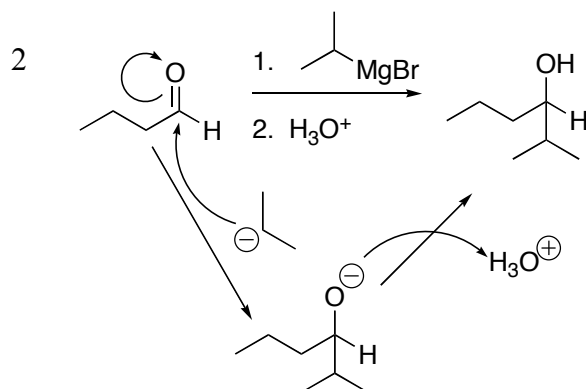
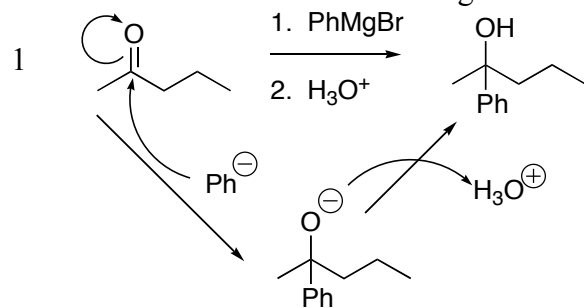
Draw products from the following reactions.



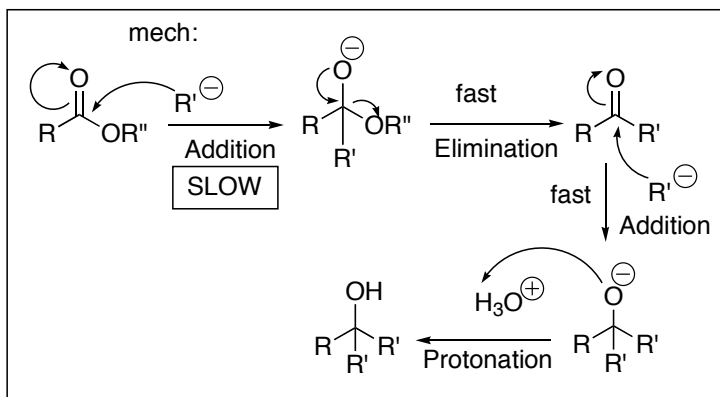
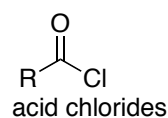
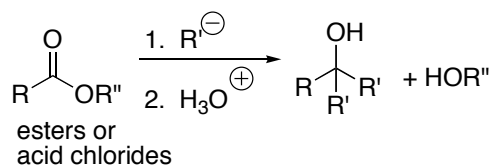
Reaction Mechanisms for Grignard ReactionsFormaldehyde, Aldehyde, or Ketone as Carbonyl Compound (Reactions 4, 5, and 6)

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

Draw mechanisms for the following reactions:



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



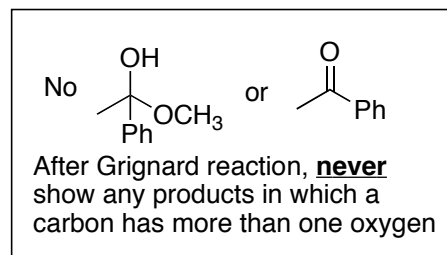
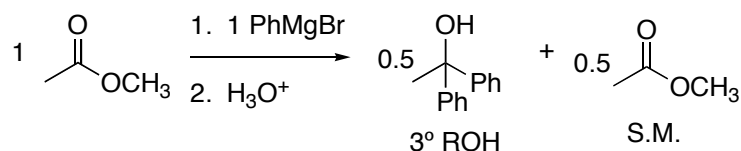
1. Four Step Mechanism:

- Addition**
- Elimination**
- Addition**
- Protonation**

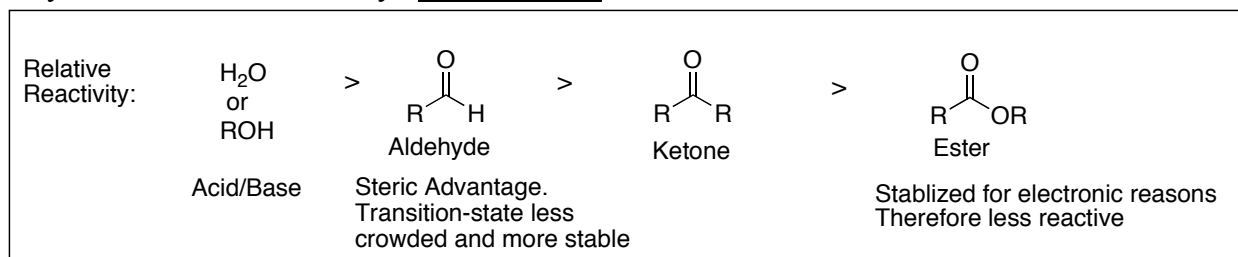
2. Timing:

- The carbanion is added first, at one point in time, under strongly anionic conditions
 - The first three steps all occur under these anionic conditions
- Acid is only added much later, in a second laboratory step. This gives a cationic environment.
- Why don't you just protonate after the first step?
 - There is no proton source available, and the elimination proceeds instead!

3. What if I add only one RMgBr?

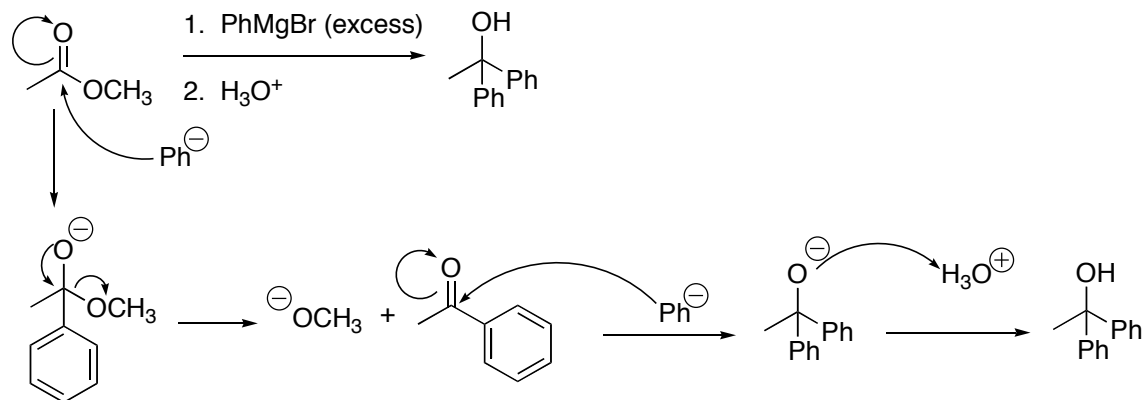


Why? Kinetics and Reactivity. **MEMORIZE.**



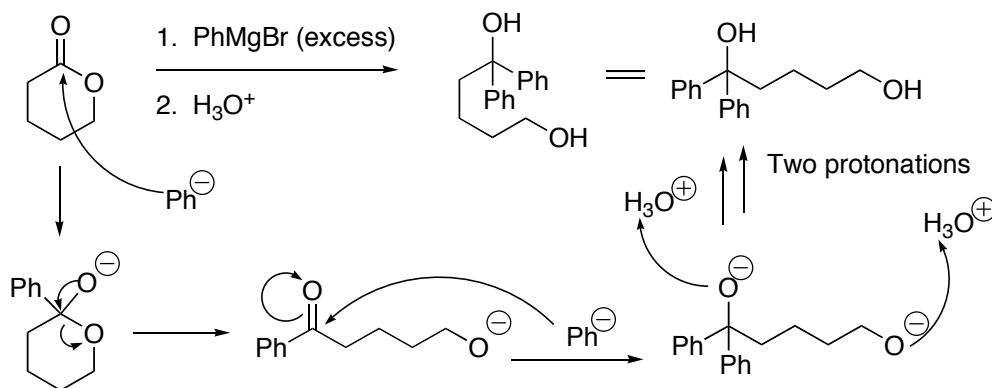
- Large differences in reactivity, with ketone > ester
- Elimination step 2 is also very fast
- Thus, under the anionic conditions, the addition is the slow step
 - After it does happen, elimination and another addition happens bang-bang.

Draw Mechanism:

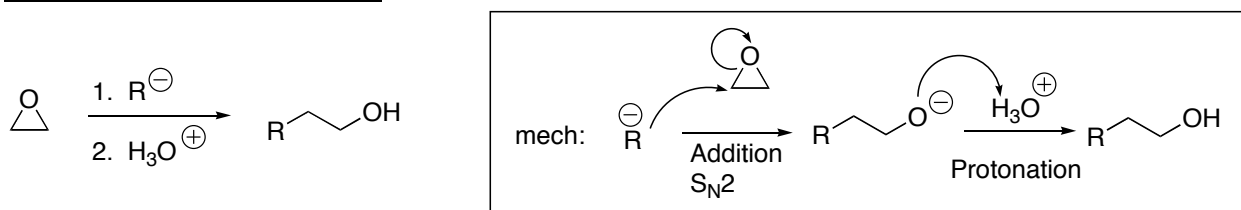


Cyclic Ester: The O-Carbonyl single bond breaks, but the other C-O single bond does **not** break -the result is formation of a dialcohol

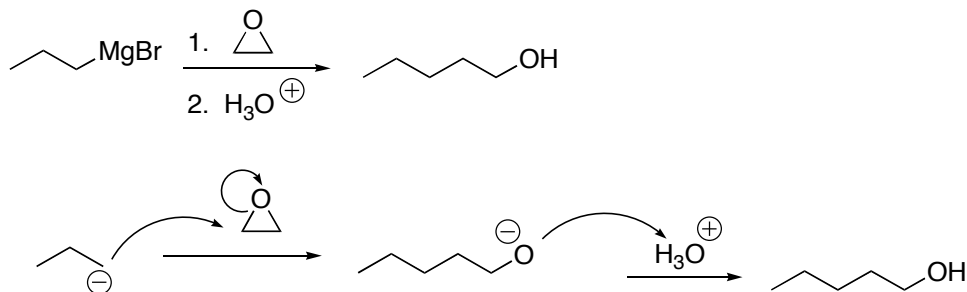
Draw product and mechanism for the following:



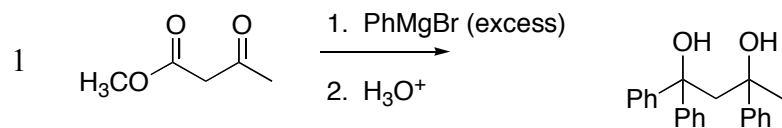
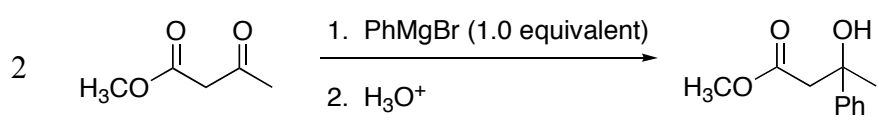
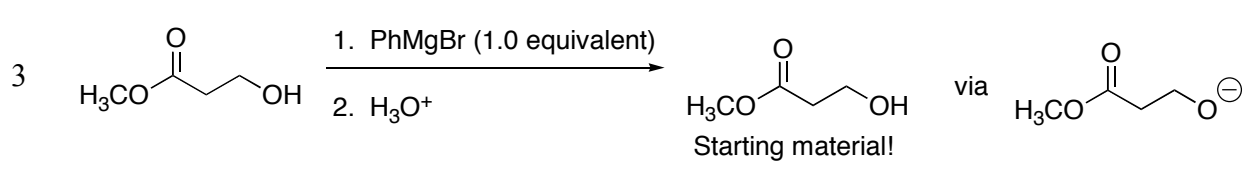
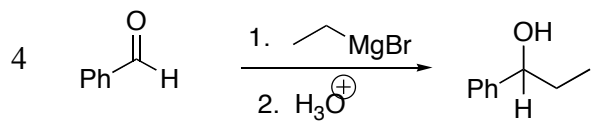
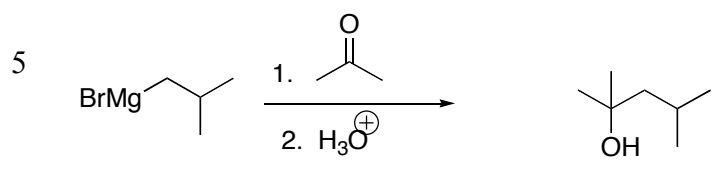
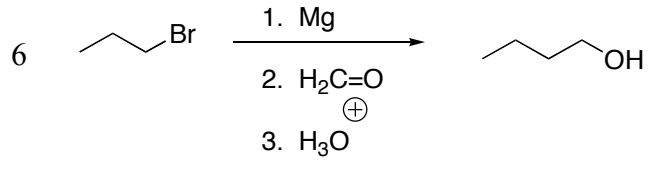
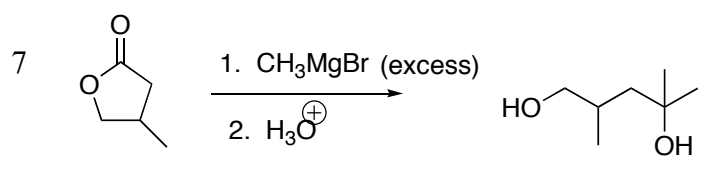
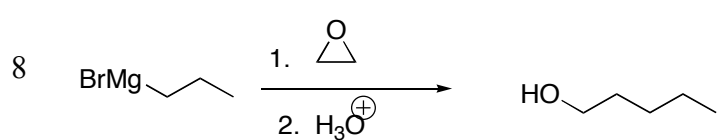
Ethylene Oxide Mechanism



Draw product and mechanism for the following:

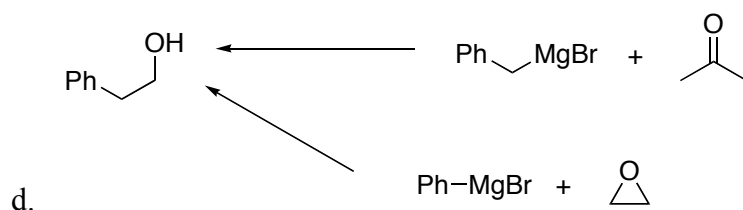
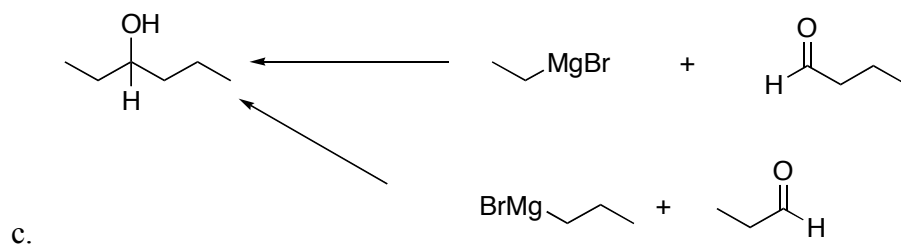
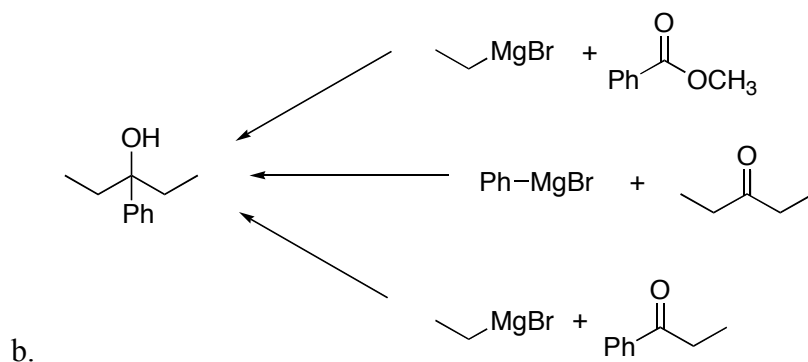
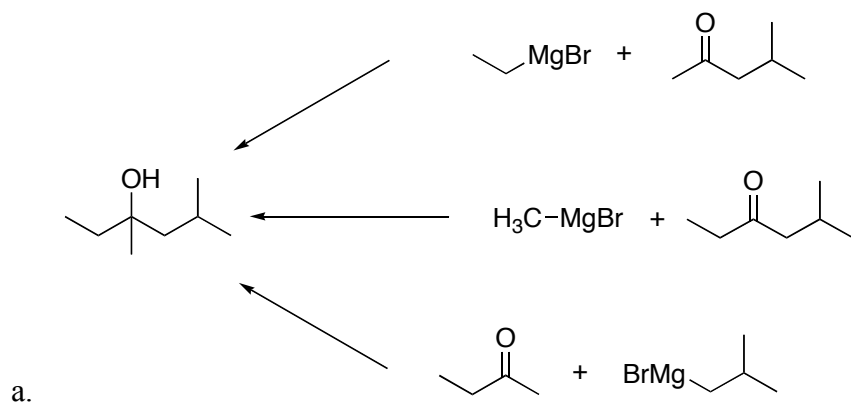


More Grignard Practice. Including polyfunctional Molecules: (Know relative reactivity)

- 1 
- 2 
- 3 
- 4 
- 5 
- 6 
- 7 
- 8 

Grignards in Synthesis: Provide Precursors.

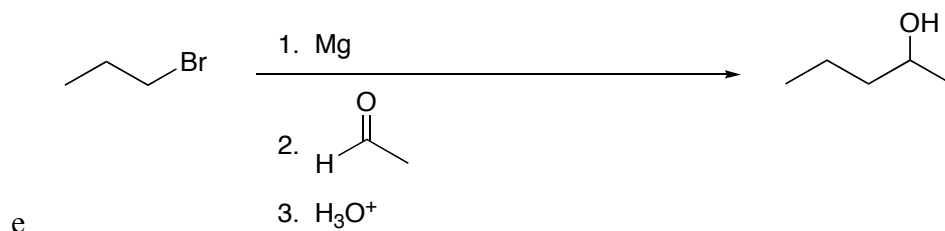
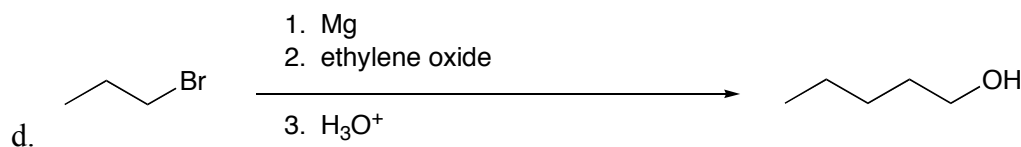
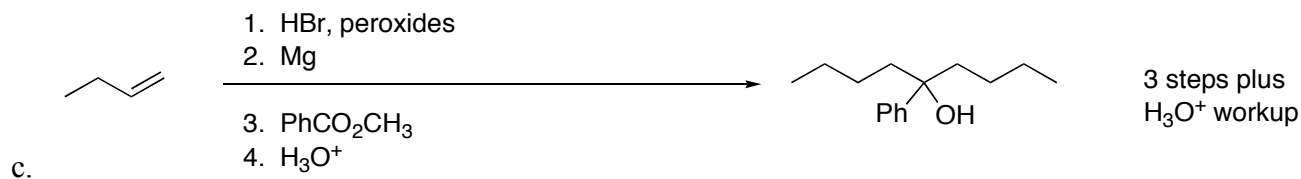
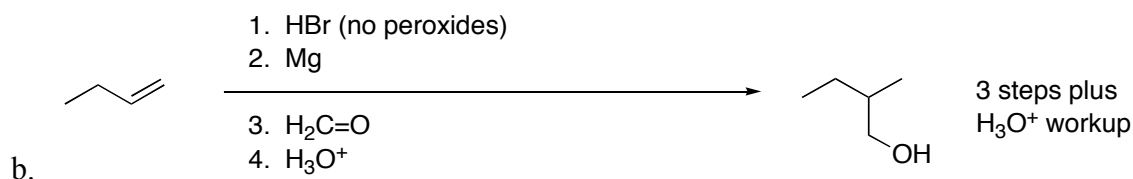
- **Think backwards from Targets to Reactants.**
- Identify possible Grignards and Grignard acceptors
- **Pattern:**
 - 3° alcohol, all three attachments different ← **Ketone Precursor**
 - 3° alcohol, two (or more) of the attachments identical ← **Ester**
 - 2° alcohol ← **Aldehyde**
 - 1° alcohol ←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

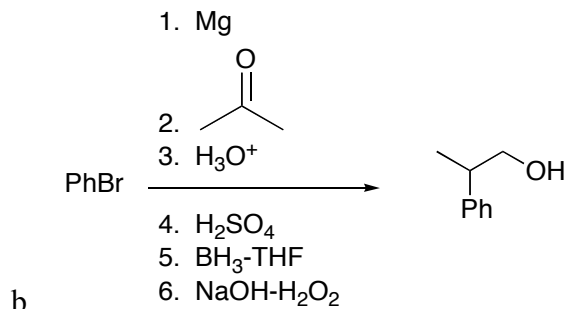
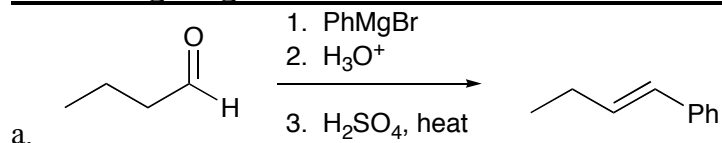


Oops. The carbonyl to the left should be formaldehyde, with two hydrogens, not acetone, with two methyls as shown.

Provide Reagents for the Following Transformations. 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



Combining Grignard Reactions with Other Reactions

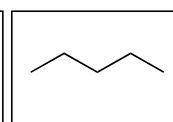
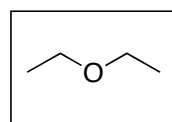
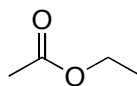
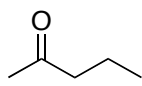
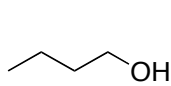
10.10 Restrictions on Grignard Reactions

- RMgBr = R[⊖] 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

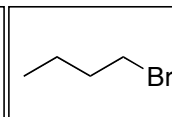
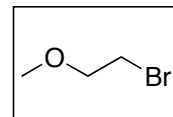
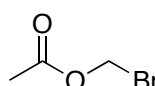
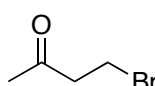
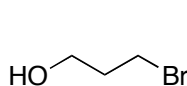
- H₂O
- ROH
- Any solvent with a C=O

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



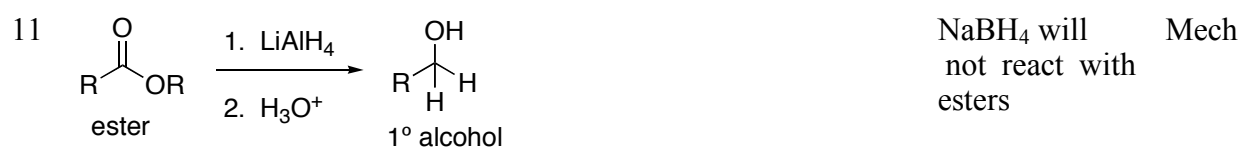
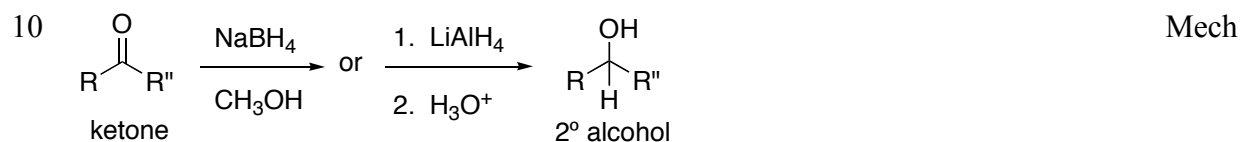
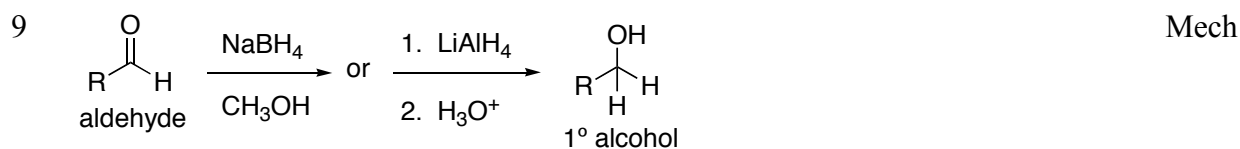
2. Substrate limitations. Any organohalide that also contains an OH or C=O bond can't be converted into a useful RMgBr, because it will self-destruct.

Which substrates could be converted into RMgBr, and subsequently reacted with CH₃CHO?

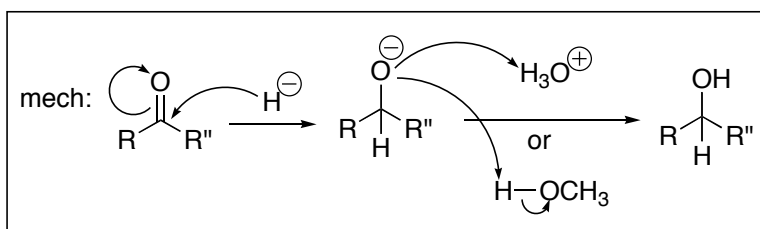
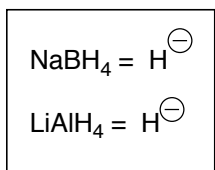
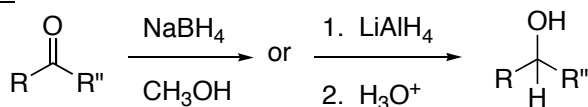
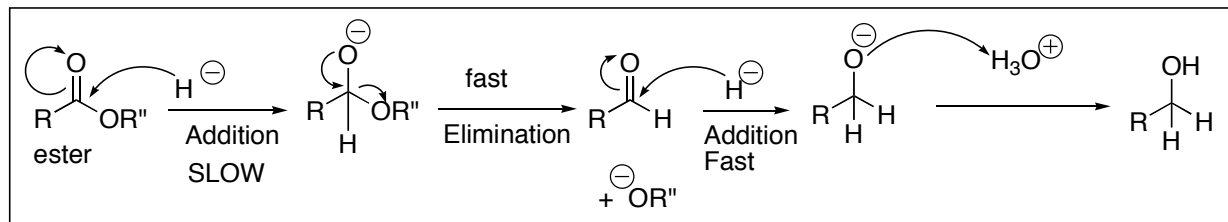
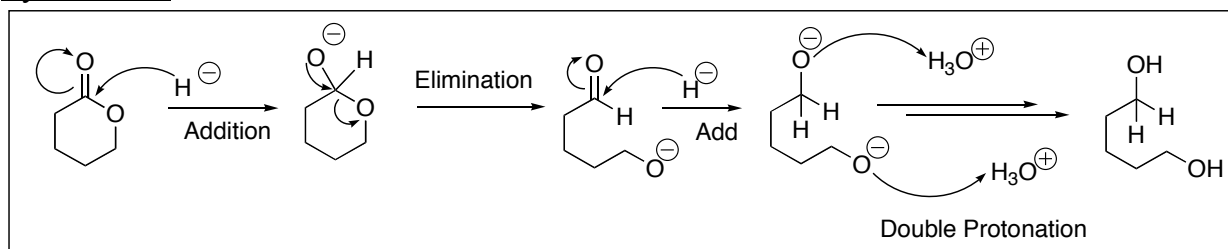


3. Atmosphere/Glassware/Storage limitations. Make, store, and use in:

- 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.

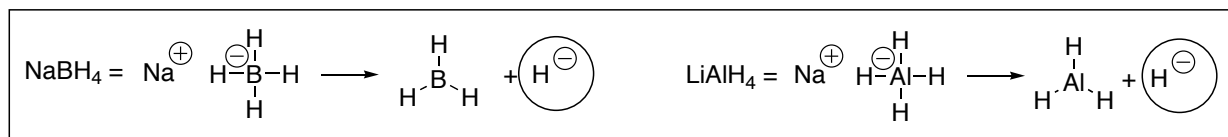
10.11 Alcohols by Reduction of Carbonyls: H^- AdditionMechanismAldehydes and Ketones

aldehyde
or ketone
or formaldehyde

EstersCyclic Esters

Notes:

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



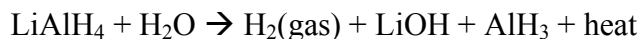
- Boron is one row higher than aluminum, and in keeping with normal periodic patterns is more electronegative
 - Because boron is more electronegative, the BH_4^- anion is more stable, and less reactive.
 - The boron holds the H^- more tightly.
 - Aluminum being less electronegative doesn't attract and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

Reactivity

	Aldehydes	Ketones	Esters
LiAlH_4	Yes	Yes	Yes
NaBH_4	Yes	Yes	No

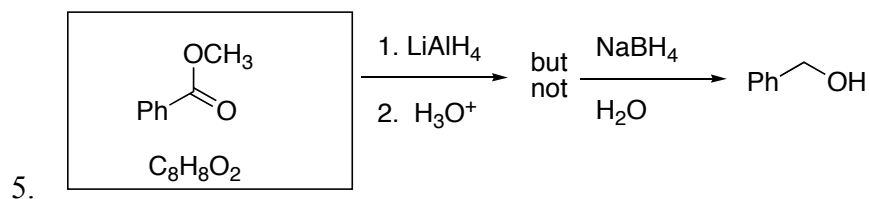
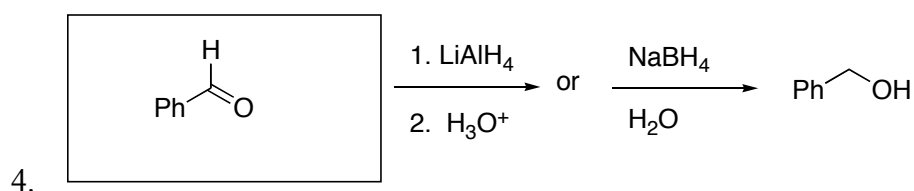
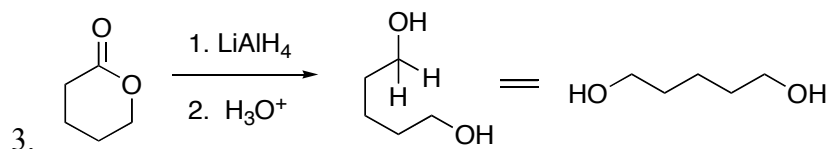
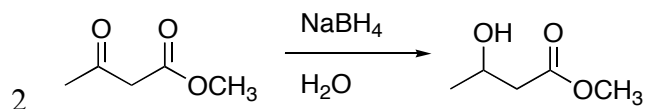
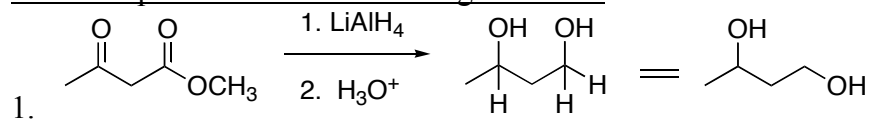
 LiAlH_4 is much stronger, NaBH_4 much weaker

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**



- 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.



Draw the mechanism for the following reaction.

