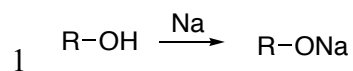
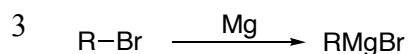
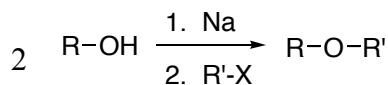


Summary of Alcohol Syntheses, Ch. 17 (and Review of Old Ones).

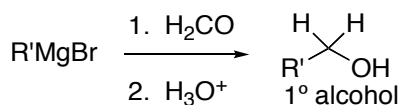
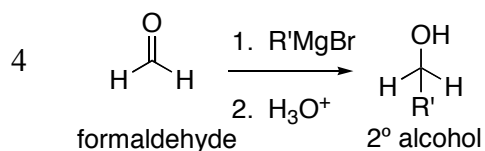
- Potassium (K) analogous.
- Key way to convert alcohol to alkoxide, reactive as $\text{S}_{\text{N}}2$ nucleophile and $\text{E}2$ base.
- 17.3
- Alkoxide formation- $\text{S}_{\text{N}}2$ route to ether
- The electrophile $\text{R}'\text{-X}$ must be $\text{S}_{\text{N}}2$ reactive, preferably 1° with a good leaving group
- 17.3



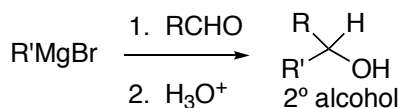
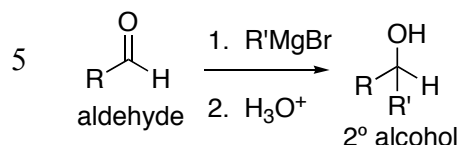
-Li is analogous for making RLi , which also act analogously.

-MgBr is spectator: R^\ominus is key.
-10.8

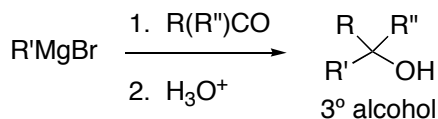
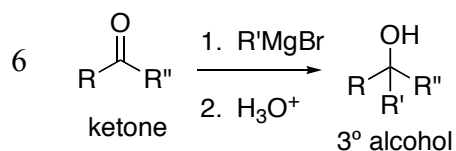
Mech?



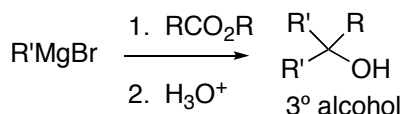
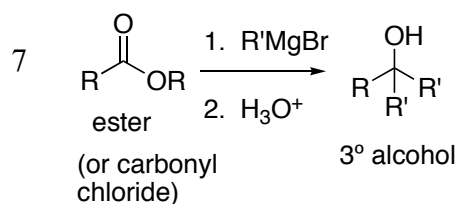
1 carbon chain extension
Mech



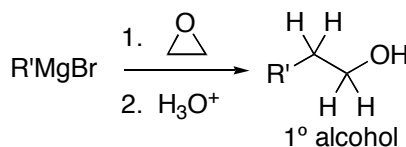
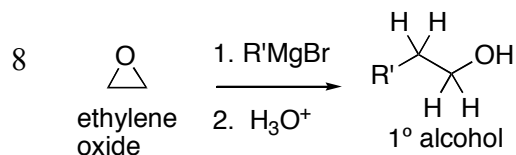
Mech



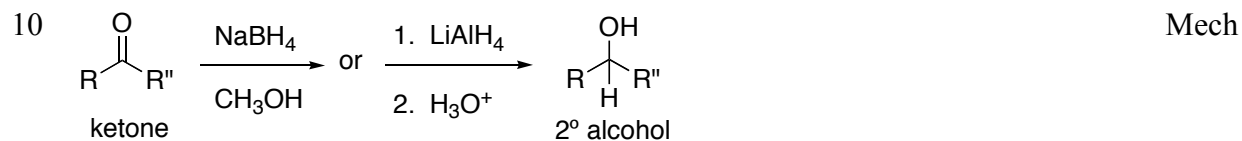
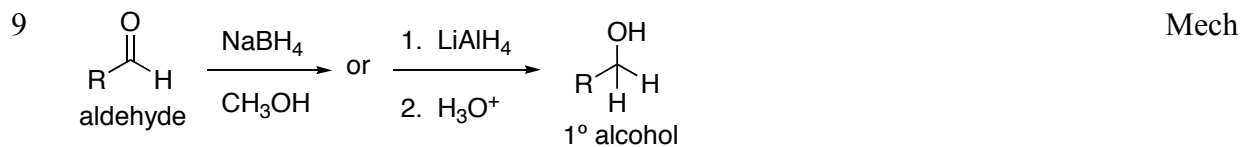
All three R groups can be different.
Mech



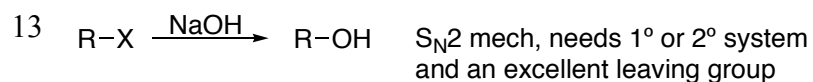
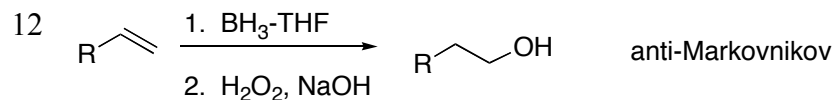
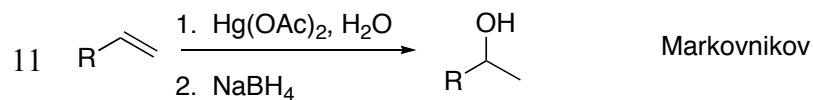
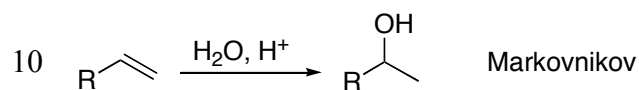
At least 2 R groups must be the same
Mech

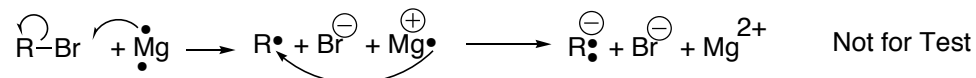


2-Carbon chain extension
Mech

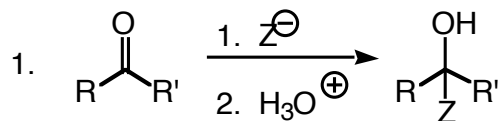
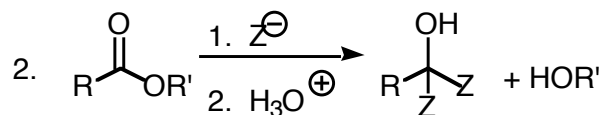
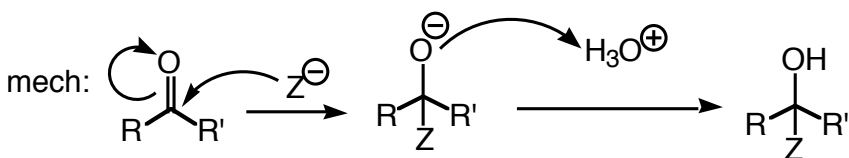



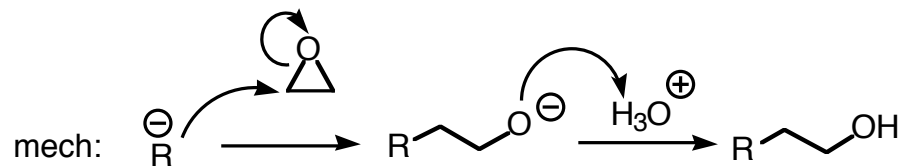
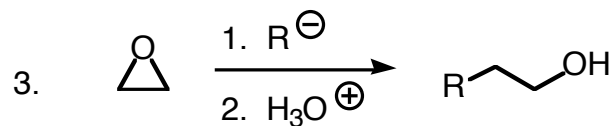
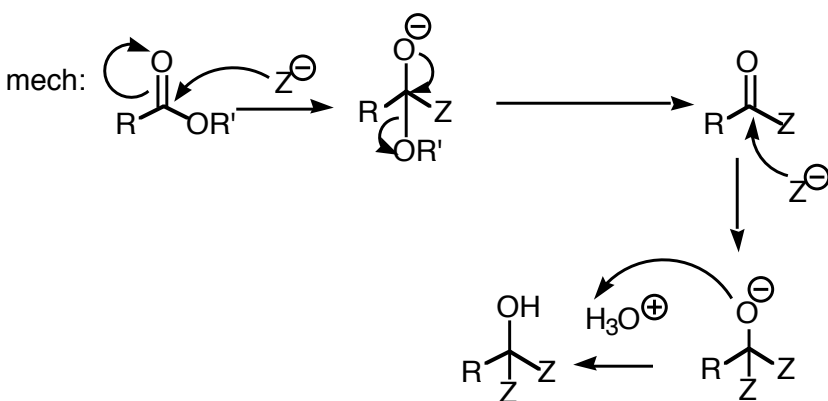
Review Routes to Alcohols



Summary of Mechanisms, Ch. 17

For Test:

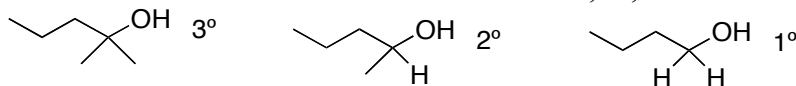
aldehyde
or ketone
or formaldehyde Z^\ominus may be R^\ominus (RMgBr)
or H^\ominus (NaBH₄ or LiAlH₄)


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

17.1 Intro, Classification

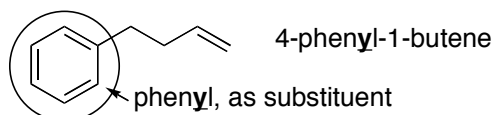
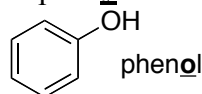
“**Alcohol**”: OH attached to a saturated, sp^3 , “alkyl” carbon

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

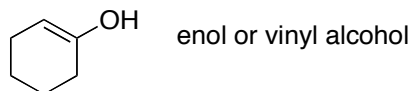


“**Phenol**”: OH attached to an aromatic

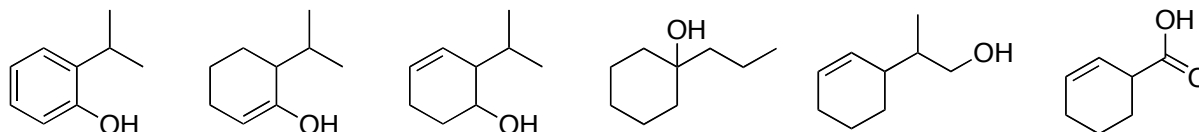
-Note: phenol, not phenyl



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

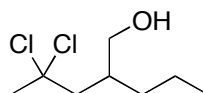
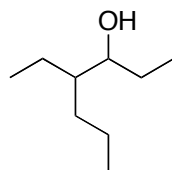


Problem: Classify each of the following either as a phenol, as a carboxylic acid, or as a 1°, 2°, 3°, or vinyl alcohol:

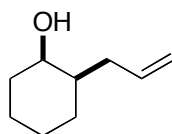
Nomenclature

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

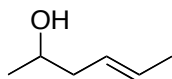


B. Cycloalkanols: The OH-carbon is automatically Number 1

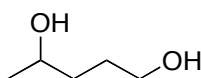


C. **x-Alken-z-ol**. When an alkene is in the main carbon chain, you need two number descriptors, one for the alkene, the second for the alcohol.

- 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)



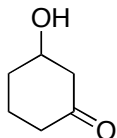
D. Diols: x,y-alkanediol



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**”



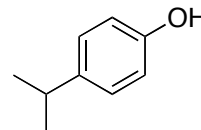
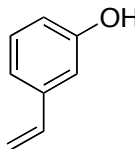
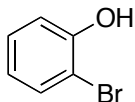
G. Common Names: Alkyl alcohol

CH_3OH



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

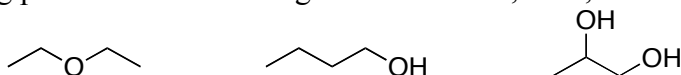


IUPAC:

Common:

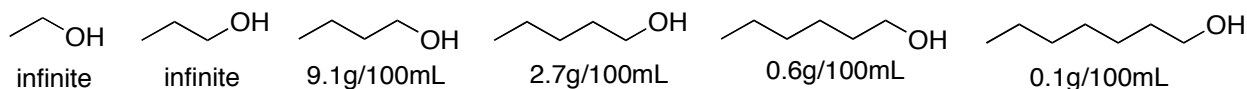
17.2 Physical Properties: Dominated by H-Bonding

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



Water solubility: water solubility decreases as hydrophobic R gets longer

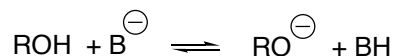
- In general,
 - $R \leq 4$ carbons, ROH substantially water soluble
 - $R \geq 5$ carbons, ROH minimal water solubility

Commercially Important Alcohols

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

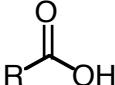
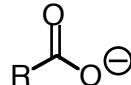
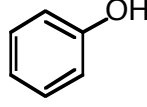
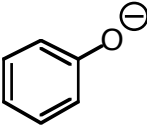
CH_3OH		
<ul style="list-style-type: none"> Cheap Solvent Fuel 100 mL \rightarrow death 15 mL \rightarrow blindness 	<ul style="list-style-type: none"> 200 mL (7 oz) \rightarrow death Least toxic alcohol Alcoholic beverages Fermentation Solvent 	<ul style="list-style-type: none"> Rubbing alcohol 100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

11.3 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

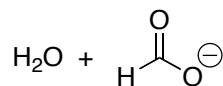
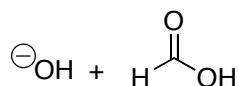
<u>Class</u>	<u>Structure</u>	<u>K_a</u>	<u>Acid Strength</u>	<u>Anion</u>	<u>Base Strength</u>
Strong Acids	H-Cl	10 ²		Cl [⊖]	
Carboxylic Acid		10 ⁻⁵			
Phenol		10 ⁻¹⁰			
Water	H ₂ O	10 ⁻¹⁶		HO [⊖]	
Alcohol	ROH	10 ⁻¹⁸		RO [⊖]	
Amine (N-H)	RNH ₂	10 ⁻³³		RNH [⊖]	
Alkane (C-H)	RCH ₃	10 ⁻⁵⁰		RCH ₂ [⊖]	

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?)

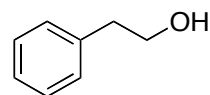
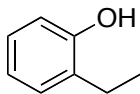
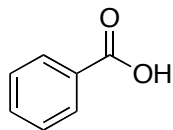


- Which of the following will deprotonate methanol?



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

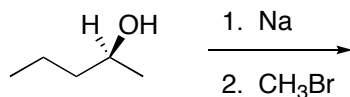
3. When the following are dissolved in ether and then treated with NaOH/water, which would extract out of the ether layer into the water layer?



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

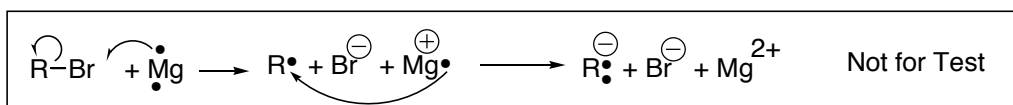
Reaction 1: Key source of nucleophilic/basic alkoxides



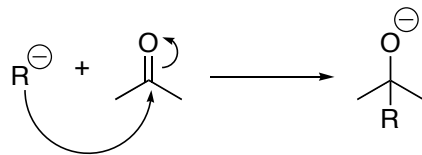
17.3 Synthesis of Alcohols: Review: See p. 2, from Alkyl Halides ($\text{S}_{\text{N}}2$) and Alkenes

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

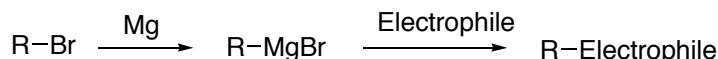
1. We will focus on the magnesium reagents $RMgBr$
2. $RMgBr$ = "Grignard Reagents" (Victor Grignard)
3. Key: This is the way to make R^{\ominus} , strong nucleophiles/bases
4. $RMgBr$ are formed via redox reaction.
 - Mg gives up two electrons, is oxidized
 - Bromine is reduced to bromide anion
 - Carbon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



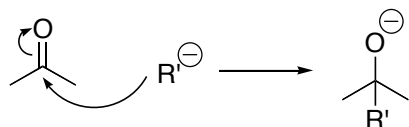
5. The formation of Grignard Reagents is completely general for all R-Halides:
 - 3°, 2°, and 1° alkyl halides all work well
 - Aryl and Vinyl halides as well as alkyl halides work well
 - RCl , RBr , and RI all work well
 - For class, we will normally use bromides, due to synthetic accessibility
6. **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.



17.5 Addition of RMgBr to Carbonyl Compounds: Alcohols are Produced



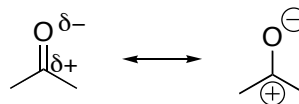
Exothermic Addition of Carbon or Hydrogen Anions:

- 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

	<u>From Carbonyl's Perspective</u>	<u>From Grignard's Perspective</u>		
4	<p>formaldehyde</p> <p>2° alcohol</p>	<p>1° alcohol</p>	1 carbon chain extension	Mech
5	<p>aldehyde</p> <p>2° alcohol</p>	<p>2° alcohol</p>		Mech
6	<p>ketone</p> <p>3° alcohol</p>	<p>3° alcohol</p>	All three R groups can be different.	Mech
7	<p>ester (or carbonyl chloride)</p> <p>3° alcohol</p>	<p>3° alcohol</p>	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
 - o Replace not only the carbonyl π -bond, but also the "extra" C-O or C-Cl single bond
4. Product output:
 - o Formaldehyde (2 H's) \rightarrow 1° alcohol
 - o Aldehyde (1 H) \rightarrow 2° alcohol
 - o Ketone (0 H) \rightarrow 3° alcohol. No need for all 3 attachments to be the same.
 - o Ester (0 H) \rightarrow 3° alcohol. At least two common attachments at end.

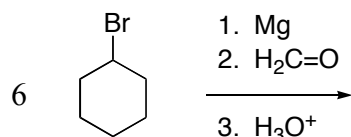
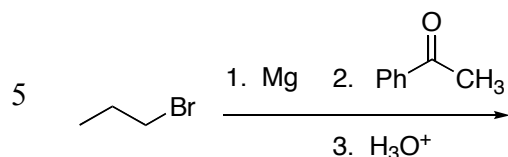
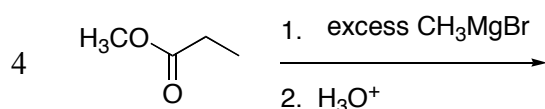
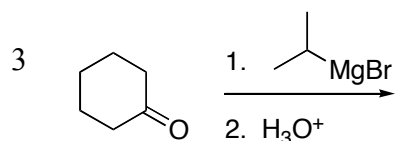
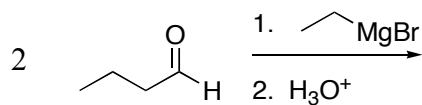
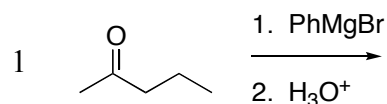
Predicting Grignard Reaction Products

- 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

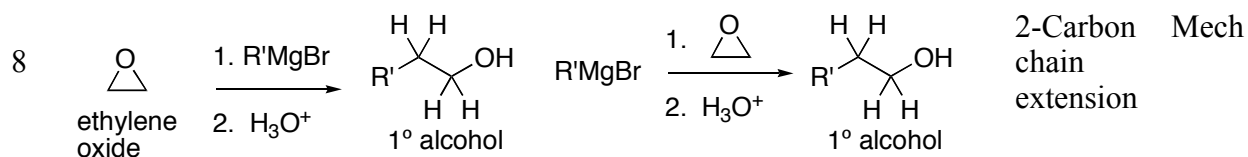
Note: Be sure that in the product, no carbon has more than one C-O bond

Draw products from the following reactions.

1°, 2° or 3°?



18.6 Grignard Reaction with Ethylene Oxide (Simplest Epoxide)

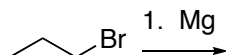
Notes

- 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 \rightarrow the OH is 1° and the OH is two carbons removed from the carbanion R
 - Ethanal \rightarrow the OH is 2° and the OH and carbanion R are both connected to the same carbon

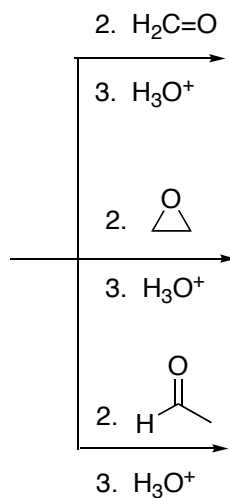
Draw products from the following reactions.

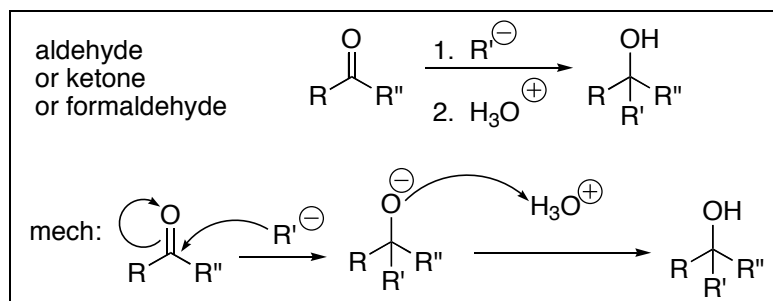
1

2



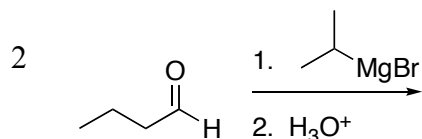
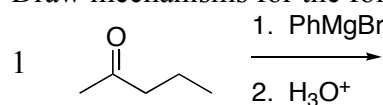
3



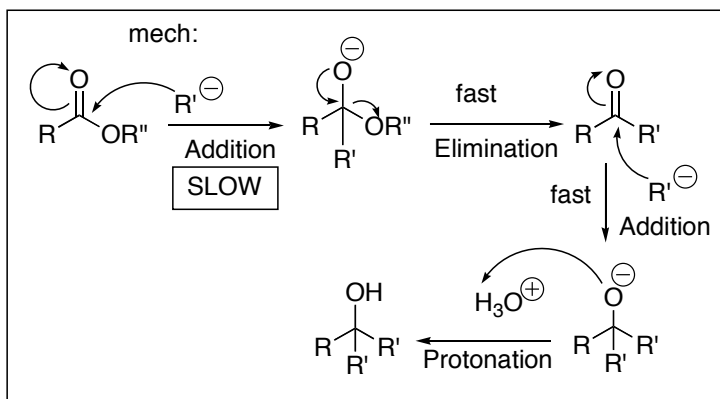
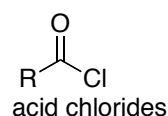
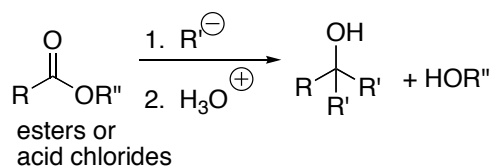
Reaction Mechanisms for Grignard Reactions**Formaldehyde, Aldehyde, or Ketone as Carbonyl Compound (Reactions 4, 5, and 6)**

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. $\text{RMgBr} = \text{R-MgBr} = \text{R}^{\ominus}$ carbanion
 - a. The MgBr^{\oplus} 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:



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



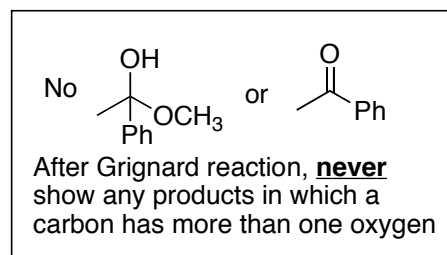
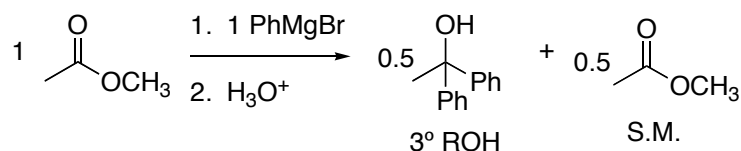
1. Four Step Mechanism:

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

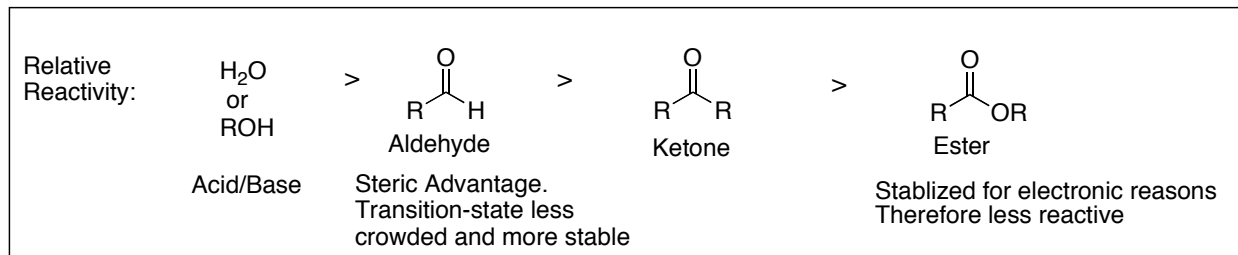
2. Timing:

- 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?

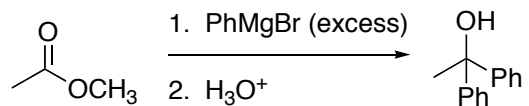


Why? Kinetics and Reactivity. **MEMORIZE.**



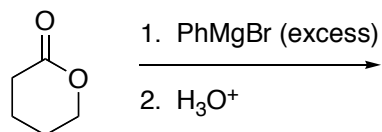
- Large differences in reactivity, with ketone > ester
- Elimination step 2 is also very fast
- Thus, under the anionic conditions, the addition is the slow step
 - After it does happen, elimination and another addition happens bang-bang.

Draw Mechanism:

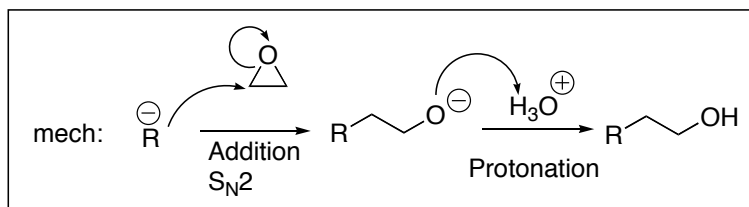
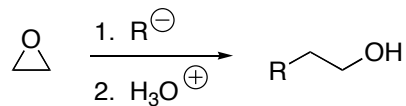


Cyclic Ester: The O-Carbonyl single bond breaks, but the other C-O single bond does **not** break -the result is formation of a dialcohol

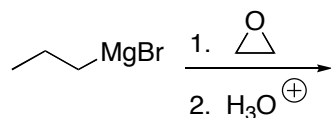
Draw product and mechanism for the following:

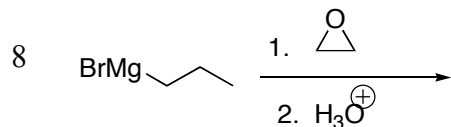
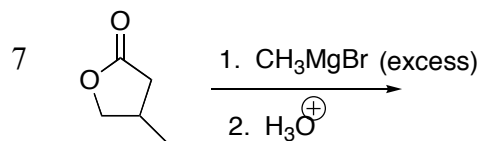
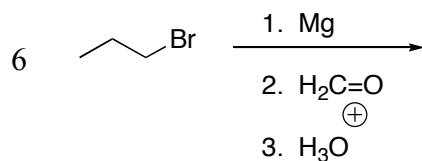
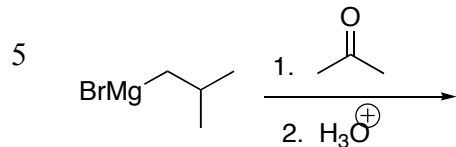
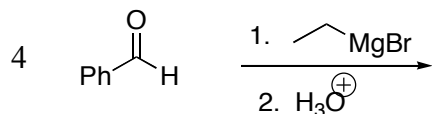
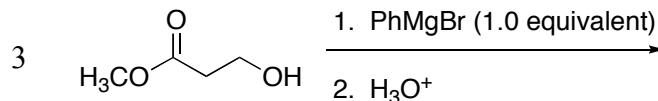
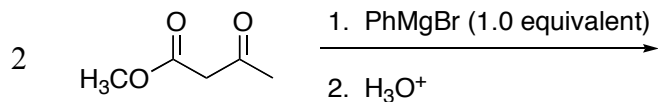
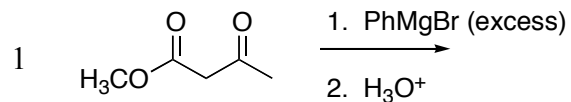


Ethylene Oxide Mechanism



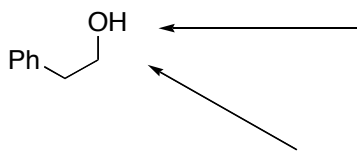
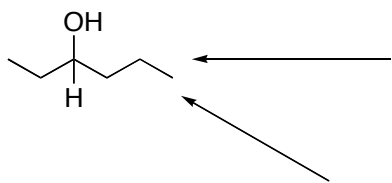
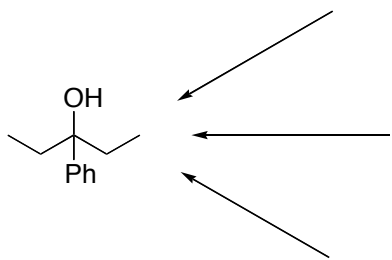
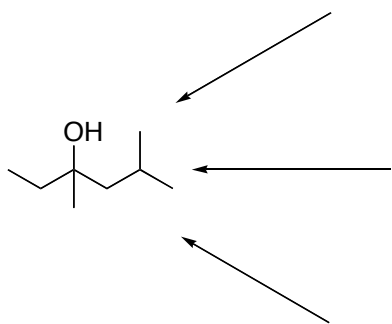
Draw product and mechanism for the following:



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

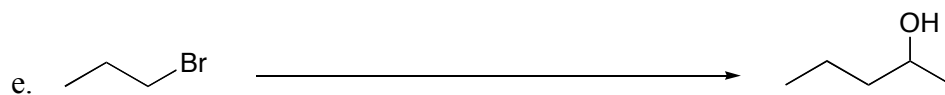
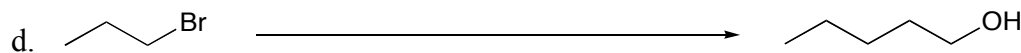
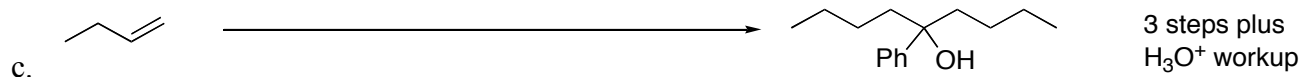
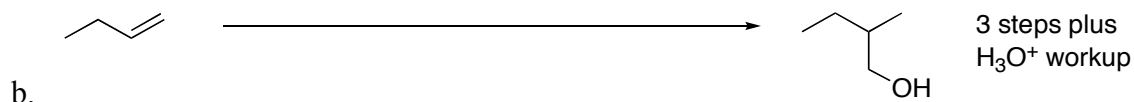
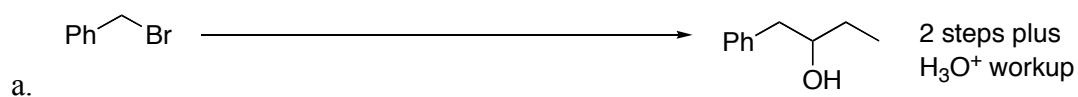
Grignards in Synthesis: Provide Precursors.

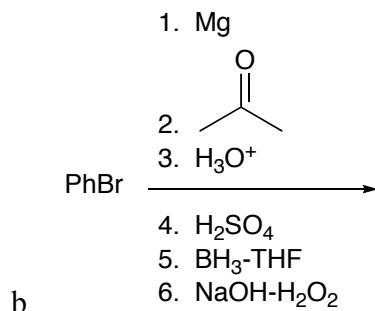
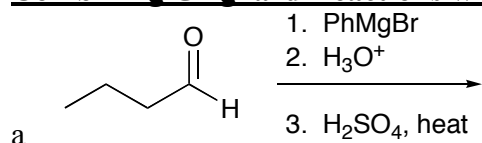
- **Think backwards from Targets to Reactants.**
- Identify possible Grignards and Grignard acceptors
- **Pattern:**
 - 3° alcohol, all three attachments different ← **Ketone Precursor**
 - 3° alcohol, two (or more) of the attachments identical ← **Ester**
 - 2° alcohol ← **Aldehyde**
 - 1° alcohol ←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



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

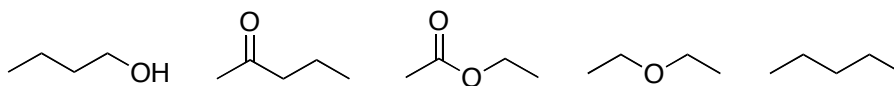
- Key: Try to identify key C-C connection in the product that wasn't present to start with
- Try to identify the where the reactant carbons are in the final product
- Numbering your carbon chains is very helpful.
- Usually best to work backwards from the product



Combining Grignard Reactions with Other Reactions**Restrictions on Grignard Reactions**

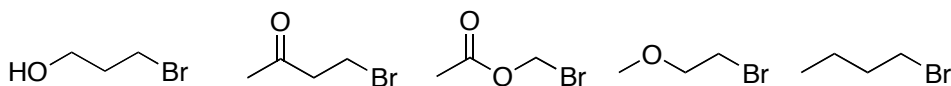
- $\text{RMgBr} = \text{R}^\ominus$ carbanion, highly unstable, highly reactive.
- Unstable in the presence of:
 1. OH's (get proton transfer reaction)
 2. Carbonyls (get Grignard-type nucleophilic addition)
- 1. Solvent limitations. RMgBr cannot be formed and used in the presence of
 - H_2O
 - ROH
 - Any solvent with a $\text{C}=\text{O}$

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

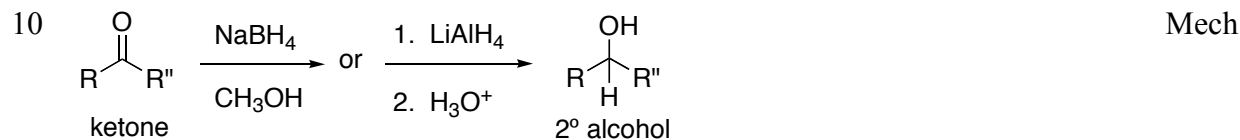
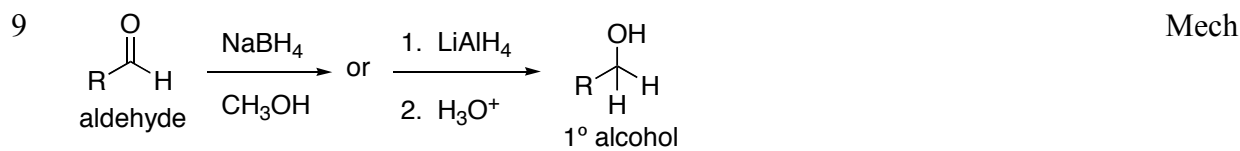


2. Substrate limitations. Any organohalide that also contains an OH or $\text{C}=\text{O}$ bond can't be converted into a useful RMgBr , because it will self-destruct.

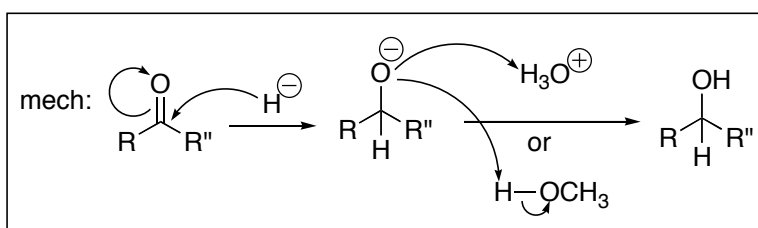
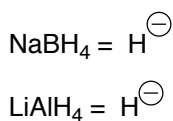
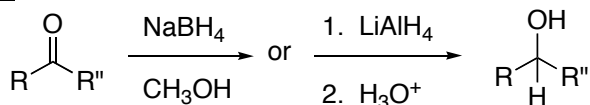
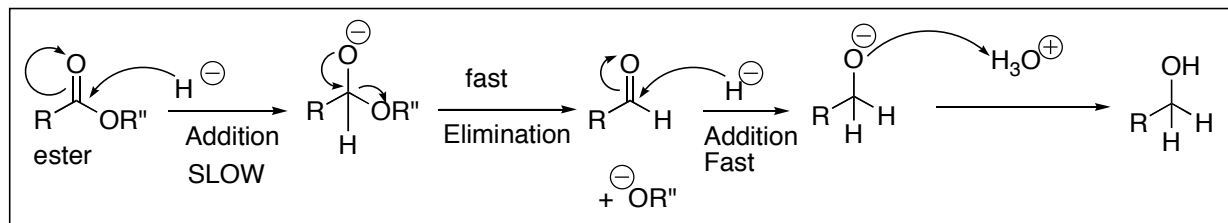
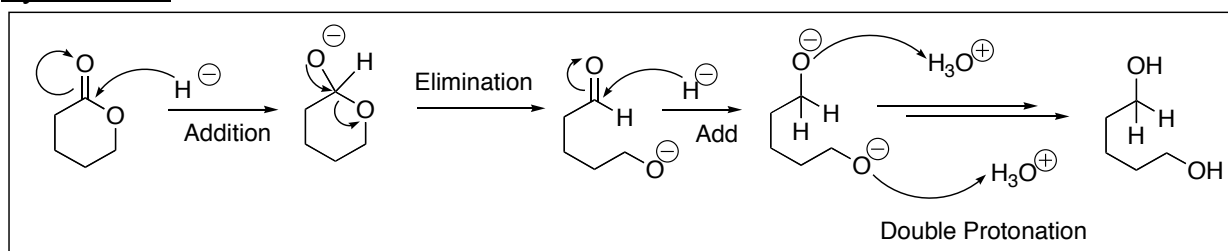
Which substrates could be converted into RMgBr , and subsequently reacted with CH_3CHO ?



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.

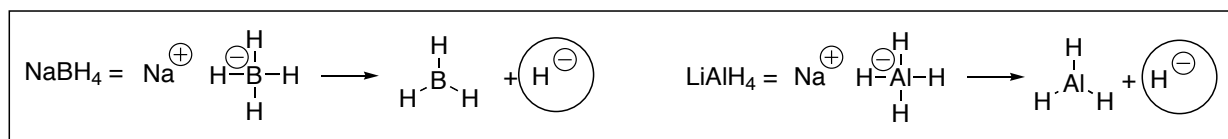
17.4 Alcohols by Reduction of Carbonyls: H^- AdditionMechanismAldehydes and Ketones

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...



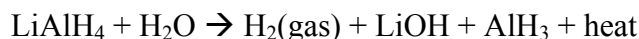
- Boron is one row higher than aluminum, and in keeping with normal periodic patterns is more electronegative
 - Because boron is more electronegative, the BH_4^- anion is more stable, and less reactive.
 - The boron holds the H^- more tightly.
 - Aluminum being less electronegative doesn't attract and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

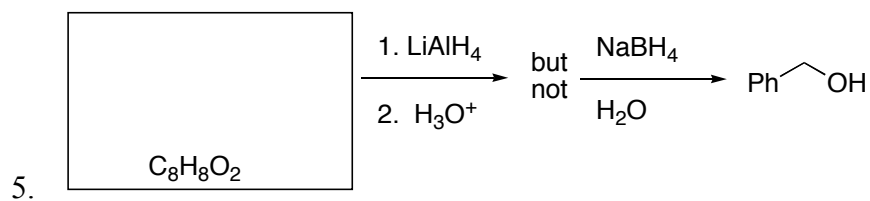
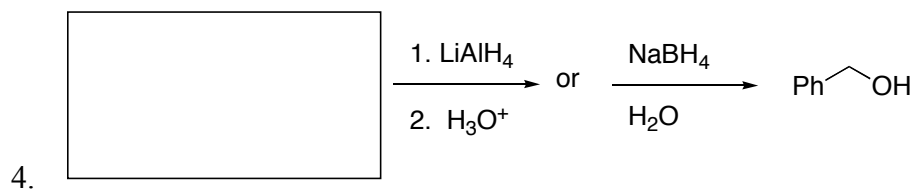
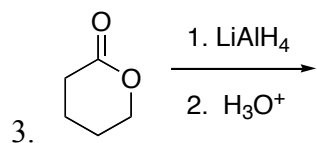
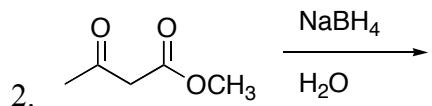
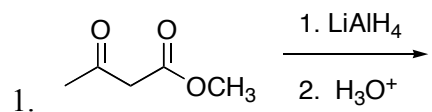
 LiAlH_4 is much stronger, NaBH_4 much weaker

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**

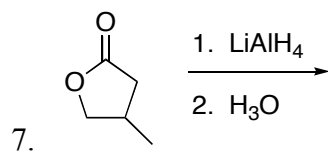
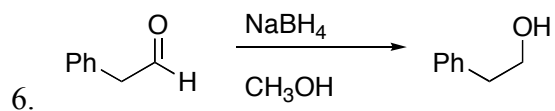


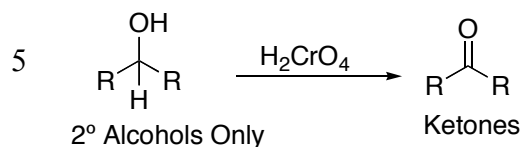
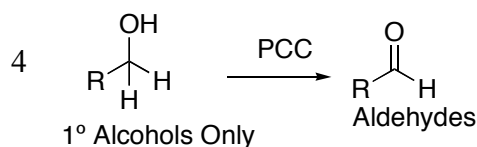
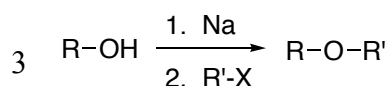
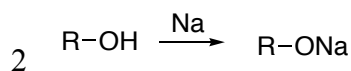
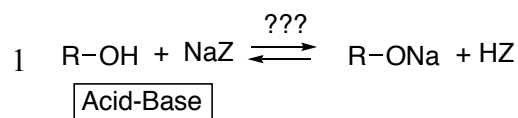
- a. As a result, LiAlH_4 is harder to use and store
 - b. Acid has to be added in a subsequent step with the LiAlH_4 ; (thus, 2-step recipe)
 - c. NaBH_4 can be run in alcohol solvent which serves as a proton source for protonating alkoxide
 - d. Solvent restrictions, glassware must be dry, wet air 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.

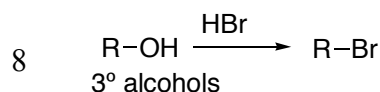
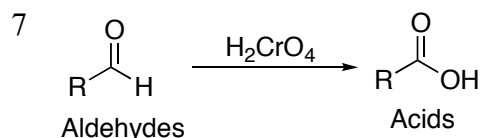
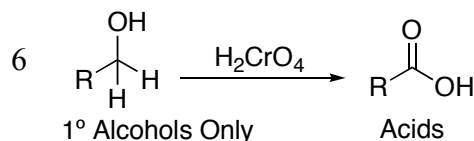


Draw the mechanism for the following reaction.



Summary of Alcohol Reactions, Ch. 17.

$\text{H}_2\text{CrO}_4 = \text{Na}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4 \text{ or } \text{CrO}_3/\text{H}_2\text{O}$



Mech: Be able to draw!

1. Deprotonation by a base.
2. Controlled by relative stability of RO^- versus Z^- .
3. Consider relative electronegativity and whether either anion is resonance stabilized.

- Potassium (K) analogous.
- Key way to convert alcohol to alkoxide, reactive as $\text{S}_{\text{N}}2$ nucleophile and E2 base.

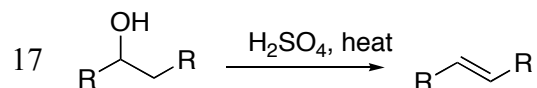
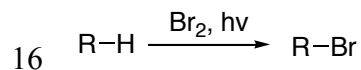
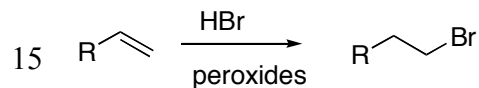
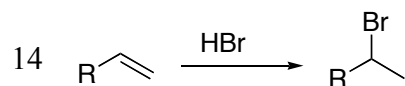
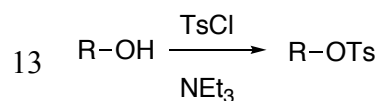
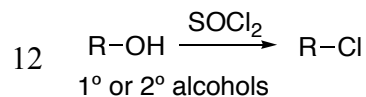
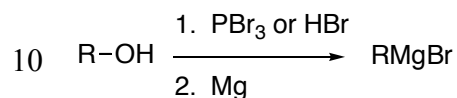
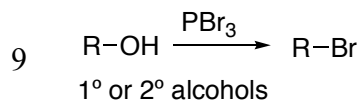
- Alkoxide formation- $\text{S}_{\text{N}}2$ route to ether
- The electrophile $\text{R}'\text{-X}$ must be $\text{S}_{\text{N}}2$ reactive, preferably 1° with a good leaving group

- Key access to aldehydes, which are useful for more Grignard chemistry.
- Note difference between PCC and H_2CrO_4
- PCC does not react with 2° alcohols very rapidly

- Key access to ketones.
- PCC does not react very fast with 2° alcohols

- Note difference between PCC and H_2CrO_4 when reacting with 1° alcohols.

- HI, HCl analogous
- Converts alcohol into a bromide that can be used in Grignards, E2 reactions
- Cation mechanism
- Usually not method of choice for 1°, 2° alcohols



- Converts alcohol into a bromide that can be used in Grignards, E2, S_N2 reactions
- Inversion of stereochem
- Not good for 3° alcohols

- Quick 2-step conversion of alcohol into a nucleophilic Grignard

- Retention of stereo!

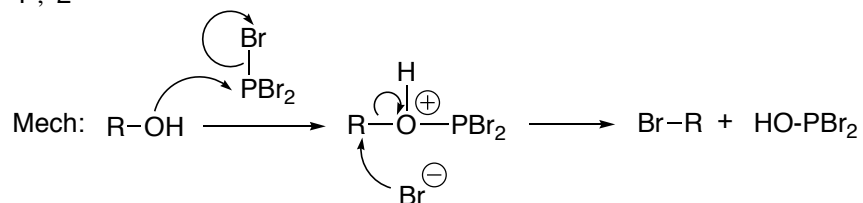
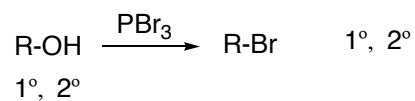
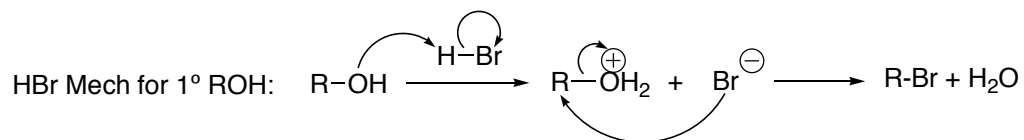
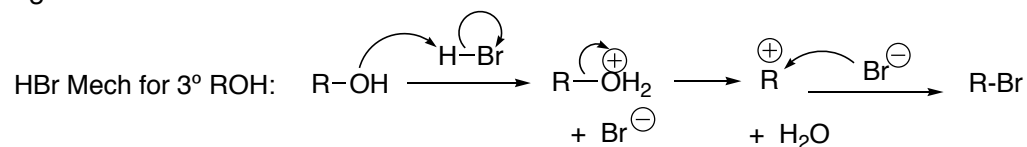
- Tosylates are super leaving groups, better even than iodides.
- Tosylates are well suited to S_N2 and E2 reactions.

- Markovnikov addition

- anti-Markovnikov addition

- Radical mechanism, 3° > 2° > 1°

- Zaytsev elimination

Mechanisms for ROH \rightarrow RBr Reactions

Ch. 17.6-8 Reactions of Alcohols

A. Conversion to Alkoxides (Sections 17.2)

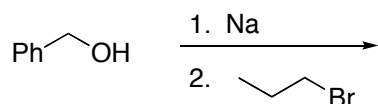
“alkoxide” = RO^- anion

- By acid-base deprotonation
 - A rather reactive anion base is required that is *less* stable than an alkoxide anion
 - Carbanions (RMgBr) or nitrogen anions can do this
 - NaOH can't
- By redox reaction with sodium or potassium (or some other metals)

1	$\text{R-OH} + \text{NaZ} \xrightleftharpoons{???} \text{R-ONa} + \text{HZ}$ <div style="border: 1px solid black; padding: 2px; width: fit-content; margin: 5px 0;">Acid-Base</div>	<ol style="list-style-type: none"> Deprotonation by a base. Controlled by relative stability of RO^- versus Z^-. Consider relative electronegativity and whether either anion is resonance stabilized.
2	$\text{R-OH} \xrightarrow{\text{Na}} \text{R-ONa}$	<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.

B. Conversion to Ethers via Alkoxide

3	$\text{R-OH} \xrightarrow[2. \text{R}'\text{-X}]{1. \text{Na}} \text{R-O-R}'$	<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
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C. Oxidation of Alcohols to Carbonyl Compounds (17.7)

Summary: 2 Oxidants

1. **PCC = mild** 1° alcohols \rightarrow aldehydes

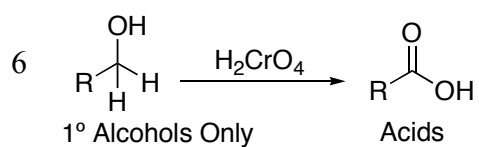
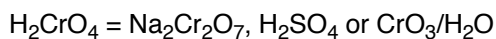
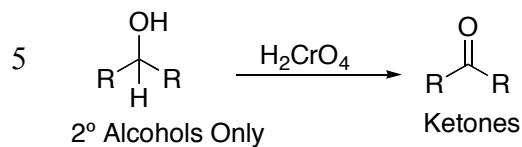
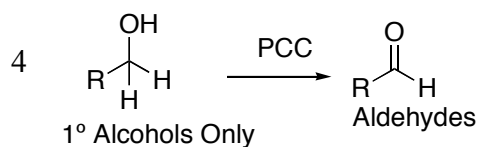
- “Pyridinium chlorochromate”: soluble in water-free dichloromethane
- Mild, selective for 1° over 2° alcohols, and when 1° alcohols are used stops at aldehyde

2. **H_2CrO_4 = strong**a. 2° alcohols \rightarrow ketonesb. 1° alcohols \rightarrow carboxylic acidsc. 3° alcohols \rightarrow no reactiond. aldehydes \rightarrow carboxylic acids

- $\text{H}_2\text{CrO}_4 = \text{CrO}_3 + \text{H}_2\text{O}$ or $\text{Na}_2\text{Cr}_2\text{O}_7 + \text{H}_2\text{SO}_4$ (make in the reaction flask)

- Always made and used in the presence of some water

- Very strong, when 1° alcohols are used goes $1^\circ \text{RCH}_2\text{OH} \rightarrow \text{RCHO} \rightarrow \text{RCO}_2\text{H}$ without stopping at aldehyde

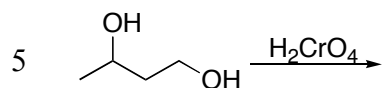
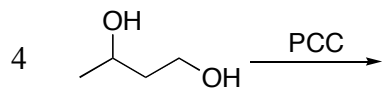
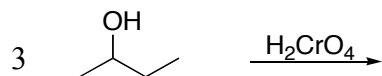
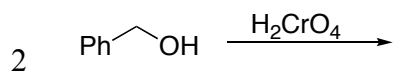
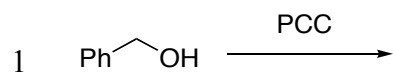


- Key access to aldehydes, which are useful for more Grignard chemistry.
- Note difference between PCC and H_2CrO_4
- PCC does not react with 2° alcohols very rapidly

- Key access to ketones.
- PCC does not react very fast with 2° alcohols

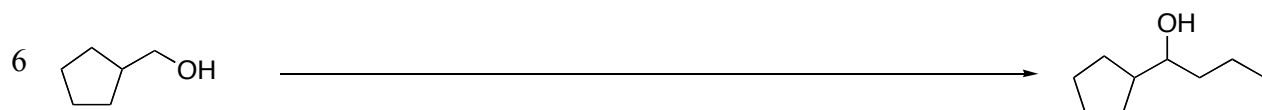
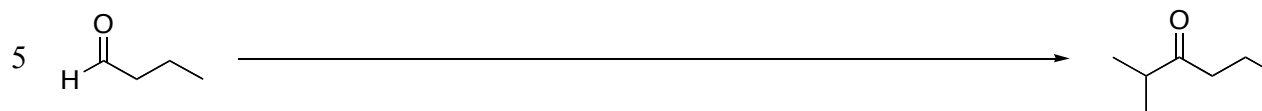
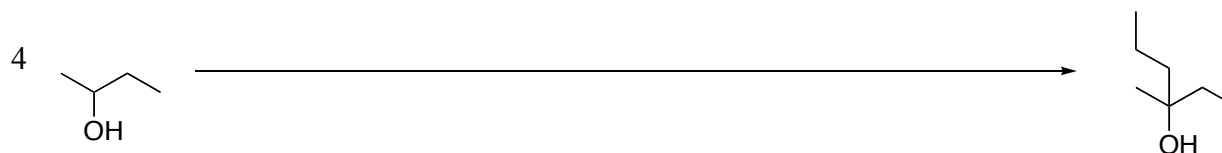
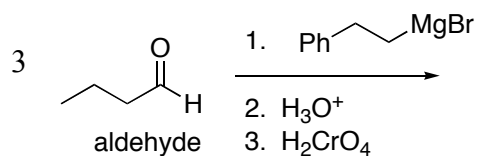
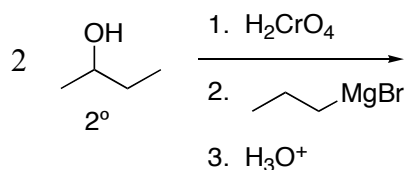
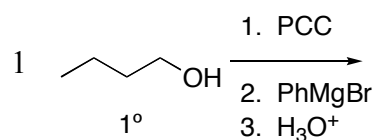
- Note difference between PCC and H_2CrO_4 when reacting with 1° alcohols.

Draw the products for the following oxidation reactions.



Oxidation Combined with Grignard Reactions (in either order): Indirectly Enables Substitution of Carbon for Hydrogen

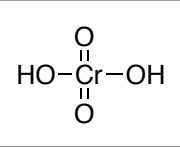
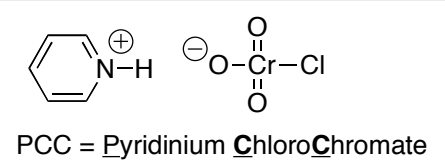
1. **1° alcohol** + PCC \rightarrow aldehyde + RMgBr \rightarrow **2° alcohol**
2. **2° alcohol** + H₂CrO₄ \rightarrow ketone + RMgBr \rightarrow **3° alcohol**
 - Oxidation followed by Grignard reaction essentially substitutes a carbon group for a hydrogen
3. **Aldehyde** + RMgBr \rightarrow 2° alcohol + H₂CrO₄ \rightarrow **ketone**
 - Grignard reaction followed by oxidation essentially substitutes a carbon group for a hydrogen

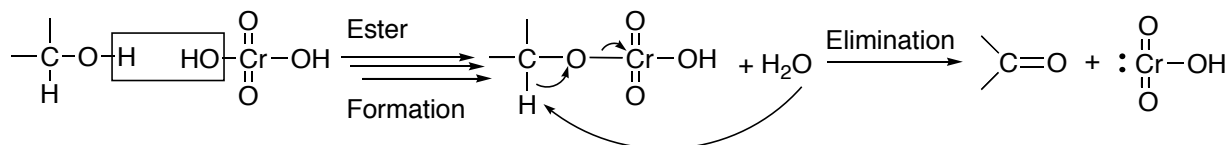


Jones Test H₂CrO₄ for Alcohols (test responsible)

- H₂CrO₄ (Jones Reagent) is clear orange
- Treatment of an unknown with Jones reagent:
 - Solution stays clear orange → no 1° or 2° alcohol present (negative reaction)
 - Solution gives a green/brown precipitate → 1° or 2° alcohol present (positive reaction)
 - 3°, vinyl, and aryl alcohols do not react. Nor do ketones, ethers, or esters.

Structure and Mechanism (not test responsible)

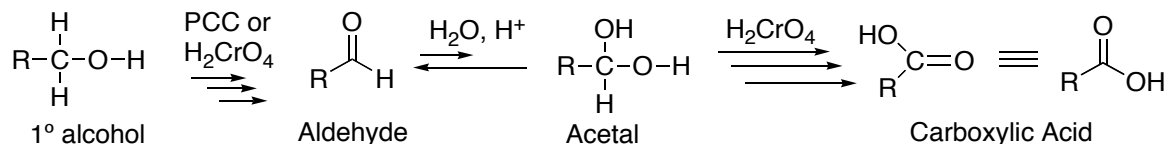
<p>H₂CrO₄ = chromic acid = Na₂Cr₂O₇ = CrO₃/H₂O = Cr⁺⁶ oxidation state</p> <ul style="list-style-type: none"> • Water soluble 	
<p>Pyridinium cations renders PCC soluble in organic solvents, thus it is functional in organic solvent and in the absence of water</p>	 <p>PCC = Pyridinium ChloroChromate</p>

General Mechanism

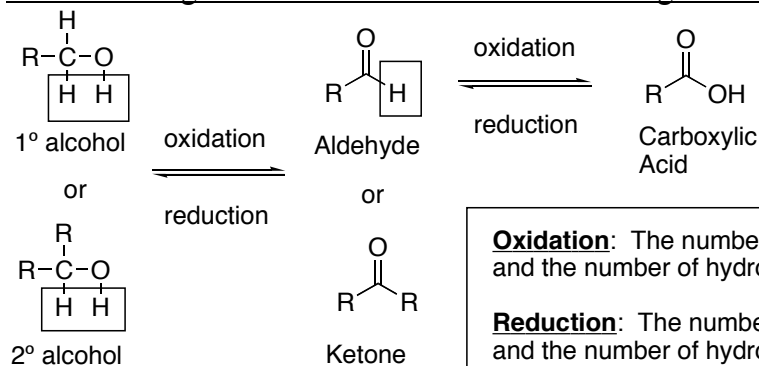
- PCC operates analogously

1° Alcohols, Aldehydes, and the Presence or Absence of Water:

Q: Why does Anhydrous PCC stop at Aldehyde but Aqueous H₂CrO₄ Continues to Carboxylic Acid?



1. Both PCC and H₂CrO₄ convert 1° alcohols to aldehydes
2. In the presence of acidic water, aldehydes undergo an equilibrium addition of water to provide a small equilibrium population of acetal
3. The acetal form gets oxidized (very rapidly) to carboxylic acid
 - The aldehyde form cannot itself get oxidized to carboxylic acid
 - Since PCC is used in absence of water, the aldehyde is not able to equilibrate with acetal and simply stays aldehyde.
 - Since it can't convert to acetal, therefore no oxidation to carboxylic acid can occur
4. Chromic acid, by contrast, is in water
 - Therefore the aldehyde is able to equilibrate with acetal
 - The acetal is able to be oxidized.
 - Thus, the aldehyde via the acetal is able to be indirectly oxidized to carboxylic acid, and in fact does so very rapidly.

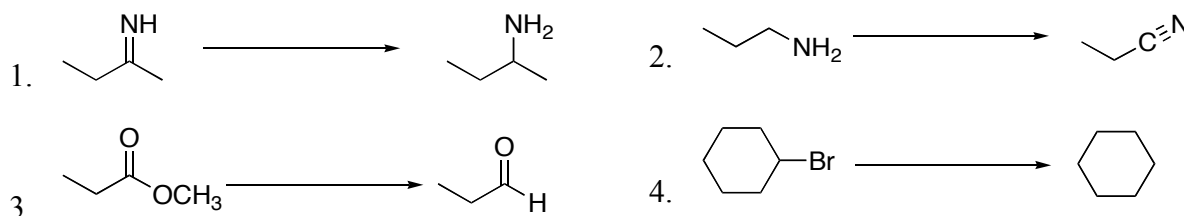
General Recognition of Oxidation/Reduction in Organic Chemistry

Oxidation: The number of oxygen bonds to a carbon increases, and the number of hydrogens bonded to a carbon decreases

Reduction: The number of oxygen bonds to a carbon is reduced, and the number of hydrogens bonded to a carbon increases.

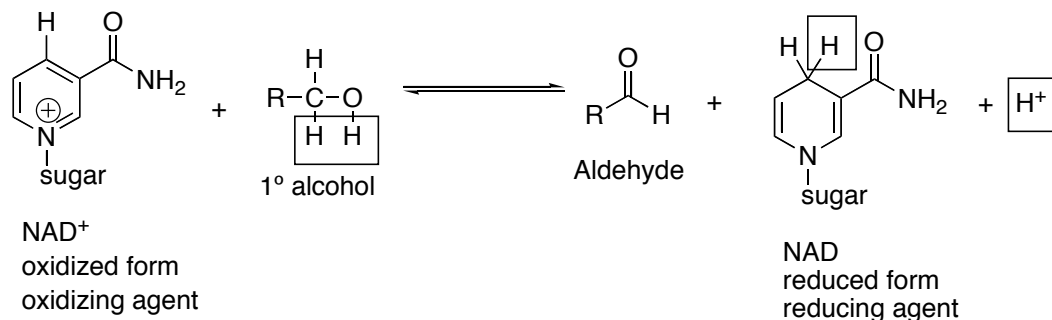
More General: # of bonds to heteroatoms versus to hydrogens

Classify the following transformations as “oxidations” or “reductions”

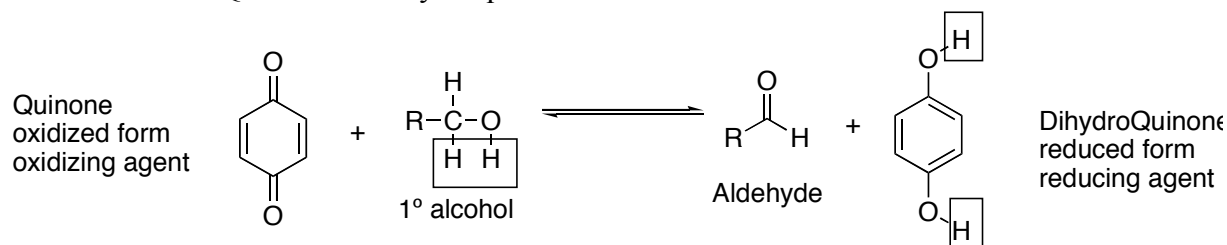
Other methods for Oxidizing Alcohols. (No test)

There are lots of other recipes used for oxidizing alcohols (and for other oxidation reactions)

1. KMnO_4
2. CuO
3. “Jones”: H_2CrO_4 with acetone added to temper reactivity
4. Collins: H_2CrO_4 with pyridine added to temper reactivity
5. “Swern”: $(\text{COCl})_2$ and $(\text{CH}_3)_2\text{S}=\text{O}$ then NEt_3
6. HNO_3
7. Biological Oxidant 1: “ NAD^+ ” “nicotinamide adenine dinucleotide”



8. Biological Oxidant 2: “Quinones and hydroquinones”



In General: Recognizing Oxidizing versus Reducing Agents**Oxidizing Agents:** Often have:

- Highly Oxidized Metals or Nonmetals
- Extra Oxygen

OsO₄ (+8)
 KMnO₄ (+7)
 CrO₄ (+6)
 H₂CrO₄ (+6)
 HNO₃ (+5)
 H₂O₂ → H₂O
 RCO₃H → RCO₂H
 O₃ → O₂

Reducing Agents: Often involve:

- Hydrides in Formulas
- Highly Reduced Metals
- Metals + H₂
- Metals + acid

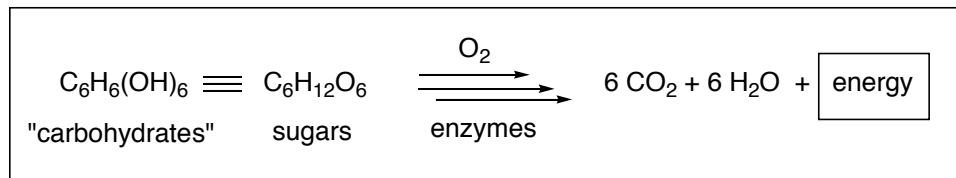
LiAlH₄
 NaBH₄
 Li, Na, K, Mg, Zn, Al, etc.
 Pd/H₂, Pt/H₂, Ni/H₂ etc.
 Zn/HCl, Fe/HCl, Zn/Hg/HCl, etc..

- The ability to qualitatively recognize when a transformation involves an oxidation or reduction can be very helpful.
- The ability to recognize a reactant as an oxidizing agent or a reducing agent can be very helpful
- Often on standardized tests!

Some Biological Alcohol Oxidations (Not for Test)

1. Oxidation of “carbohydrates” or “sugars” is the primary source of bioenergy

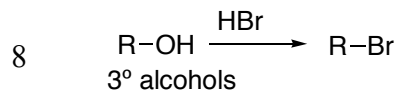
- multiple enzymes are involved for the many steps
- A “carbohydrate” basically has a formula with one OH per carbon



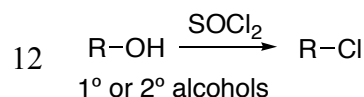
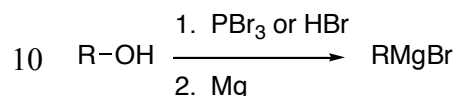
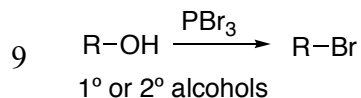
2. Most alcohols are biooxidized to give toxic carbonyl derivatives (“intoxication”)

- the presence of substantial aldehydes and especially ketones in the blood is symptomatic of various problems
 - intoxication
 - alcoholism
 - uncontrolled diabetes
 - etc (other metabolic disorders)

17.6 Conversion of Alcohols to Alkyl Halides



Mech: Be able to draw!



- HI, HCl analogous
- Converts alcohol into a bromide that can be used in Grignards, E2 reactions
- Cation mechanism
- Usually not method of choice for 1°, 2° alcohols

- Converts alcohol into a bromide that can be used in Grignards, E2, S_N2 reactions
- **Inversion of stereochem**
- Not good for 3° alcohols

- Quick 2-step conversion of alcohol into a nucleophilic Grignard

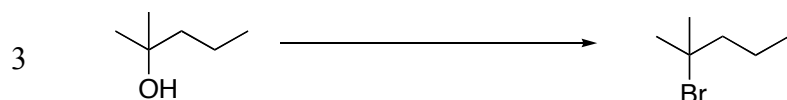
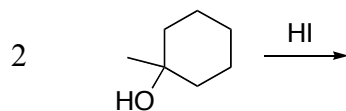
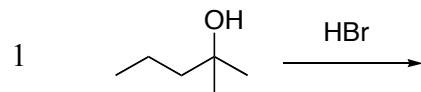
- Retention of stereo!
- Section 11-9

Summary:

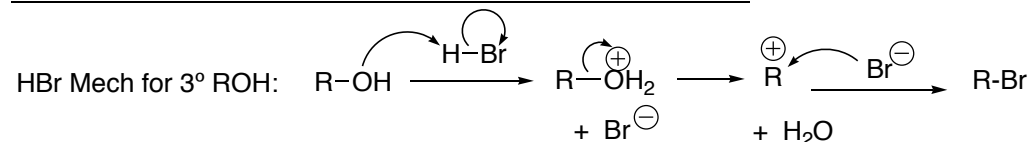
Class	<u>R-Br</u>	<u>R-Cl</u>
1° ROH	PBr ₃	SOCl ₂
2° ROH	PBr ₃	SOCl ₂
3° ROH	HBr	HCl
Vinyl or Aryl	Nothing works	Nothing works

Straight Reaction with H-X (Section 17.7)

- Ideal only for 3° ROH,
- sometimes works with 1° alcohols, with a complex mechanism
- Only occasionally for 2° alcohols
- **Method of choice for 3°, but not for 1° or 2°**

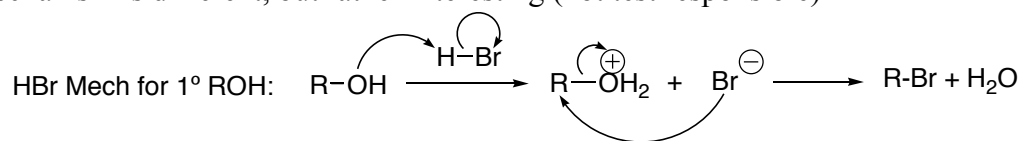


Mechanism for H-X reactions with 3° Alcohols: Cationic



Notes:

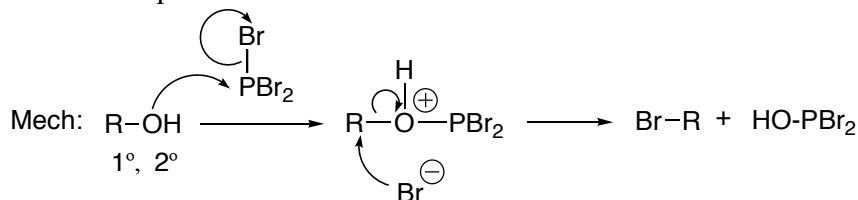
- Memorize the 3° alcohol mechanism (test responsible)
 - Protonate
 - Leave to give Cation. This is the slow step for 3° alcohols
 - Capture
- Analogous with HI or HCl
 - HCl slower, normally enhanced with ZnCl₂, which enhances rate of cation formation (Lucas test, see later)
 - Outside of 3° systems, side reactions are common and yields aren't often very good
- Outside of 3° alcohols, side reactions are common and yields aren't often very good
 - Elimination reactions and cation rearrangements...
- S_N1 type: carbocation-forming step is the rate-determining step, so R⁺ stability key
 - 3° alcohols fastest
 - 2° alcohols are way slower
 - 1° alcohols can't react at all via this mechanism, because 1° R⁺ are too unstable.
 - Ditto for vinyl or aryl alcohols
- HBr can also react with 1° ROH to give 1° RBr, although it is not often the method of choice
 - The mechanism is different, but rather interesting (not test responsible)



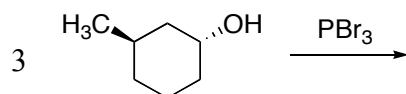
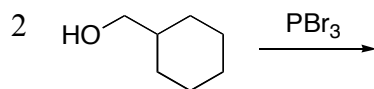
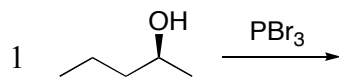
- carbocation formation never occurs
- bromide ion simply does S_N2 on the protonated alcohol, with water as an excellent leaving group
- yields tend to be pretty inconsistent

Reaction of 1° and 2° Alcohols with PBr₃

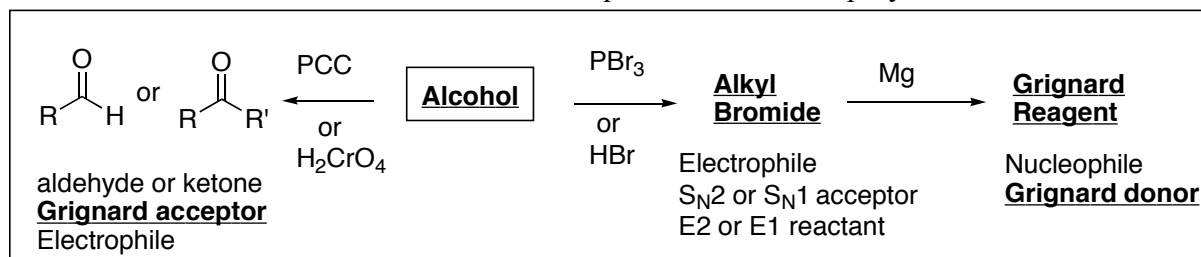
- Default recipe for 1° and 2° alcohols



- PBr₃ is an exceptional electrophile, and reacts even with neutral alcohols
- The first step activates the oxygen as a leaving group.
- The second step involves an S_N2 substitution
 - stereochemical inversion occurs chirality present (common for 2° alcohols)
- Because the second step is an S_N2 substitution, the reaction fails for 3° ROH



Conversions of Alcohols into Other Reactive Species in Multi-Step Syntheses



- oxidation can convert an alcohol into a carbonyl = **Grignard acceptor (electrophile)**
- PBr₃/Mg or HBr/Mg can convert an alcohol into RMgBr = **Grignard donor (nucleophile)**
- PBr₃ or HBr can convert an alcohol into RBr, capable of normal substitution and elimination reactions.

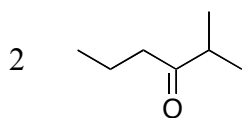
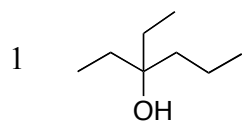
Retrosynthesis Problems (In which you decide what to start from): Design syntheses for the following.

Allowed starting materials include:

Bromobenzene	cyclopentanol	any acyclic alcohol or alkene with ≤4 carbons
any esters	ethylene oxide	formaldehyde (CH ₂ O)
any "inorganic" agents (things that won't contribute carbons to your skeleton)		

Tips:

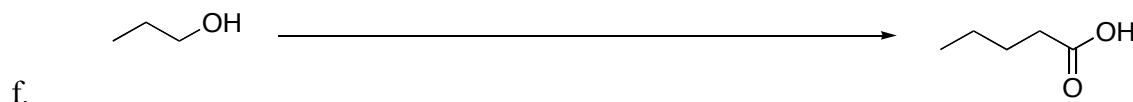
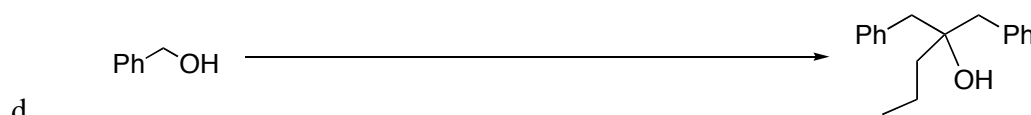
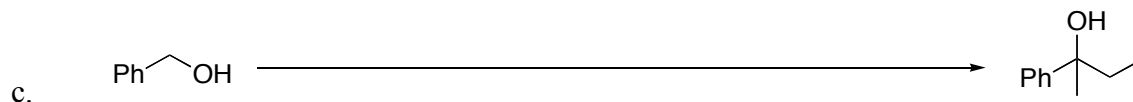
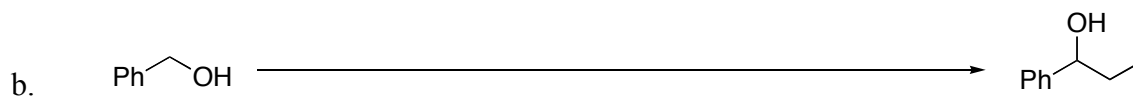
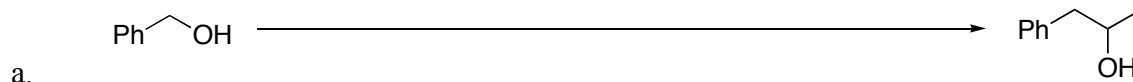
- Focus on the functionalized carbon(s)
- Try to figure out which groups of the skeleton began together, and where new C-C bonds will have been formed
- When "breaking" it up into sub-chunks, try to make the pieces as large as possible (4 carbon max, in this case, for acyclic pieces)
- Remember which direction is the "true" laboratory direction.
- Be careful that you aren't adding or subtracting carbons by mistake



Normal Synthesis Design: In which you are given at least one of the starting Chemicals.

Provide Reagents. You may use whatever reagents, including ketones or aldehydes or Grignards or esters, that you need. Tips:

- Identify where the reactant carbons are in the product
- Is the original carbon still oxygenated? → it will probably function as a Grignard acceptor
- Is the original carbon not still oxygenated? → it should probably function as Grignard donor
- Working backwards helps.



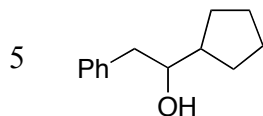
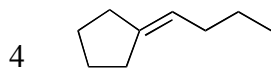
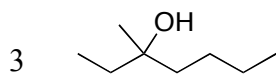
Retrosynthesis Problems: Design syntheses for the following.

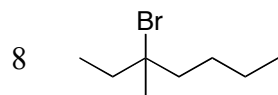
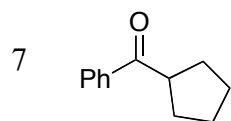
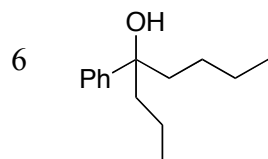
Allowed starting materials include:

Bromobenzene	cyclopentanol	any acyclic alcohol or alkene with ≤ 4 carbons
any esters	ethylene oxide	formaldehyde (CH ₂ O)
any "inorganic" agents (things that won't contribute carbons to your skeleton)		

Tips:

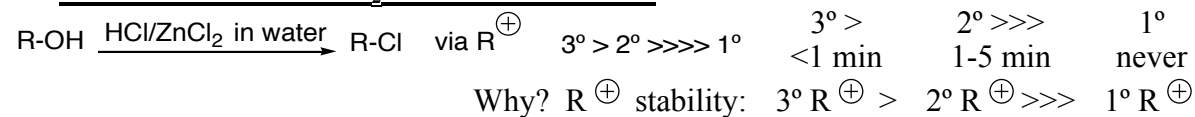
1. Focus on the functionalized carbon(s)
2. Try to figure out which groups of the skeleton began together, and where new C-C bonds will have been formed
3. When "breaking" it up into sub-chunks, try to make the pieces as large as possible (4 carbon max, in this case, for acyclic pieces)
4. Remember which direction is the "true" laboratory direction.
5. Be careful that you aren't adding or subtracting carbons by mistake





Unknowns and Chemical Tests1. H₂/Pt test for alkenes2. Br₂ test for alkenes**3. Jones reagent (H₂CrO₄) Test for 1° or 2° alcohols**

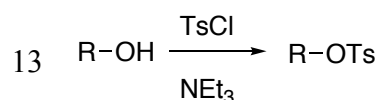
- 3° alcohols do not react
- 2° alcohols keep the same number of oxygens but lose two hydrogens in the formula
- 1° alcohols lose two H's but also add one oxygen

4. Lucas Test: HCl/ZnCl₂ for 3° or 2° alcohols

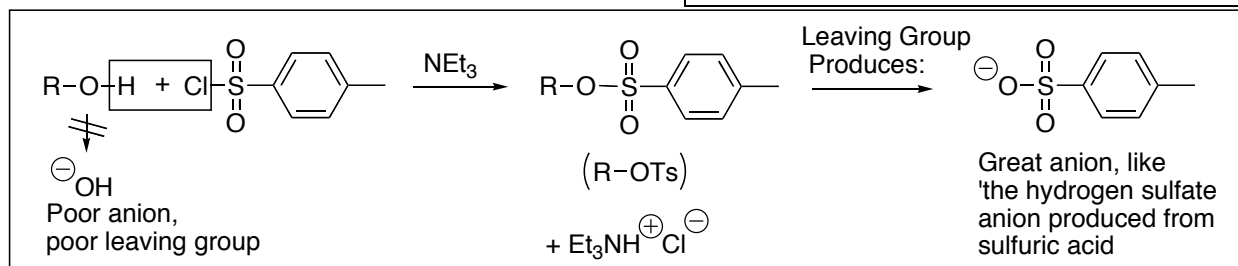
- 3° alcohols are fastest
- 1° alcohols don't react at all
- R[⊕] stability is the key
- Test is based on **solubility**: The R-Cl product is nonpolar and water insoluble, so it separates out from water. Alcohols are quite soluble especially in highly acidic water.
- Test fails is useless for alcohols with so many carbons that it doesn't even dissolve in the original HCl/ZnCl₂/water solution

	Jones (H₂CrO₄)	Lucas (HCl/ZnCl₂)	H₂/Pt	Required Facts	Possible Answers
1 C ₅ H ₁₀ O	Yes	No	Yes		
2 C ₆ H ₁₂ O	Yes	Yes, 1-5 min	No		
3 C ₆ H ₁₂ O	No	Yes	Yes		
4 C ₇ H ₁₂ O	Yes	Yes	Yes, Produces C ₇ H ₁₄ O		
5 C ₃ H ₆ O	No	No	Yes		
6 C ₃ H ₆ O	No	No	No		
7 C ₃ H ₆ O	Yes, produces C ₃ H ₄ O ₂	No	Yes		
8 C ₃ H ₆ O	Yes, produces C ₃ H ₄ O	Yes	No		
9 C ₃ H ₆ O	No	No	Yes		

Conversion of Alcohols to "Tosylates", and their use as Exceptional Leaving Groups in S_N2 , S_N1 , E2, and E1 Reactions



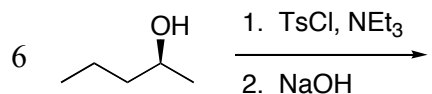
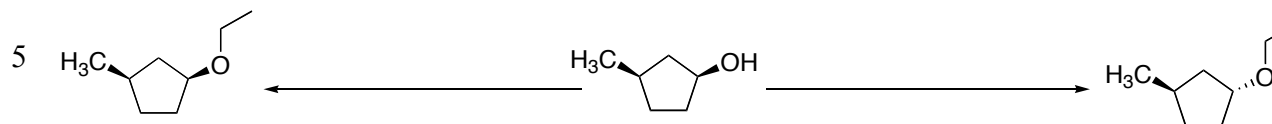
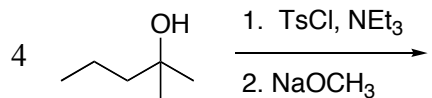
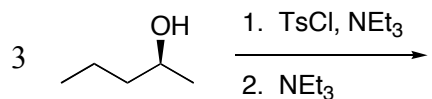
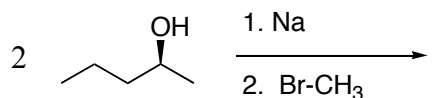
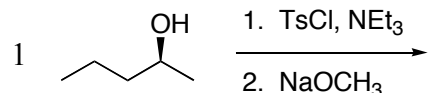
- Tosylates are super leaving groups, better even than iodides.
- Tosylates are well suited to S_N2 and E2 reactions.



Notes:

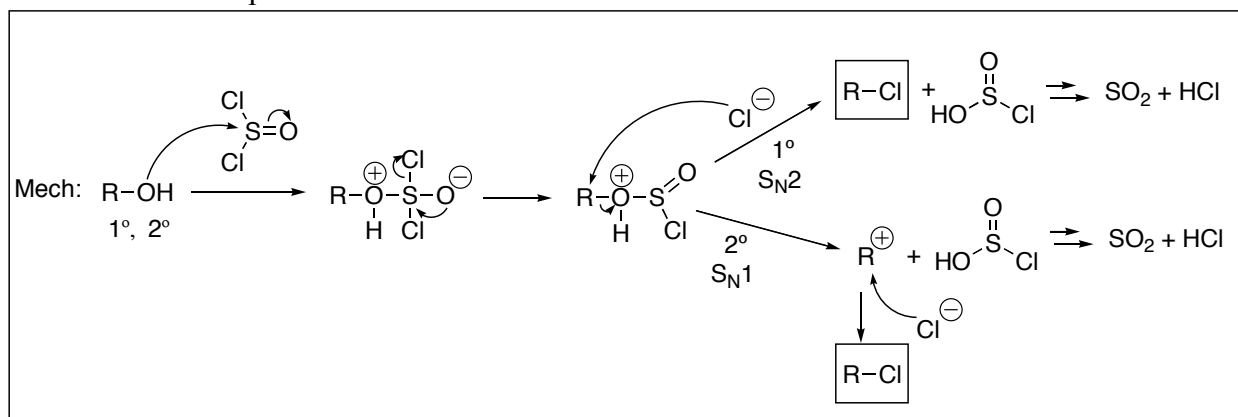
1. Tosylates are easy to form
2. "Toluene sulfonate"
3. Tosylate anion is really stable, comparable to the anion from sulfuric acid
 - Both the electronegative sulfur and the resonance/charge sharing with the other oxygens helps
4. Whereas a normal OH has a poor leaving group (hydroxide anion), conversion to the tosylate provides a super good leaving group.
5. Leaving Group Reactivity: Better than the best of the halides
 - $OTs \gg I > Br > Cl$
6. Tosylates are highly reactive toward S_N2 , S_N1 , E2, and E1 Reactions
7. Triethylamine is used as an HCl scavenger in the tosylate formation
 - Often a weaker amine base called pyridine is used, to avoid unintentionally providing E2 on the tosylate

Draw Products



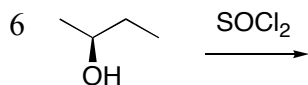
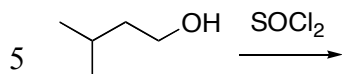
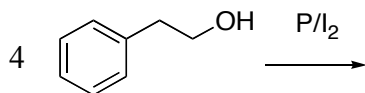
Reaction of 1° and 2° Alcohols with SOCl₂

- Default recipe for 1° and 2° alcohols



- Mechanism: Not for test responsibility
- Mechanism differs for 1° and 2° alcohols
- 1° involve an S_N2 substitution
- 2° involve an S_N1 type substitution
- The chloride that captures the cation is normally on the same side of the molecule on which the oxygen began, and often captures the cation very rapidly from that same side
- This results in a very unusual **retention of stereochemistry.**
- When they work, these reactions are convenient because the side products, SO₂ and HCl, are both gases. So workup is really easy. Simply rotovap the mixture down, and everything except for product is gone.

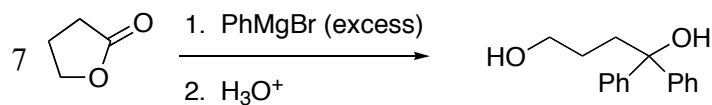
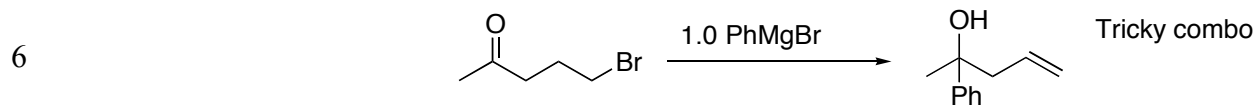
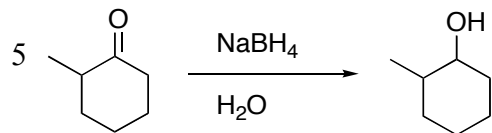
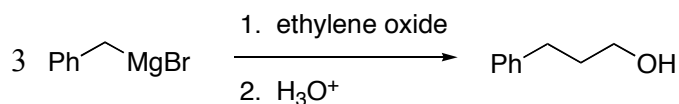
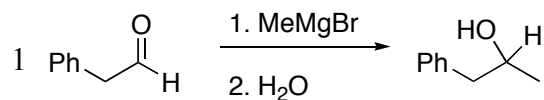
Draw Products or Provide Appropriate Reactants for the following Transformations



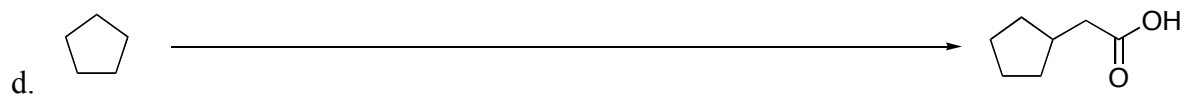
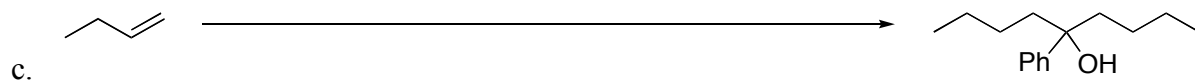
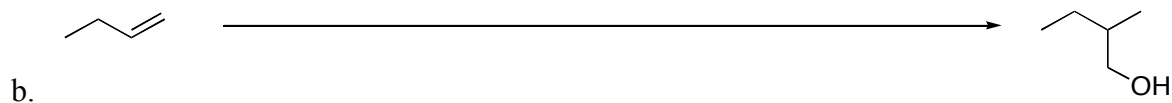
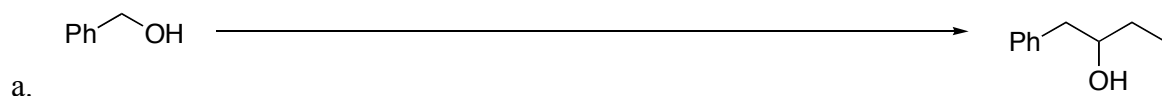
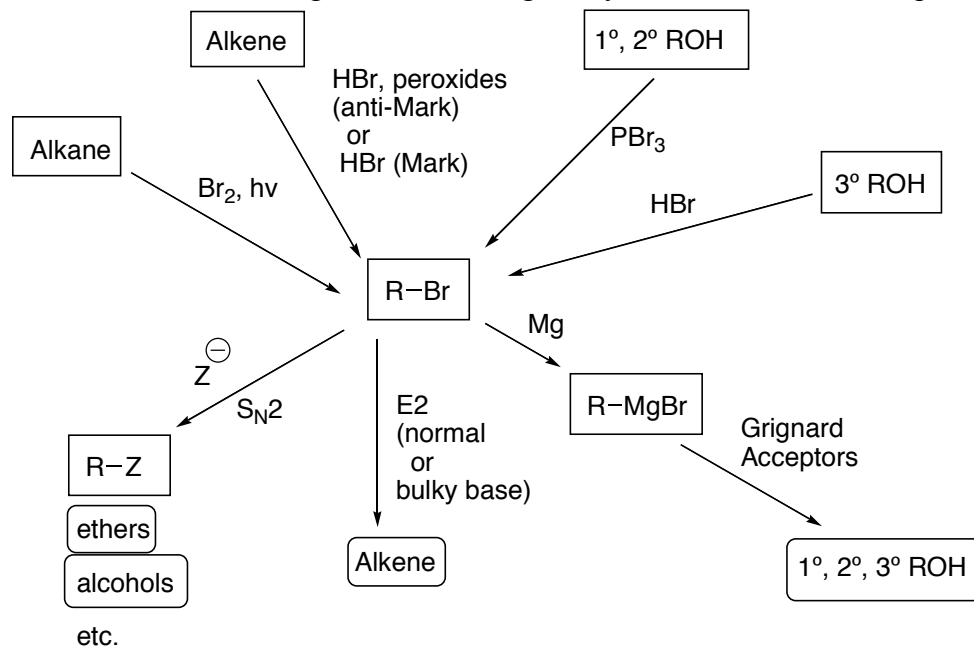
Draw the Mechanism:

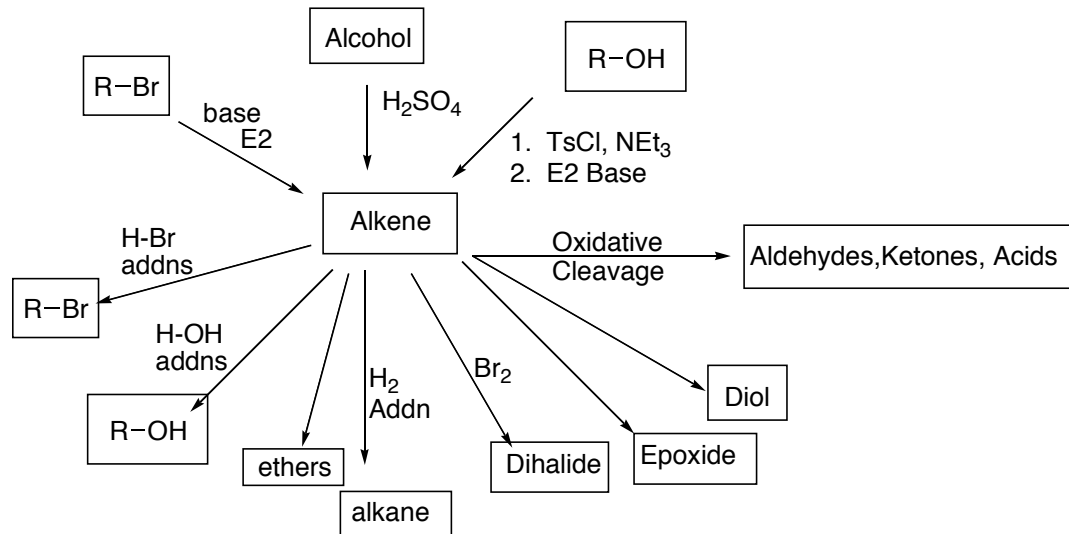


Draw the mechanisms for the following reactions.



REVIEW. To make organometallic reagents, you must have RBr compounds (or RCl or RI).



Alkene Concept Map**Ether Concept Map**