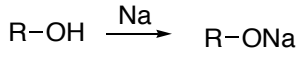
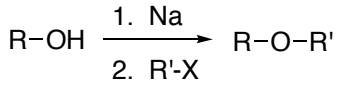
Summary of Alcohol Syntheses, Ch. 10 (and Review of Old Ones).

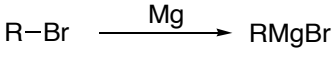
1 

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

2 

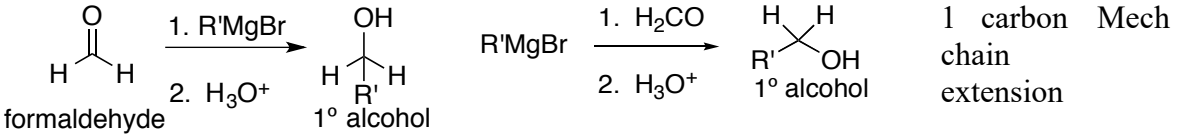
- Alkoxide formation-S_N2 route to ether
- The electrophile R'-X must be S_N2 reactive, preferably 1º with a good leaving group

Mech?

3 

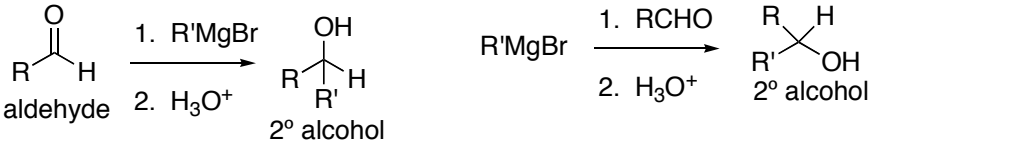
-Li is analogous for making RLi, which also act analogously.

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

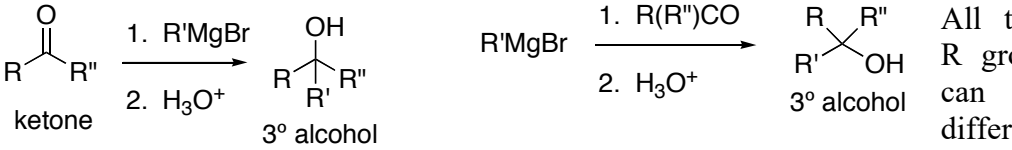
4 

1 carbon chain extension

Mech

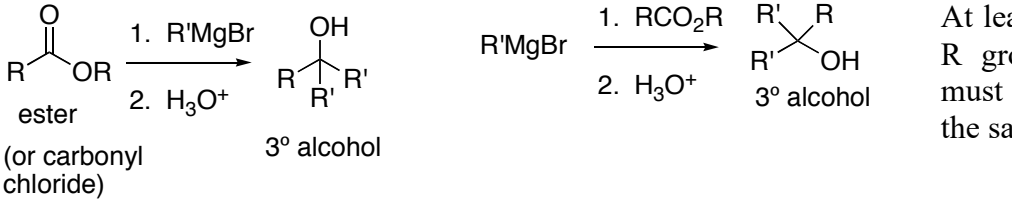
5 

Mech

6 

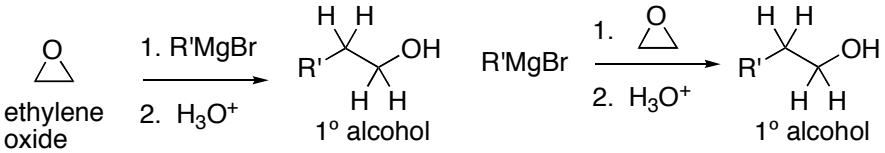
All three R groups can be different.

Mech

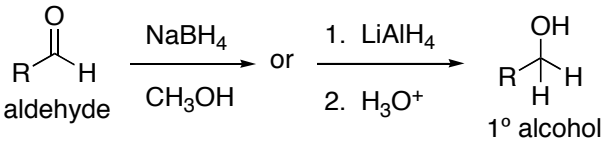
7 

At least 2 R groups must be the same

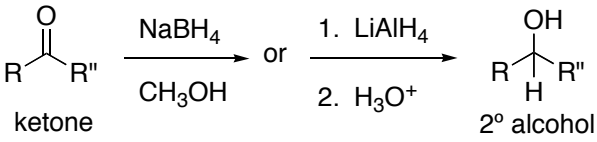
Mech

8 

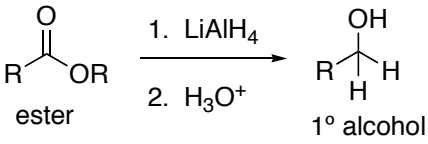
2-Carbon chain extension Mech

9 

Mech

10 

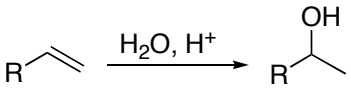
Mech

11 

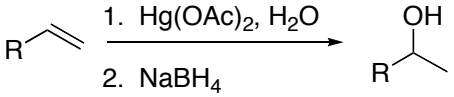
$NaBH_4$ will not react with esters

Mech

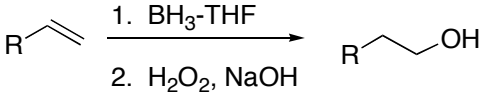
Review Routes to Alcohols

10 

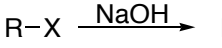
Markovnikov

11 

Markovnikov

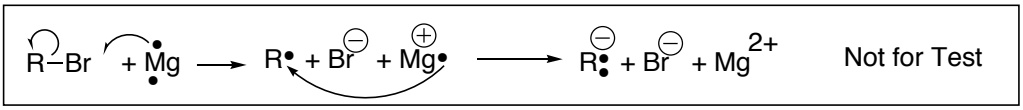
12 

anti-Markovnikov

13 

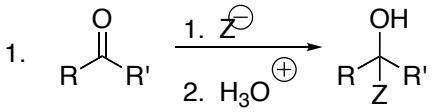
S_N2 mech, needs 1° or 2° system and an excellent leaving group

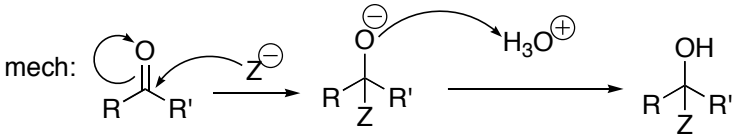
Summary of Mechanisms, Ch. 10



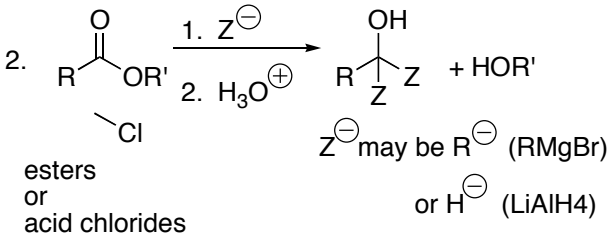
For Test:

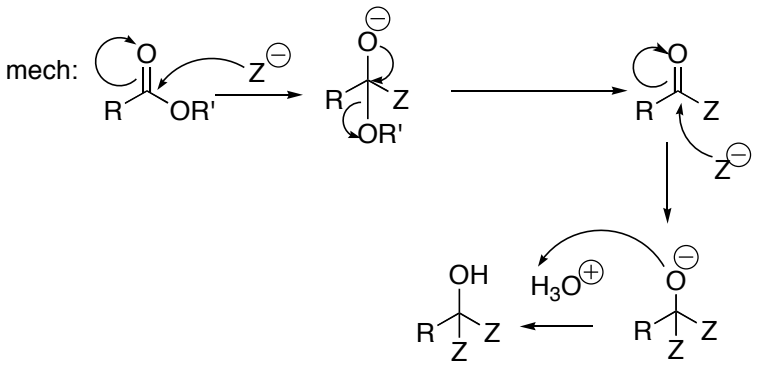
Aldehydes, Ketones, and Formaldehyde



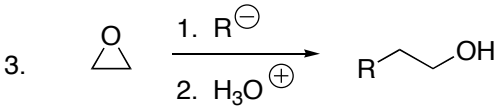


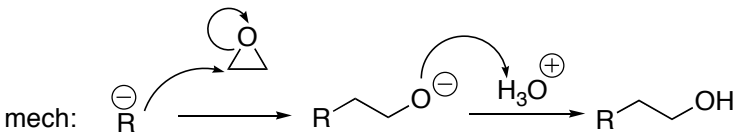
Esters





Epoxides

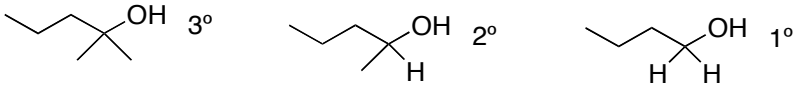




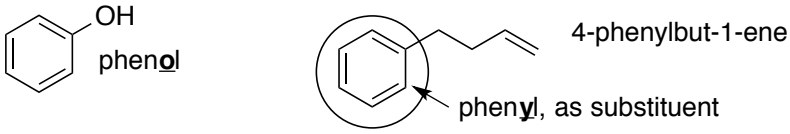
10.1,2 Intro, Classification

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

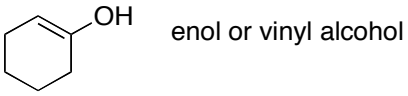
1º, 2º, 3º Alcohols: based on whether the carbon with the OH is 1º, 2º, or 3º



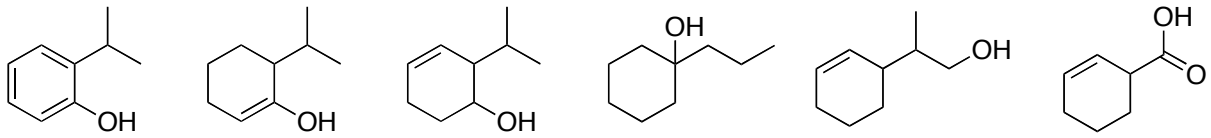
"**Phenol**": OH attached to an aromatic
-Note: phen**o**l, not phen**y**l



"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 1º, 2º, 3º, or vinyl alcohol:

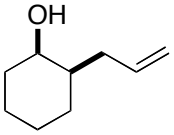


10.3 Nomenclature

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

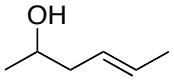
- Choose longest carbon chain **that has the OH attached**
- Remember to number! (including if it's on carbon number 1)
- The oxygen itself does not count as a number

B. Cycloalkanols: The OH-carbon is automatically Number 1. Don't need "-1-" in front of "ol".

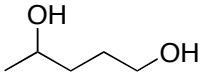


C. **Alk-**x-**en-z-ol**. When an alkene is in the main carbon chain, you need two number descriptors, one for the alkene, the second for the alcohol.

- The OH still dictates the numbering. Number from end nearest the OH.
- The OH number right before the "ol"
- The alkene number in front of the "en"



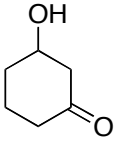
D. Diols: alkane-x,y-**diol**



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

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

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

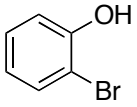


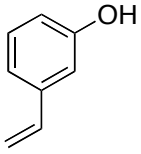
G. Common Names: Alkyl alcohol

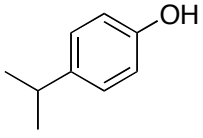
CH_3OH 

H. Substituted Phenols

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





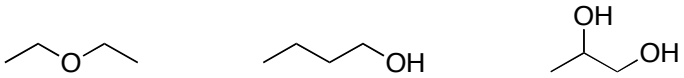


IUPAC:

Common:

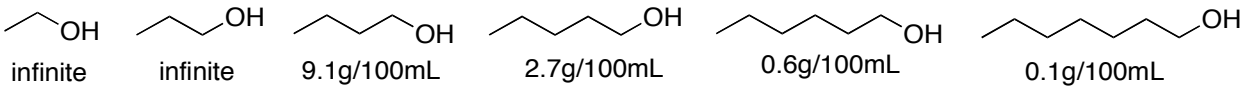
10.4 Physical Properties: Dominated by H-Bonding

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



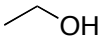
Water solubility: water solubility decreases as hydrophobic R gets longer

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



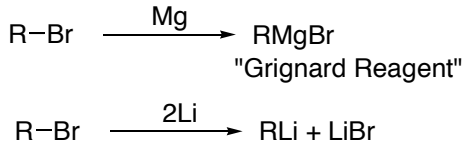
10.5 Commercially Important Alcohols

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

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

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

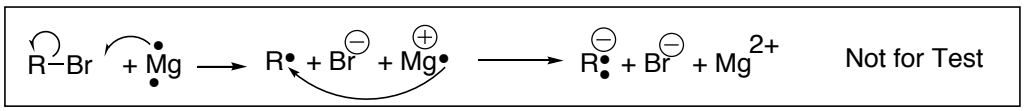
10.8 Organometallics: RM (M = Metal) = $R^{\ominus}$ $M^{\oplus}$



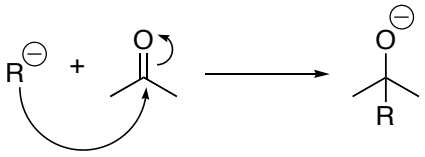
-Li is analogous for making RLi, which also act analogously.

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

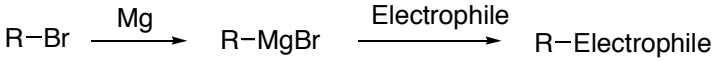
1. We will focus on the magnesium reagents RMgBr
2. RMgBr = "Grignard Reagents" (Victor Grignard)
3. Key: This is the way to make $R^{\ominus}$, strong nucleophiles/bases
4. RMgBr are formed via redox reaction.
   - Mg gives up two electrons, is oxidized
   - Bromine is reduced to bromide anion
   -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



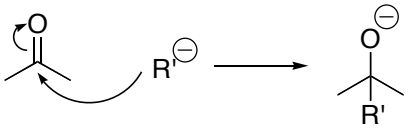
5. The formation of Grignard Reagents is completely general for all R-Halides:
   - 3º, 2º, and 1º alkyl halides all work well
   - Aryl and Vinyl halides as well as alkyl halides work well
   - RCl, RBr, and RI all work well
   - For class, we will normally use bromides, due to synthetic accessibility
6. **<u>View as carbanions: RMgBr = $R^{\ominus}$ Super Strong Bases and Nucleophiles</u>**
   - The counterion metal is a spectator
   - Stability-reactivity principle: very unstable → very reactive
   - This great reactivity is very useful (as nucleophile)
   - This great reactivity (as base) has implication for proper technical use (see following)
7. Solvent and handling: Grignard reactants RMgBr must be made, stored, and handled in special solvents under special conditions:
   - No water allowed
     - $R^{\ominus} + H_2O \rightarrow R\text{-}H + HO^{\ominus}$ 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



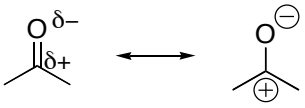
Exothermic Addition of Carbon or Hydrogen Anions:

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

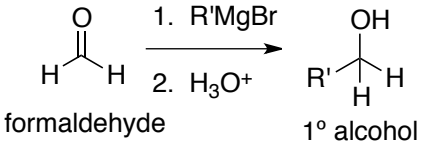
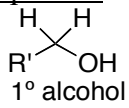
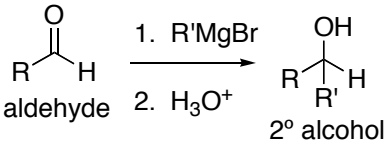
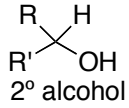
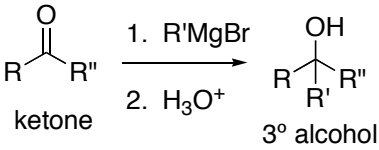
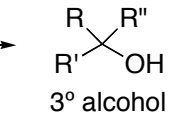
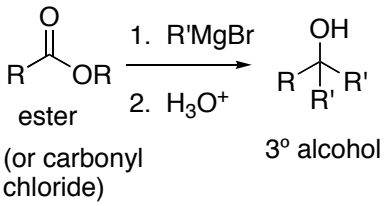
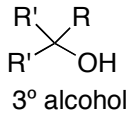
Carbonyl is strongly electrophile

-much stronger even than a 1º alkyl iodide!

1. Breakable π bond
2. Carbonyl polarity



Additions of Grignard Reagents to Carbonyl Compounds

	From Carbonyl's Perspective		From Grignard's Perspective			
4	 formaldehyde → 1º alcohol		R'MgBr	 1º alcohol	1 carbon chain extension	Mech
5	 aldehyde → 2º alcohol		R'MgBr	 2º alcohol		Mech
6	 ketone → 3º alcohol		R'MgBr	 3º alcohol	All three R groups can be different.	Mech
7	 ester (or carbonyl chloride) → 3º alcohol		R'MgBr	 3º alcohol	At least 2 R groups must be the same	Mech

Pattern:

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

Predicting Grignard Reaction Products

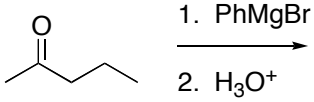
1. From carbonyl perspective:
   - The carbanion R' adds to the carbonyl carbon
   - The carbonyl =O gets replaced by –OH
   - For formaldehyde, aldehydes, and ketones: the two attachments on the original carbonyl carbon remain attached as spectators
   - For esters or acid chlorides: the one non-heteroatom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

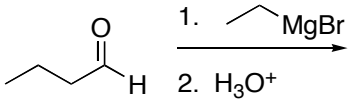
2. From Grignard perspective:
   - Where R-MgBr begins, R-C-OH ends.
     - In other words, the MgBr gets replaced by the carbonyl carbon

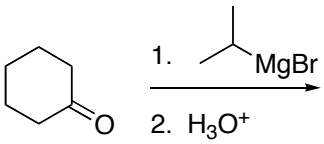
Note: Be sure that in the product, no carbon has more than one C-O bond

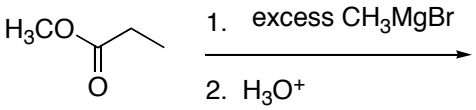
Draw products from the following reactions.

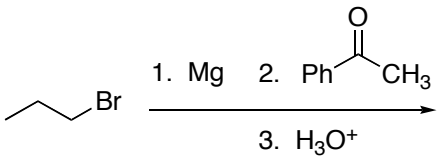
1º, 2º or 3º?

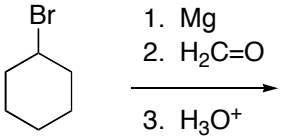
1 

2 

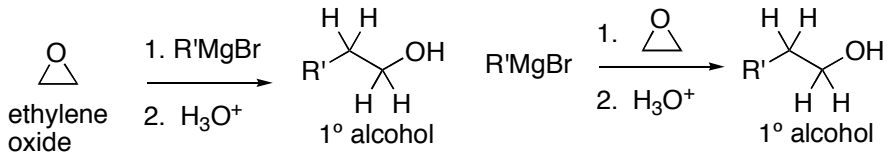
3 

4 

5 

6 

10.9E Grignard Reaction with Ethylene Oxide (Simplest Epoxide)

8 

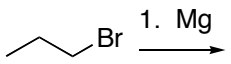
2-Carbon chain extension Mech

Notes

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

Draw products from the following reactions.

1

2 

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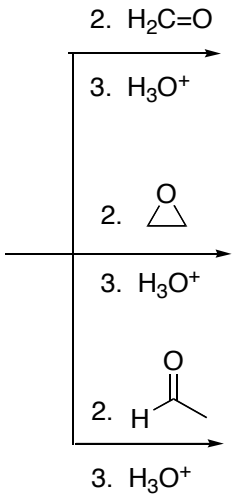
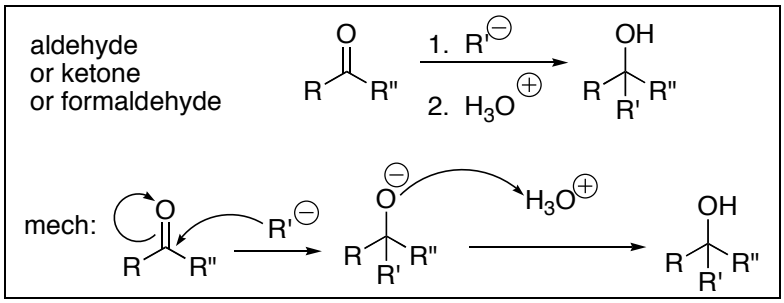


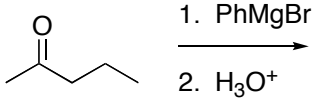
Reaction Mechanisms for Grignard Reactions

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



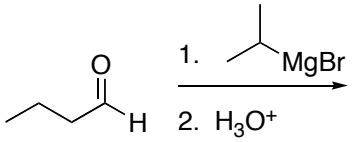
1. Two simple steps:
   - **a. Addition**
   - **b. Protonation**
2. Timing:
   - a. The carbanion is added first, at one step in time, under strongly anionic conditions
   - b. Later acid is added, in a second laboratory step. This provides a cationic environment
3. RMgBr = R-MgBr = R$^{\ominus}$ carbanion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

Draw mechanisms for the following reactions:

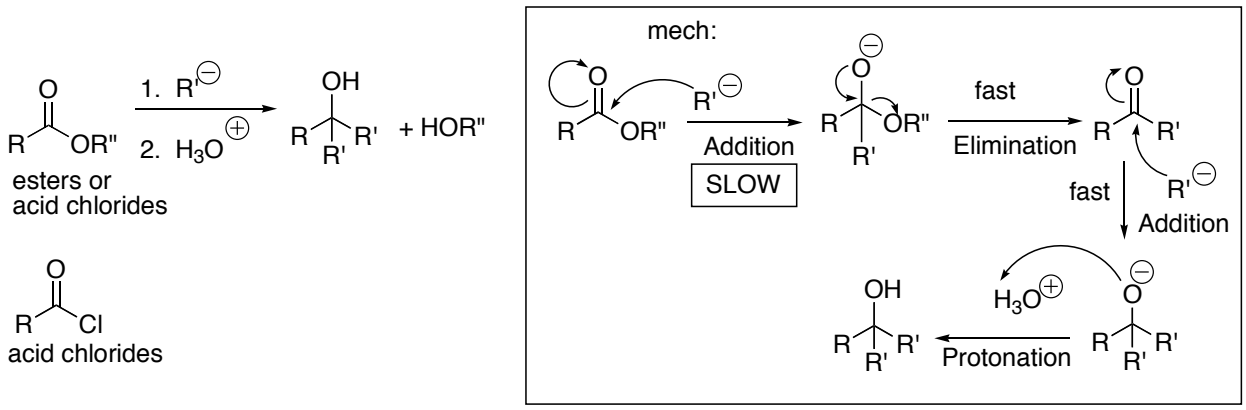
1 

Standard Simple Grignard Mechanism:
1. Add Anionic Nucleophile, to produce an oxyanion
2. Protonate

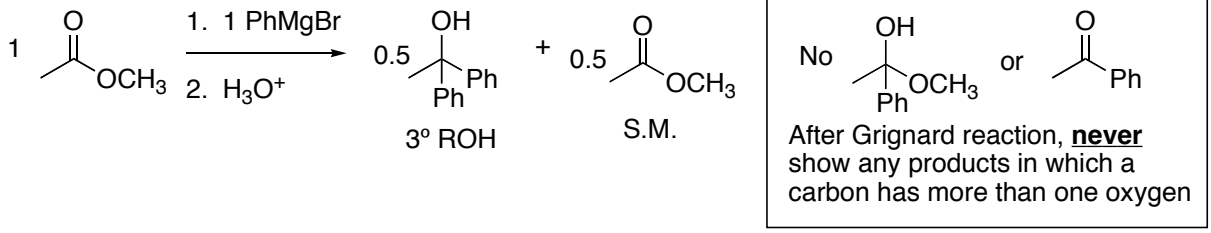
Mechanism requirement notes. Must:
1. draw intermediate(s)
2. show correct electron/arrow flow
3. Specific arrow source and target
4. MgBr can be left out (convenience)
5. Anion produces anion
6. H+ changes anion/cation conditions

2 

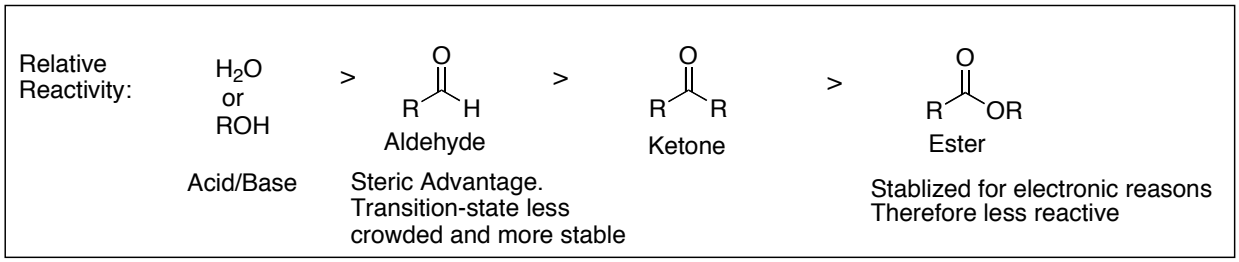
Esters or Acid Chlorides: More Complex, Needs to Explain Two Additions and More Bond Breakings



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

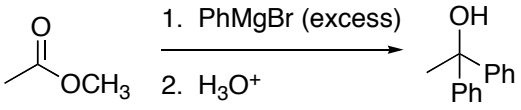


Why? Kinetics and Reactivity. **MEMORIZE**.



- 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:

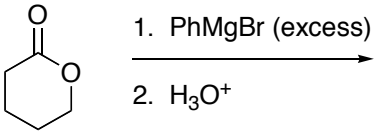


Ester Mechanism:

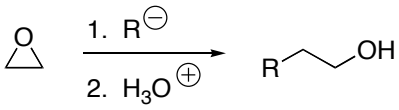
1. Add
2. Eliminate
3. Add Again
4. Protonate

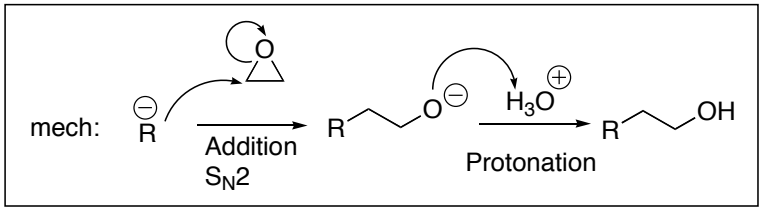
Cyclic Ester: The O-Carbonyl single bond breaks, but the other C-O single bond does **not** break -the result is formation of a dialcohol

Draw product and mechanism for the following:

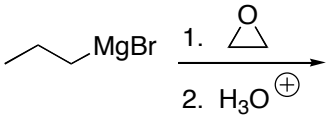


Ethylene Oxide Mechanism





Draw product and mechanism for the following:

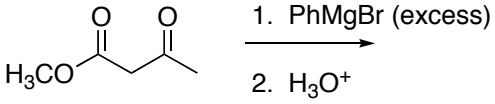


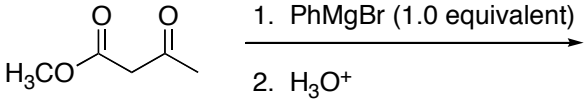
Mechanism:

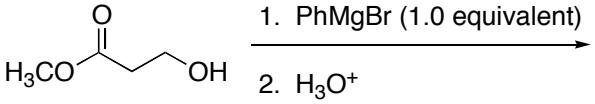
1. Add
2. Protonate

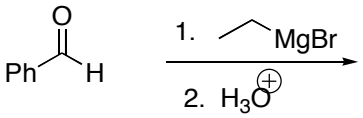
- Very Similar to the ketone/aldehyde mechanism, except you break a sigma rather than a pi bond.

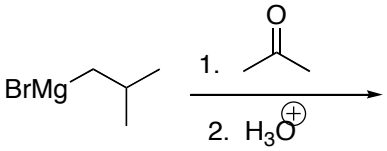
More Grignard Practice. Including polyfunctional Molecules: (Know relative reactivity)

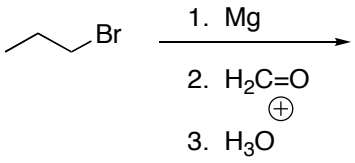
1 

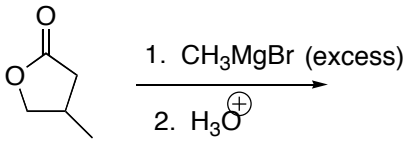
2 

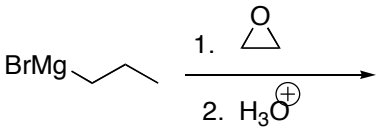
3 

4 

5 

6 

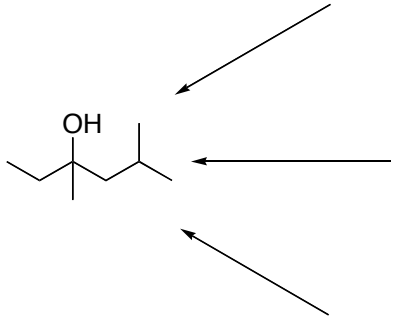
7 

8 

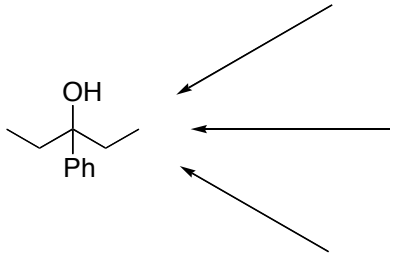
Grignards in Synthesis: Provide Precursors.

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

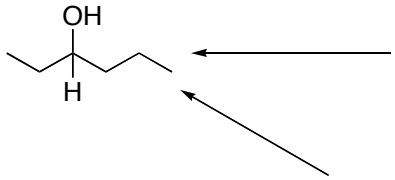
a.



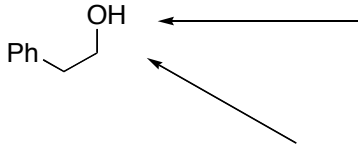
b.



c.

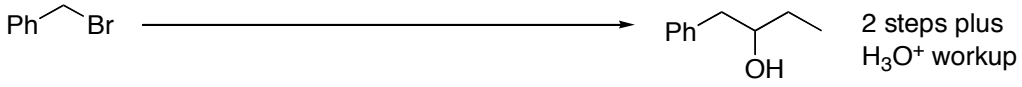


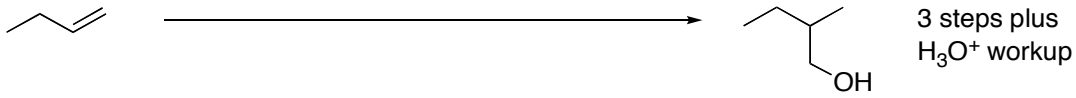
d.

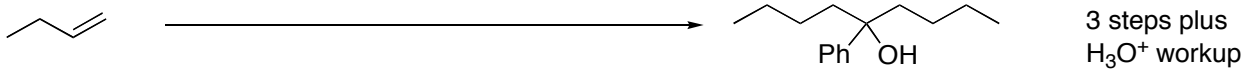


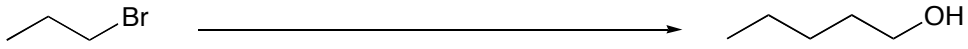
Provide Reagents for the Following Transformations. You may use whatever reagents, including ketones or aldehydes or Grignards or esters, that you need.

- 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

a. 

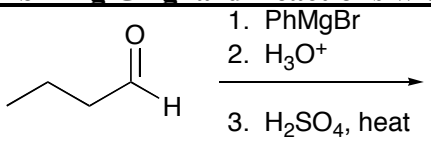
b. 

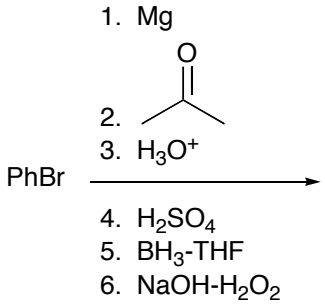
c. 

d. 

e. 

Combining Grignard Reactions with Other Reactions

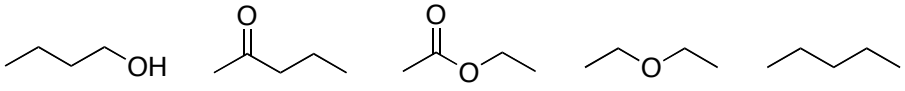
a. 

b. 

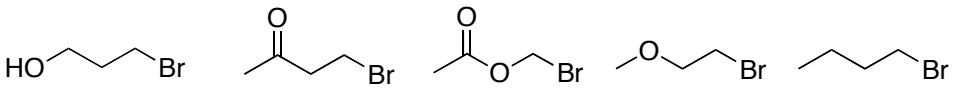
10.10 Restrictions on Grignard Reactions

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

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

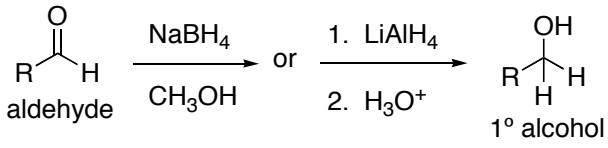
Which Solvents (if any) Would be OK for Handling RMgBr?, 

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

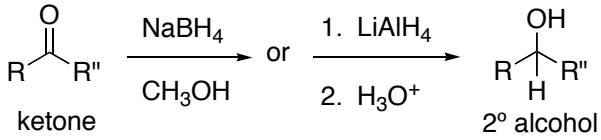
Which substrates could be converted into RMgBr, and subsequently reacted with CH_3CHO? 

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

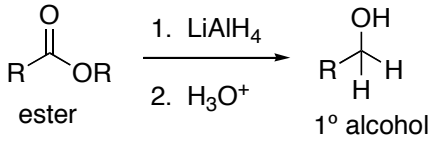
10.11 Alcohols by Reduction of Carbonyls: H $^{\ominus}$ Addition

9 

Mech

10 

Mech

11 

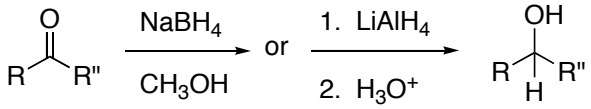
$NaBH_4$ will not react with esters

Mech

Mechanism

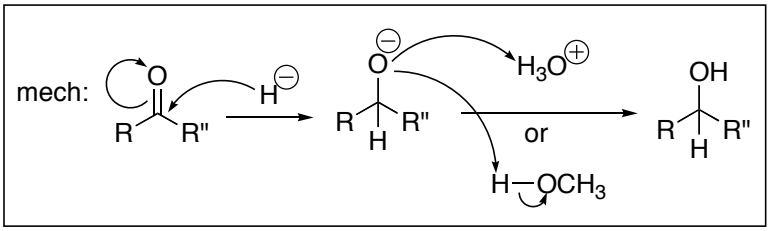
Aldehydes and Ketones

aldehyde
or ketone
or formaldehyde

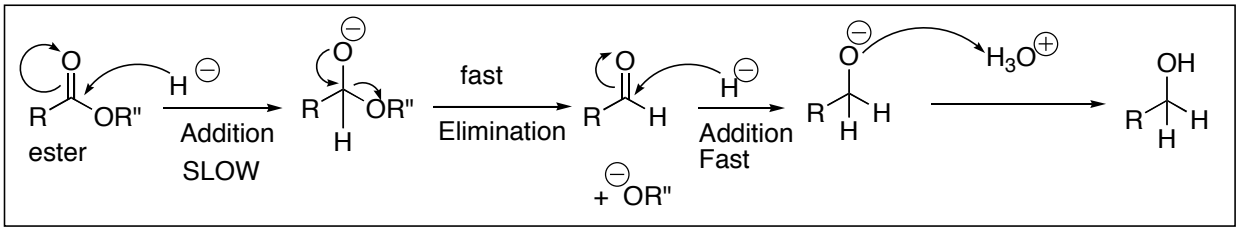


$NaBH_4 = H^{\ominus}$

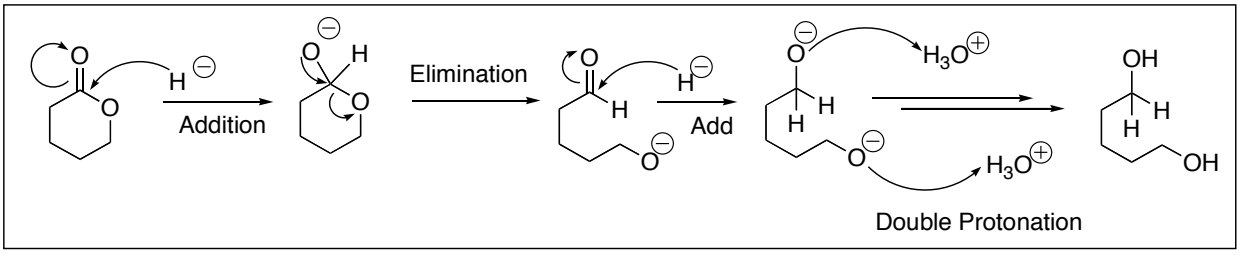
$LiAlH_4 = H^{\ominus}$



Esters

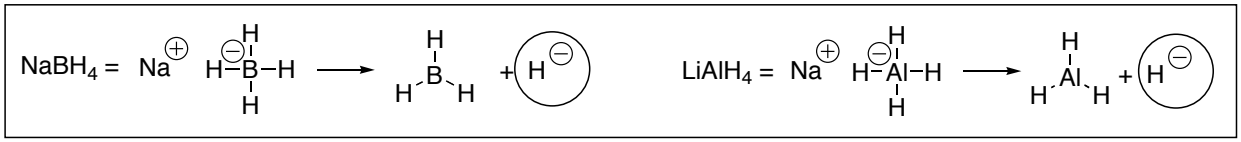


Cyclic Esters



Notes:

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



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

Reactivity

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

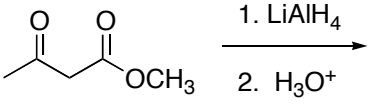
$LiAlH_4$ is much stronger, $NaBH_4$ much weaker

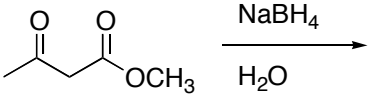
1. $LiAlH_4$ is strong enough to react with esters, $NaBH_4$ isn't
2. **Selective reduction**: if both an ester and an aldehyde/ketone are present:
   - $LiAlH_4$ reduces both
   - $NaBH_4$ selectively reduces the aldehyde/ketone but leaves the ester untouched
3. **$LiAlH_4$ is strong enough to react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

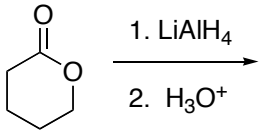
$$LiAlH_4 + H_2O \rightarrow H_2(gas) + LiOH + AlH_3 + heat$$

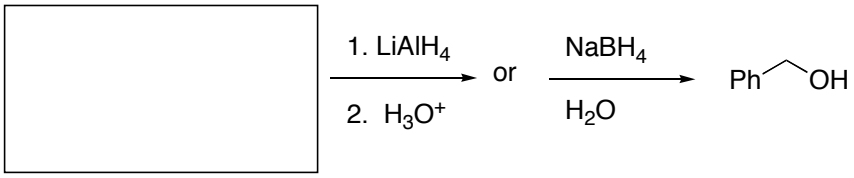
   a. As a result, $LiAlH_4$ is harder to use and store
   b. Acid has to be added in a subsequent step with the $LiAlH_4$; (thus, 2-step recipe)
   c. $NaBH_4$ can be run in alcohol solvent which serves as a proton source for protonating alkoxide
   d. Solvent restrictions, glassware must be dry, wet air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

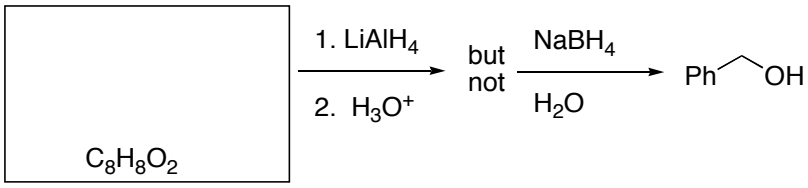
Draw the products for the following reactions.

1. 

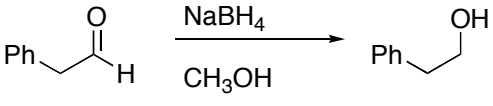
2. 

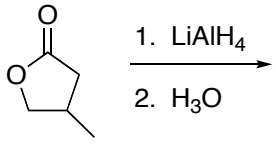
3. 

4. 

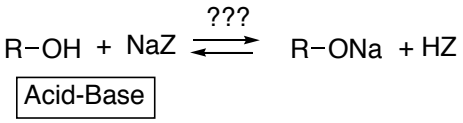
5. 

Draw the mechanism for the following reaction.

6. 

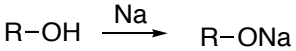
7. 

Summary of Alcohol Reactions, Ch. 11.

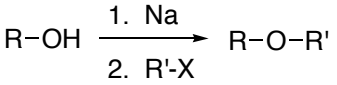
1 

Acid-Base

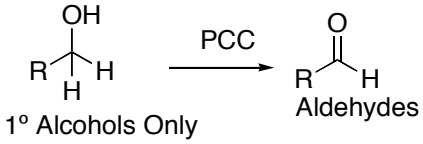
- Deprotonation by a base.
- Controlled by relative stability of RO $^{\ominus}$ versus Z $^{\ominus}$.
- Consider relative electronegativity and whether either anion is resonance stabilized.

2 

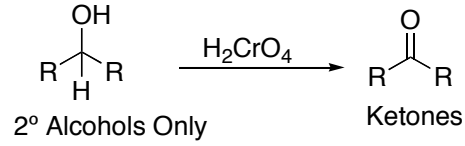
- Potassium (K) analogous.
- Key way to convert alcohol to alkoxide, reactive as S_N2 nucleophile and E2 base.

3 

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

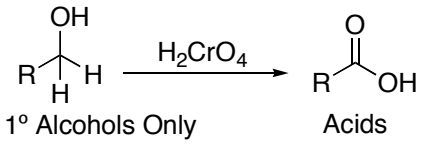
4 

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

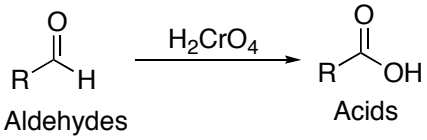
5 

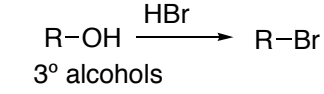
H_2CrO_4 = $Na_2Cr_2O_7$, H_2SO_4 or CrO_3/H_2O

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

6 

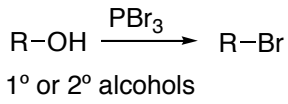
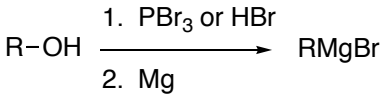
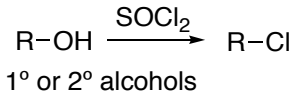
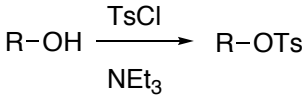
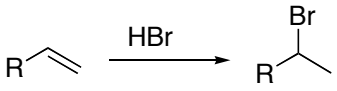
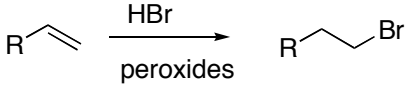
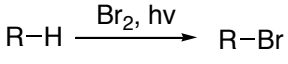
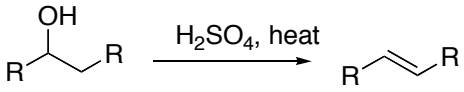
- Note difference between
- PCC and H_2CrO_4 when reacting with 1º alcohols.

7 

8 

Mech: Be able to draw!

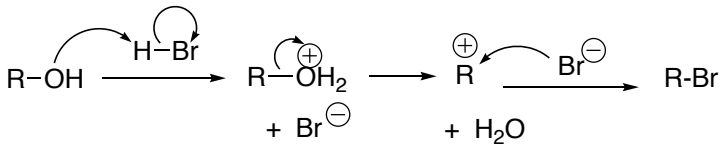
- HI, HCl analogous
- Converts alcohol into a bromide that can be used in Grignards, E2 reactions
- Cation mechanism
- Usually not method of choice for 1º, 2º alcohols

9		• Converts alcohol into a bromide that can be used in Grignards, E2, S_N2 reactions • Inversion of stereochem • Not good for 3º alcohols
10		• Quick 2-step conversion of alcohol into a nucleophilic Grignard
11		• Retention of stereo!
12		• Tosylates are super leaving groups, better even than iodides. • Tosylates are well suited to S_N2 and E2 reactions.
	Review Reactions	•
13		• Markovnikov addition
14		• anti-Markovnikov addition
15		• Radical mechanism, 3º > 2º > 1º
16		• Zaytsev elimination

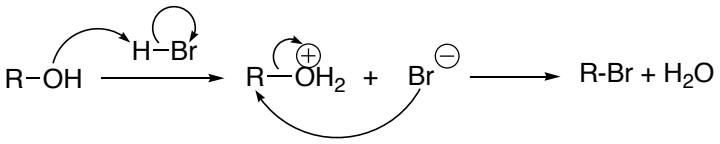
Mechanisms for ROH →RBr Reactions

R-OH (3°) $\xrightarrow{HBr}$ R-Br 3° mostly, sometimes 1°

HBr Mech for 3° ROH:

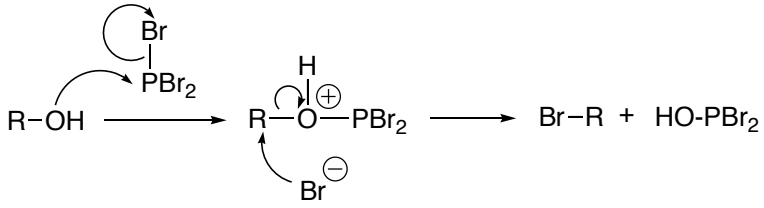


HBr Mech for 1° ROH:



R-OH (1°, 2°) $\xrightarrow{PBr_3}$ R-Br 1°, 2°

Mech:



Ch. 11 Reactions of Alcohols

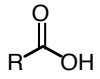
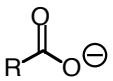
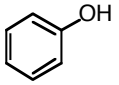
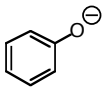
A. Conversion to Alkoxides. Acidity of Alcohols and Phenols (10.6)

"alkoxide" = $RO^{\ominus}$ anion

1	$R{-}OH + NaZ \underset{}{\overset{???}{\rightleftharpoons}} R{-}ONa + HZ$ Acid-Base	1. Deprotonation by a base. 2. Controlled by relative stability of $RO^{\ominus}$ versus $Z^{\ominus}$. 3. Consider relative electronegativity and whether either anion is resonance stabilized.

- Alcohols are weak acids → can be ionized by stronger bases
- goes to the right (alkoxide) only if resulting $RO^{\ominus}$ is more stable than $B^{\ominus}$
- ex. $^{\ominus}NH_2$, $^{\ominus}CH_3$ (nitrogen or carbon anions)
- ex. If a <u>less</u> stable oxygen anion can produce a <u>more</u> stable oxygen anion

Acidity Table

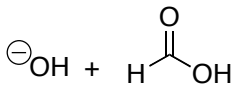
Class	Structure	Ka	Acid Strength	Anion	Base Strength	Base Stability
Strong Acids	H-Cl	10^{2}		$Cl^{\ominus}$		
Carboxylic Acid		10^{-5}				
Phenol		10^{-10}				
Water	H_2O	10^{-16}		$HO^{\ominus}$		
Alcohol	ROH	10^{-18}		$RO^{\ominus}$		
Amine (N-H)	RNH_2	10^{-33}		$RNH^{\ominus}$		
Alkane (C-H)	RCH_3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

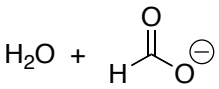
<u>Notes/skills:</u>

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

Problems

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





Key: a proton transfer will happen only if it results in a more stabilized anion

Key anion stability factors:

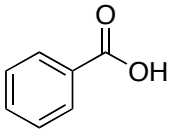
- Electronegativity (oxygen > nitrogen > carbon)
- Resonance. Carboxylate, phenoxide yes > hydroxide, alkoxide no
- Donor/withdrawer factor: hydroxide > alkoxide (electron donor destabilizes anion)

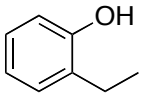
2. Which of the following will deprotonate methanol?

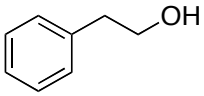
H_2O CH_3CO_2Na PhONa NaOH $NaNH_2$ CH_3MgBr

- Using the chart, an acid (left side) will only be deprotonated by an anion/base that is **lower** on the right side, because that will result in a more stable anion.
- Charge: neutral species aren't as basic as anionic analogs (H_2O versus NaOH)

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?







- Neutral species will stay in organic solvent (ether); only ionized species will extract into the water
- Thus the question of whether something will extract into the aqueous phase is really a question of whether there is something present that will cause an acid-base reaction
- NaOH is strong enough to ionize carboxylic acids and phenols, but not alcohols.

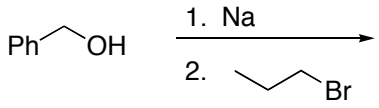
A2. Alkoxide formation by redox reaction with sodium or potassium (or other metals) (10.6B)

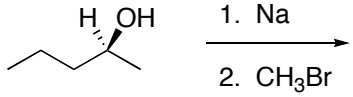
2	R–OH $\xrightarrow{Na}$ R–ONa R–OH $\xrightarrow{K}$ R–OK } R–O$^{\ominus}$	• Potassium (K) analogous. • Key way to convert alcohol to alkoxide, reactive as S_N2 nucleophile and E2 base.

- Key source of nucleophilic/basic alkoxides
- Alkoxides are used all the time as S_N2 nucleophilies and E2 bases

B. **<u>2-Step Conversion of Alcohols into Ethers via the Alkoxides (10.6B)</u>**

3	R–OH $\xrightarrow[2.\ R'\text{-}X]{1.\ Na}$ R–O–R'	• Alkoxide formation-S_N2 route to ether • The electrophile R'-X must be S_N2 reactive, preferably 1° with a good leaving group

1. 

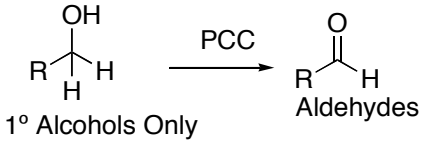
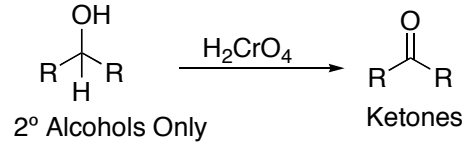
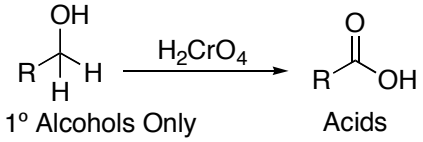
2. 

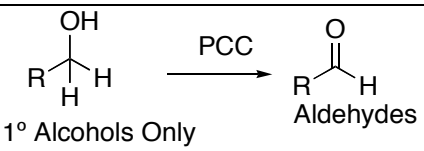
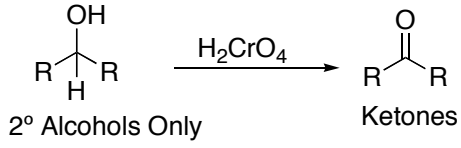
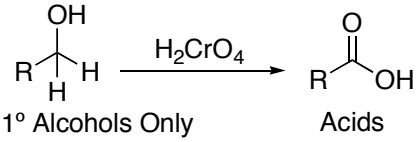
3. 

C. Oxidation of Alcohols to Carbonyl Compounds (11.1-4)
Summary: 2 Oxidants

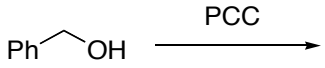
1. **PCC = mild 1º alcohols → aldehydes**
   - "**P**yridinium **c**hloro**c**hromate": soluble in water-free dichloromethane
   - Mild, selective for 1º over 2º alcohols, and when 1º alcohols are used stops at aldehyde

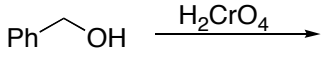
2. **H_2CrO_4 = strong**
   a. **2º alcohols → ketones**
   b. 1º alcohols → carboxylic acids
   c. 3º alcohols → no reaction
   d. aldehydes → carboxylic acids
   - $H_2CrO_4 = CrO_3 + H_2O$ or $Na_2Cr_2O7 + H_2SO_4$ (make in the reaction flask)
   - Always made and used in the presence of some water
   - Very strong, when 1º alcohols are used goes 1º RCH_2OH → RCHO → RCO_2H without stopping at aldehyde

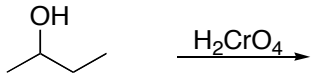
4		• Key access to aldehydes, which are useful for more Grignard chemistry. • Note difference between PCC and H_2CrO_4 • PCC does not react with 2º alcohols very rapidly
5	 $H_2CrO_4 = Na_2Cr_2O_7, H_2SO_4$ or CrO_3/H_2O	• Key access to ketones. • PCC does not react very fast with 2º alcohols
6		• Note difference between • PCC and H_2CrO_4 when reacting with 1º alcohols.

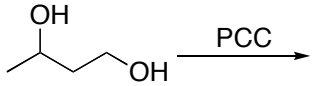
4		• Key access to aldehydes, which are useful for more Grignard chemistry. • Note difference between PCC and H_2CrO_4 • PCC does not react with 2º alcohols very rapidly
5	 H_2CrO_4 = $Na_2Cr_2O_7$, H_2SO_4 or CrO_3/H_2O	• Key access to ketones. • PCC does not react very fast with 2º alcohols
6		• Note difference between • PCC and H_2CrO_4 when reacting with 1º alcohols.

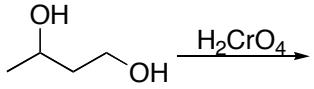
<u>Draw the products for the following oxidation reactions.</u>

1 

2 

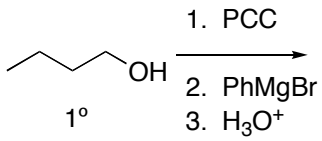
3 

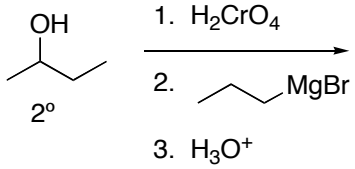
4 

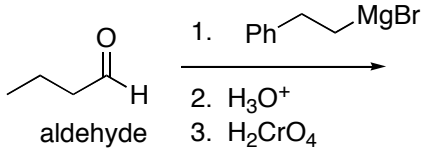
5 

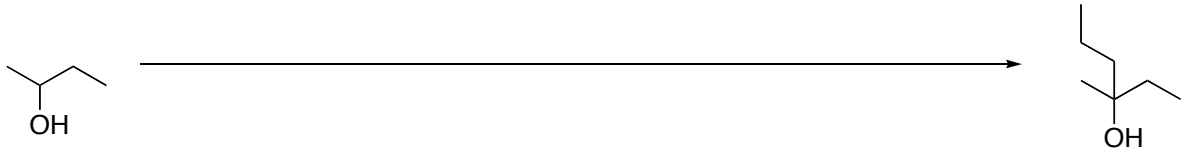
Oxidation Combined with Grignard Reactions (in either order): Indirectly Enables Substitution of Carbon for Hydrogen

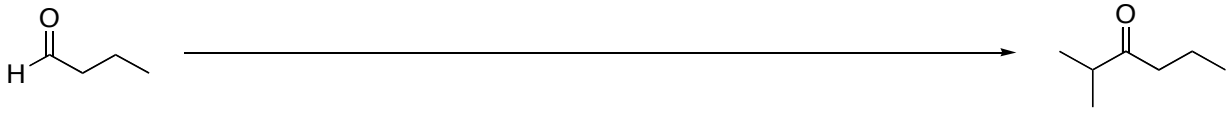
1. **1º alcohol** + PCC → aldehyde + RMgBr → **2º alcohol**
2. **2º alcohol** + H_2CrO_4 → ketone + RMgBr → **3º alcohol**
   - Oxidation followed by Grignard reaction essentially substitutes a carbon group for a hydrogen
3. **Aldehyde** + RMgBr → 2º alcohol + H_2CrO_4 → **ketone**
   - Grignard reaction followed by oxidation essentially substitutes a carbon group for a hydrogen

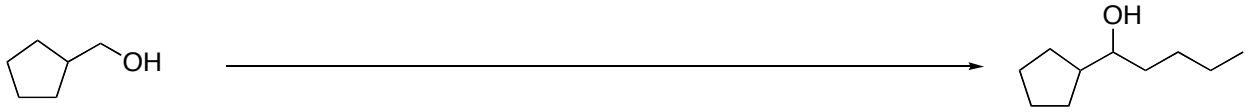
1 

2 

3 

4 

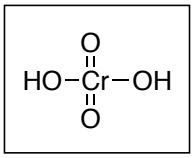
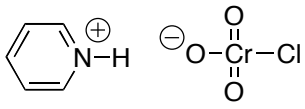
5 

6 

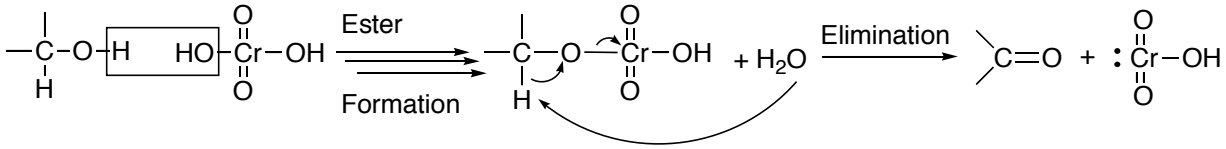
Jones Test H_2CrO_4 for Alcohols (11-2C) (test responsible)

- H_2CrO_4 (Jones Reagent) is clear orange
- Treatment of an unknown with Jones reagent:
  - Solution stays clear orange → no 1º or 2º alcohol present (negative reaction)
  - Solution gives a green/brown precipitate → 1º or 2º alcohol present (positive reaction)
  - 3º, vinyl, and aryl alcohols do not react. Nor do ketones, ethers, or esters.

Structure and Mechanism (not test responsible)

H_2CrO_4 = chromic acid = $Na_2Cr_2O_7$ = CrO_3/H_2O = Cr^{+6} oxidation state • Water soluble	
Pyridinium carbons renders PCC soluble in organic solvents, thus it is functional in organic solvent and in the absence of water	 PCC = Pyridinium Chloro**C**hromate

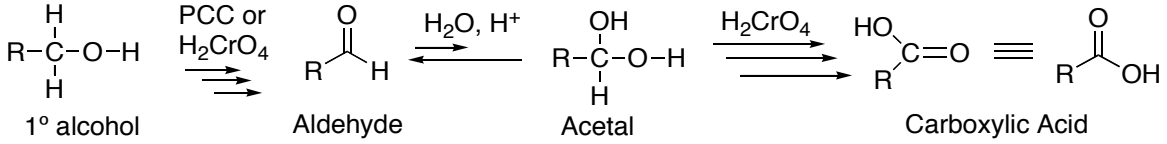
General Mechanism (not test responsible)



- PCC operates analogously

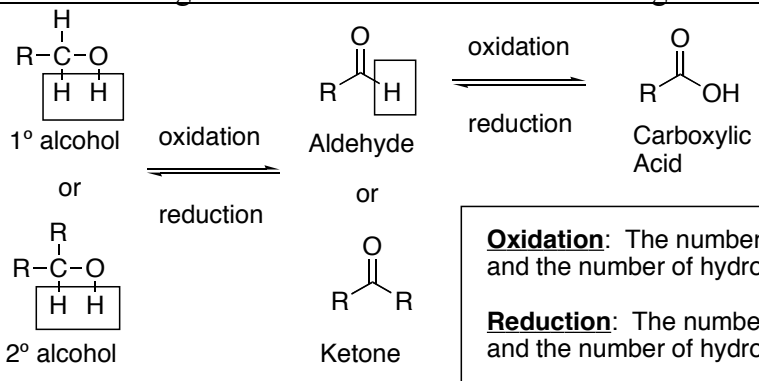
1º Alcohols, Aldehydes, and the Presence or Absence of Water: PCC vs H_2CrO_4

Q: Why does Anhydrous PCC stop at Aldehyde but Aqueous H_2CrO_4 Continues to Carboxylic Acid?



1. Both PCC and H_2CrO_4 convert 1º 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 <u>not able</u> 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 <u>is able</u> 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

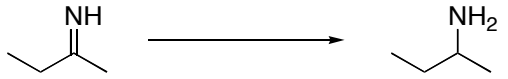


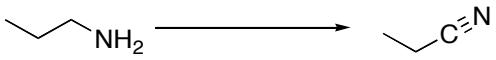
Oxidation: The number of oxygen bonds to a carbon increases, and the number of hydrogens bonded to a carbon decreases

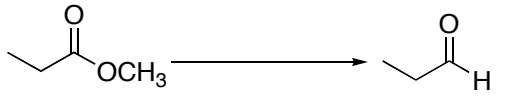
Reduction: The number of oxygen bonds to a carbon is reduced, and the number of hydrogens bonded to a carbon increases.

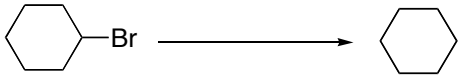
More General: # of bonds to heteroatoms versus to hydrogens

Classify the following transformations as "oxidations" or "reductions"

1. 

2. 

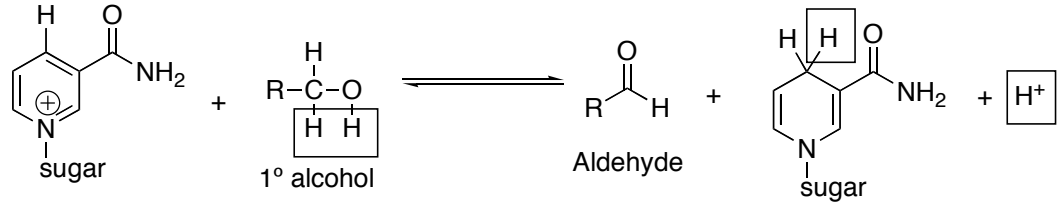
3. 

4. 

11.3, 11.4 Other methods for Oxidizing Alcohols. (No test)

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

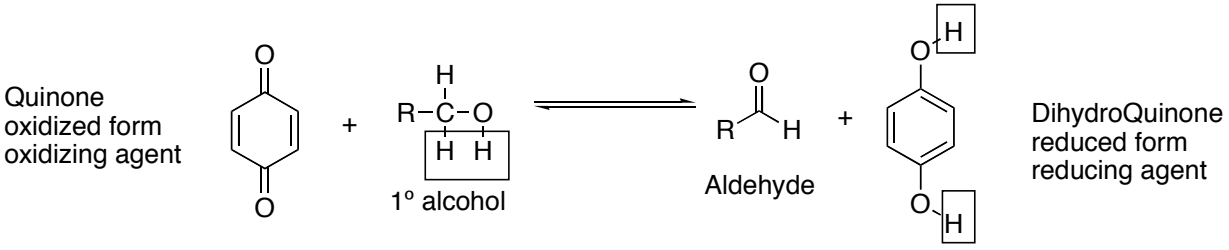
1. $KMnO_4$
2. CuO
3. "Jones": H_2CrO_4 with acetone added to temper reactivity
4. Collins: H_2CrO_4 with pyridine added to temper reactivity
5. "Swern": $(COCl)_2$ and $(CH_3)_2S{=}O$ then NEt_3
6. HNO_3
7. Biological Oxidant 1: "NAD^+" "nictonamide adenine dinucleotide"



NAD^+
oxidized form
oxidizing agent

NAD
reduced form
reducing agent

8. Biological Oxidant 2: "Quinones and hydroquinones" (Ch. 17-15)



In General: Recognizing Oxidizing versus Reducing Agents

Oxidizing Agents: Often have:

- Highly Oxidized Metals or Nonmetals
- Extra Oxygen

OsO_4 (+8)
$KMnO_4$ (+7)
CrO_3 (+6)
H_2CrO_4 (+6)
HNO_3 (+5)
$H_2O_2 \rightarrow H_2O$
$RCO_3H \rightarrow RCO_2H$
$O_3 \rightarrow O_2$

Reducing Agents: Often involve:

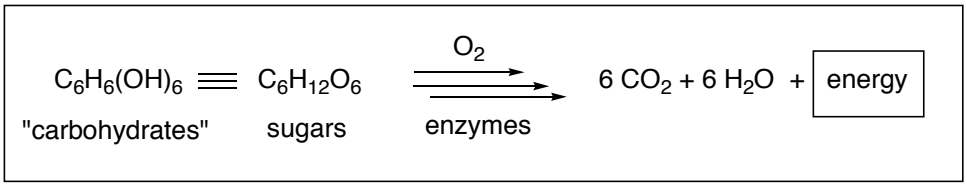
- Hydrides in Formulas
- Highly Reduced Metals
- Metals + H_2
- Metals + acid

$LiAlH_4$
$NaBH_4$
Li, Na, K, Mg, Zn, Al, etc.
Pd/H_2, Pt/H_2, Ni/H_2 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)

11.7-9 Conversion of Alcohols to Alkyl Halides

8 $R-OH \xrightarrow{HBr} R-Br$ (3º alcohols)

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 1º, 2º alcohols

9 $R-OH \xrightarrow{PBr_3} R-Br$ (1º or 2º alcohols)

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

10 $R-OH \xrightarrow[2.\ Mg]{1.\ PBr_3 \text{ or } HBr} RMgBr$

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

11 $R-OH \xrightarrow{SOCl_2} R-Cl$ (1º or 2º alcohols)

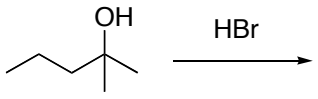
- Retention of stereo!
- Section 11-9

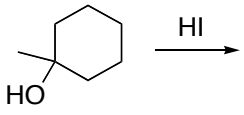
Summary:

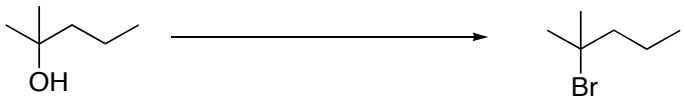
Class	**R-Br**	R-Cl
1º ROH	**PBr_3**	$SOCl_2$
2º ROH	**PBr_3**	$SOCl_2$
3º ROH	**HBr**	**HCl**
Vinyl or Aryl	Nothing works	Nothing works

Straight Reaction with H-X (Section 11.7)

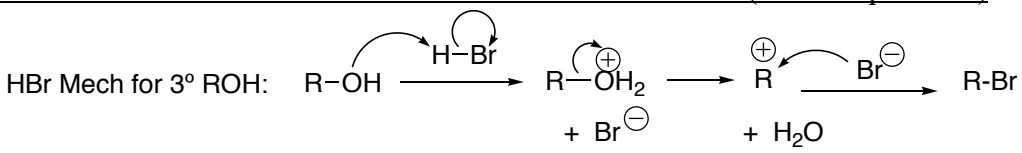
- Ideal only for 3º ROH,
- sometimes works with 1º alcohols, with a complex mechanism
- Only occasionally for 2º alcohols
- **Method of choice for 3º, but not for 1º or 2º**

1 

2 

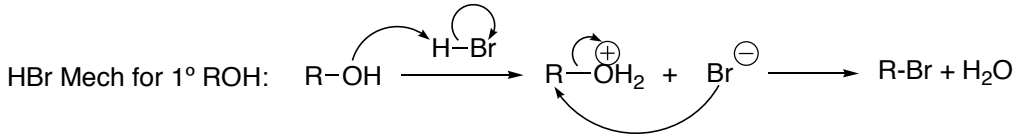
3 

Mechanism for H-X reactions with 3º Alcohols: Cationic (Test Responsible)



Notes:

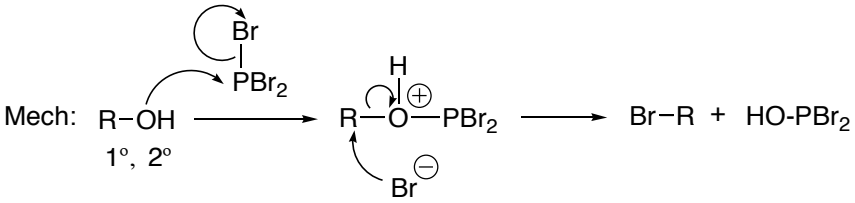
1. Memorize the 3º alcohol mechanism (test responsible)
   a. Protonate
   b. Leave to give Cation. This is the slow step for 3º alcohols
   c. Capture
2. Analogous with HI or HCl
   - HCl slower, normally enhanced with $ZnCl_2$, which enhances rate of cation formation (Lucas test, see later)
   - Outside of 3º systems, side reactions are common and yields aren't often very good
3. Outside of 3º alcohols, side reactions are common and yields aren't often very good
   - Elimination reactions and cation rearrangements…
4. S_N1 type: carbocation-forming step is the rate-determining step, so R+ stability key
   - 3º alcohols fastest
   - 2º alcohols are way slower
   - 1º alcohols can't react at all via this mechanism, because 1º R+ are too unstable.
   - Ditto for vinyl or aryl alcohols
5. HBr can also react with 1º ROH to give 1º RBr, although it is not often the method of choice
   - The mechanism is different, but rather interesting (not test responsible)



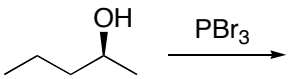
   - carbocation formation never occurs
   - bromide ion simply does S_N2 on the protonated alcohol, with water as an excellent leaving group
   - yields tend to be pretty inconsistent

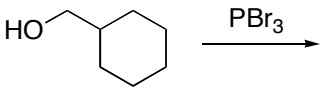
Reaction of 1º and 2º Alcohols with PBr_3 (Section 11-8)

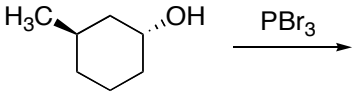
- Default recipe for 1º and 2º alcohols



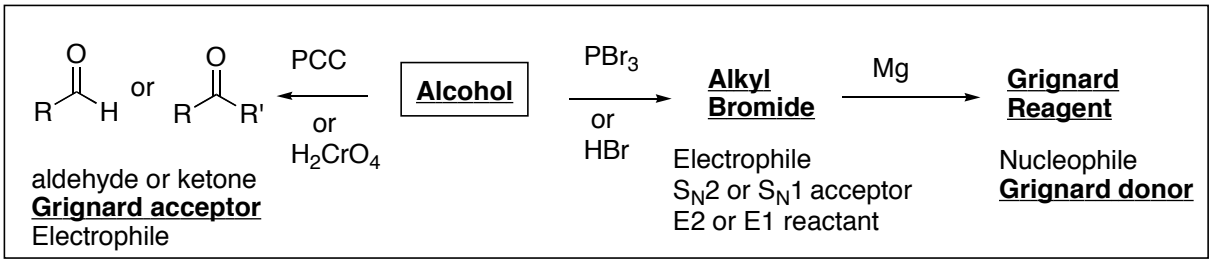
   - PBr_3 is an exceptional electrophile, and reacts even with neutral alcohols
   - The first step activates the oxygen as a leaving group.
   - The second step involves an S_N2 substitution
     - **stereochemical inversion occurs if chirality is present (common for 2º alcohols)**
   - Because the second step is an S_N2 substitution, the reaction fails for 3º ROH
   - PCl_3 does not react as well, and is not useful for making chlorides
   - PI_3 is not stable and can't be stored in a bottle. However, the combination of 1P + 1.5 I_2 → PI_3 in the reaction container (*in situ*)
     - Thus P/I_2 essentially provides the PI_3 that does the job

1 

2 

3 

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

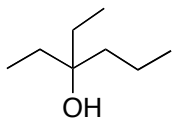


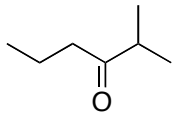
1. oxidation can convert an alcohol into a carbonyl = **Grignard acceptor (electrophile)**
2. PBr_3/Mg or HBr/Mg can convert an alcohol into RMgBr = **Grignard donor (nucleophile)**
3. PBr_3 or HBr can convert an alcohol into RBr, capable of normal substitution and elimination reactions.

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_2O)
any "inorganic" agents (things that won't contribute carbons to your skeleton)

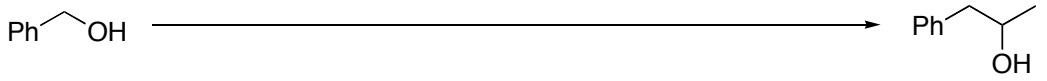
Tips:
1. Focus on the functionalized carbon(s)
2. Try to figure out which groups of the skeleton began together, and where new C-C bonds will have been formed
3. When "breaking" it up into sub-chunks, try to make the pieces as large as possible (4 carbon max, in this case, for acyclic pieces)
4. Remember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

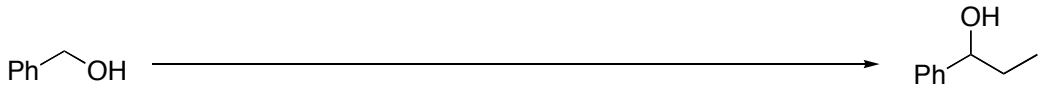
1 

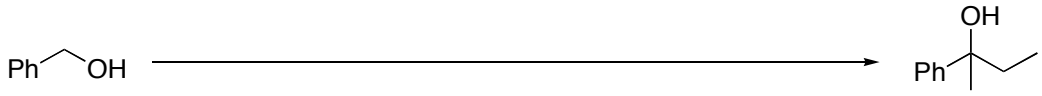
2 

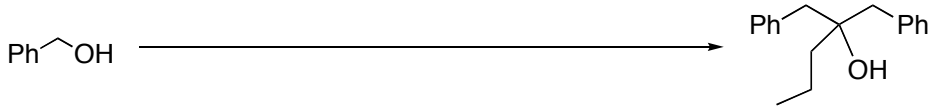
Normal Synthesis Design: In which you are given at least one of the starting Chemicals.
Provide Reagents. You may use whatever reagents, including ketones or aldehydes or Grignards or esters, that you need. **Tips**:

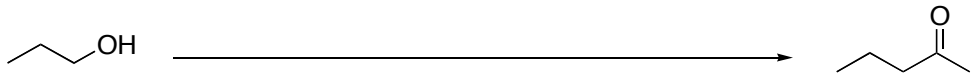
- Identify where the reactant carbons are in the product
- Is the original carbon still oxygenated? → SM should probably react via a Grignard acceptor
- Is the original carbon not still oxygenated? → SM should probably react as Grignard donor
- Working backwards helps.

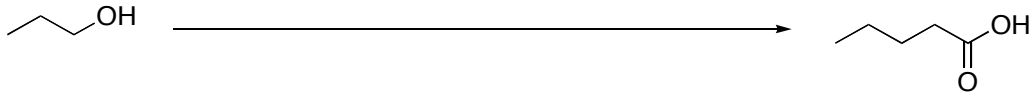
a. 

b. 

c. 

d. 

e. 

f. 

More Retrosynthesis Problems: Design syntheses for the following.

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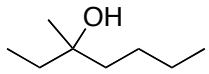
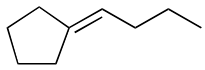
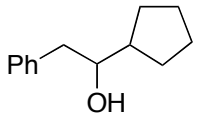
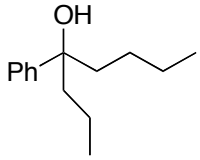
Bromobenzene cyclopentanol any acyclic alcohol or alkene with ≤4 carbons
any esters ethylene oxide formaldehyde (CH_2O)
any "inorganic" agents (things that won't contribute carbons to your skeleton)

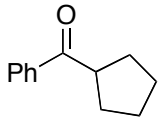
Tips:
1. Focus on the functionalized carbon(s)
2. Try to figure out which groups of the skeleton began together, and where new C-C bonds will have been formed
3. When "breaking" it up into sub-chunks, try to make the pieces as large as possible (4 carbon max, in this case, for acyclic pieces)
4. Remember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

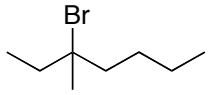
1 

2 

3 

4 

7 

5 

Unknowns and Chemical Tests (Sections 11-2C, 11-7)

1. H_2/Pt test for alkenes
2. Br_2 test for alkenes
3. **Jones reagent (H_2CrO_4) Test for 1º or 2º alcohols**
   - 3º alcohols do not react
   - 2º alcohols keep the same number of oxygens but lose two hydrogens in the formula
   - 1º alcohols lose two H's but also add one oxygen
4. **Lucas Test: HCl/$ZnCl_2$ for 3º or 2º alcohols**

R-OH $\xrightarrow{HCl/ZnCl_2 \text{ in water}}$ R-Cl via $R^{\oplus}$ 3º > 2º >>>> 1º

3º >	2º >>>	1º
<1 min	1-5 min	never

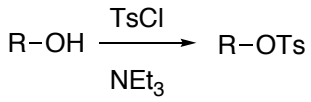
Why? $R^{\oplus}$ stability: 3º $R^{\oplus}$ > 2º $R^{\oplus}$ >>> 1º $R^{\oplus}$

- 3º alcohols are fastest
- 1º alcohols don't react at all
- $R^{\oplus}$ stability is the key

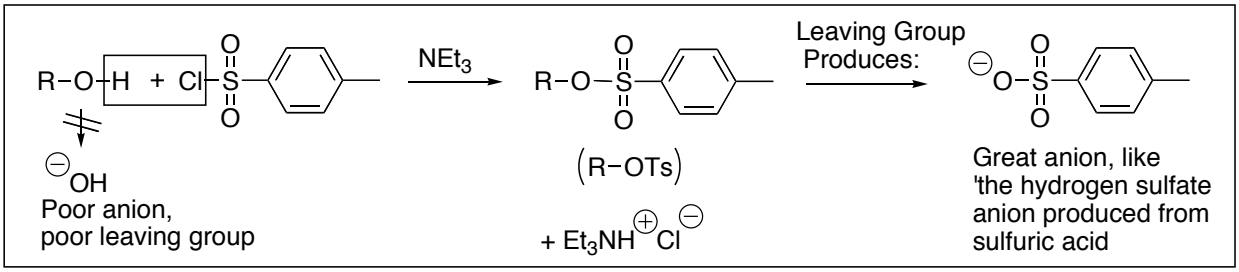
- Test is based on **solubility**: The R-Cl product is nonpolar and water insoluble, so it separates out from water. Alcohols are quite soluble especially in highly acidic water.
- Test fails is useless for alcohols with so many carbons that it doesn't even dissolve in the original HCl/$ZnCl_2$/water solution

		Jones (H_2CrO_4)	Lucas (HCl/$ZnCl_2$)	H_2/Pt	Required Facts	Possible Answers
1	$C_5H_{10}O$	Yes	No	Yes		
2	$C_6H_{12}O$	Yes	Yes, 1-5 min	No		
3	$C_6H_{12}O$	No	Yes	Yes		
4	$C_7H_{12}O$	Yes	Yes	Yes, Produces $C_7H_{14}O$		
5	C_3H_6O	No	No	Yes		
6	C_3H_6O	No	No	No		
7	C_3H_6O	Yes	No	Yes		
8	C_3H_6O	Yes,	Yes	No		

Section 11-5 Conversion of Alcohols to "Tosylates", and their use as Exceptional Leaving Groups in S_N2, S_N1, E2, and E1 Reactions

12 

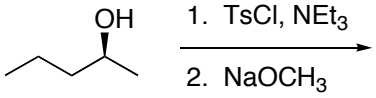
- Tosylates are super leaving groups, better even than iodides.
- Tosylates are well suited to S_N2 and E2 reactions.

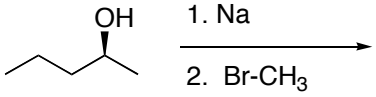


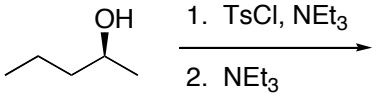
Notes:

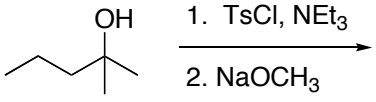
1. Tosylates are easy to form
2. "Toluene sulfonate"
3. Tosylate anion is really stable, comparable to the anion from sulfuric acid
   - Thanks to electronegative sulfur and the resonance/charge sharing with the other oxygens
4. Whereas a normal OH has a poor leaving group (hydroxide anion), conversion to the tosylate provides a super good leaving group.
5. Leaving Group Reactivity: Better than the best of the halides
   - OTs >> 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

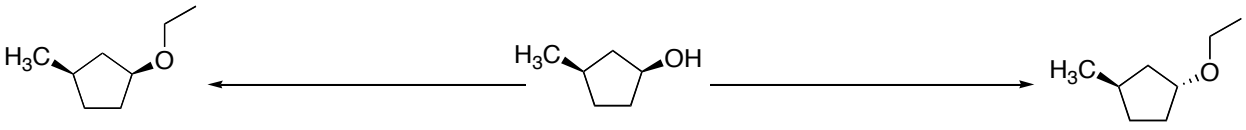
Draw Products

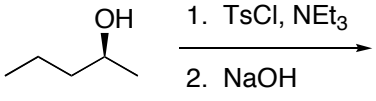
1 

2 

3 

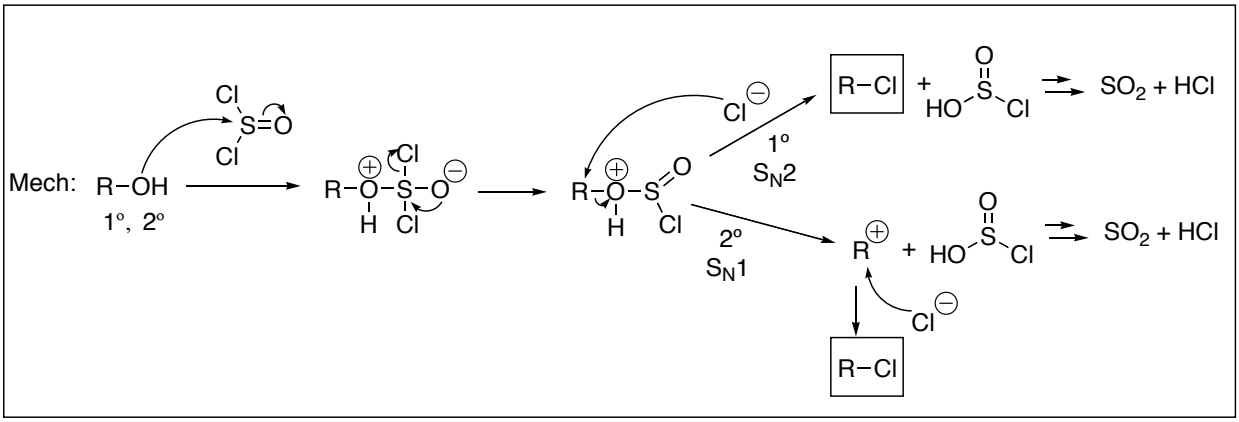
4 

5 

6 

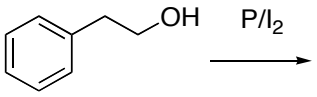
Reaction of 1º and 2º Alcohols with $SOCl_2$ (Section 11-9)

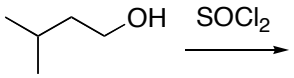
- Default recipe for chlorination of 1º and 2º alcohols

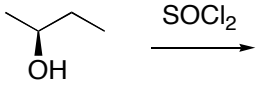


- Mechanism: Not for test responsibility
- Mechanism differs for 1º and 2º alcohols
- 1º involve an S_N2 substitution
- 2º involve an S_N1 type substitution
- The chloride that captures the cation is normally on the same side of the molecule on which the oxygen began, and often captures the cation very 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, SO_2 and HCl, are both gases. So workup is really easy. Simply rotovap the mixture down, and everything except for product is gone.

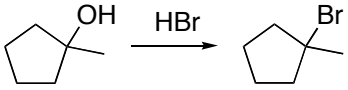
Draw Products or Provide Appropriate Reactants for the following Transformations

4 

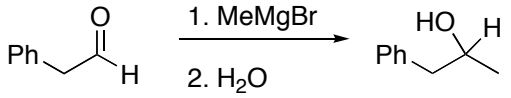
5 

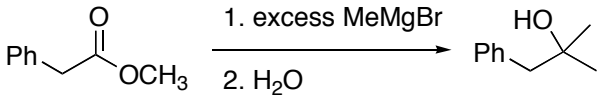
6 

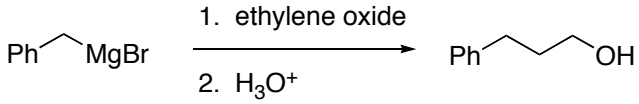
Draw the Mechanism:

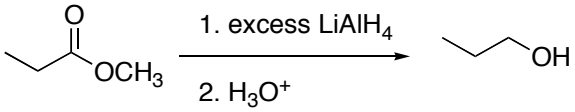


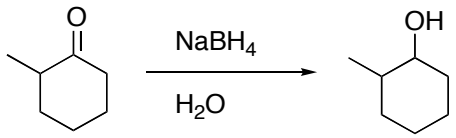
Draw the mechanisms for the following reactions.

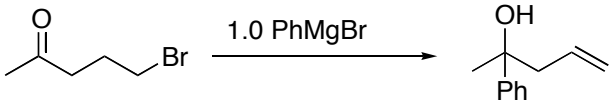
1 

2 

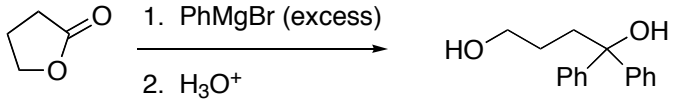
3 

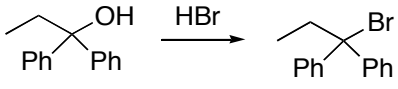
4 

5 

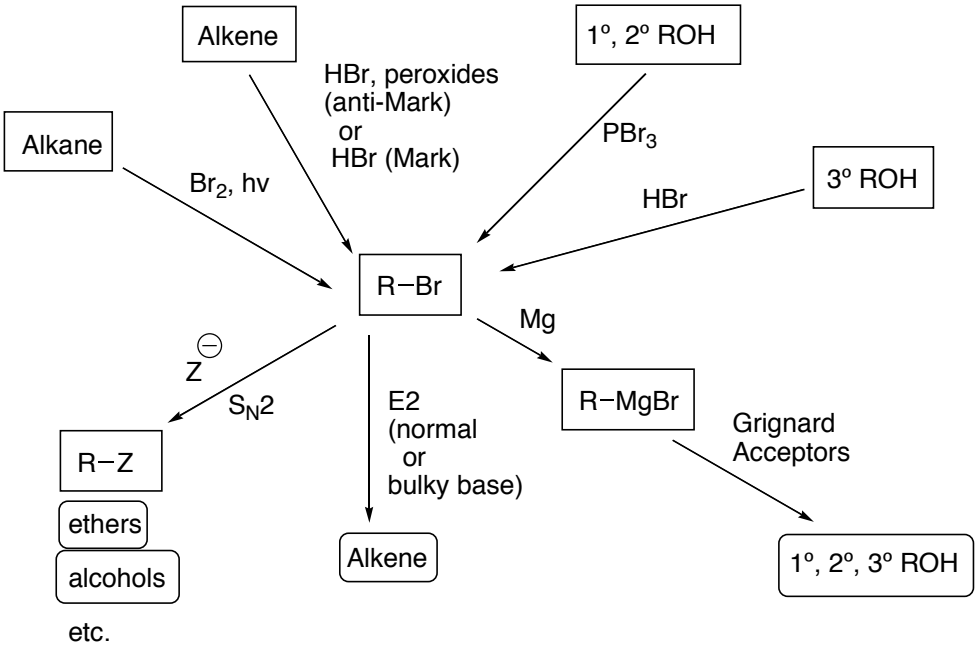
6 

Tricky combo

7 

8 

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



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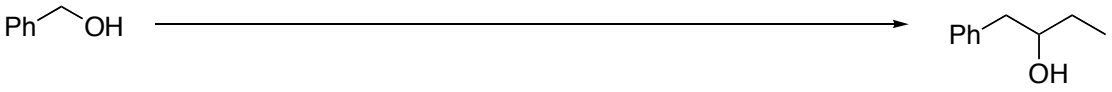

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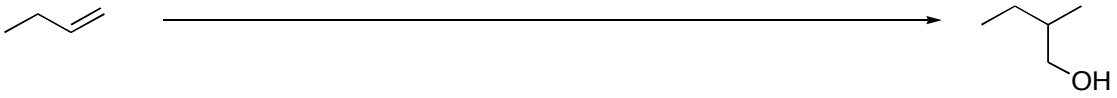

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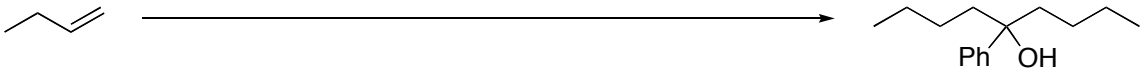
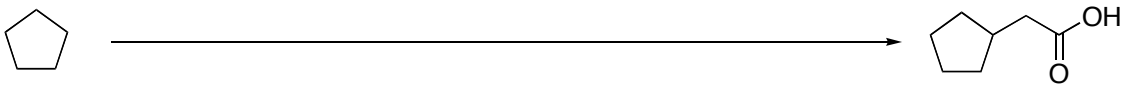
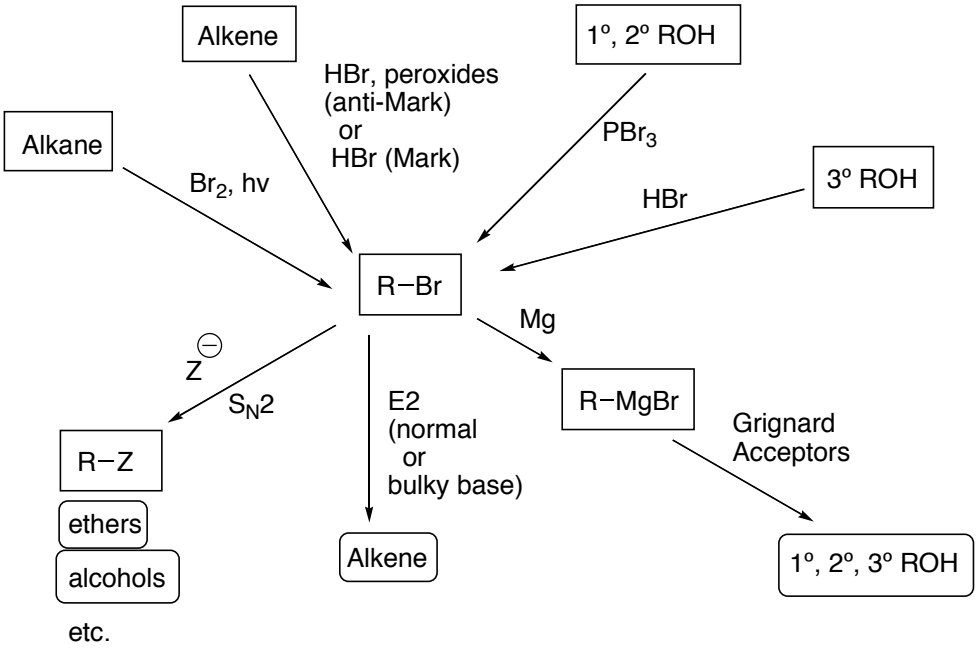


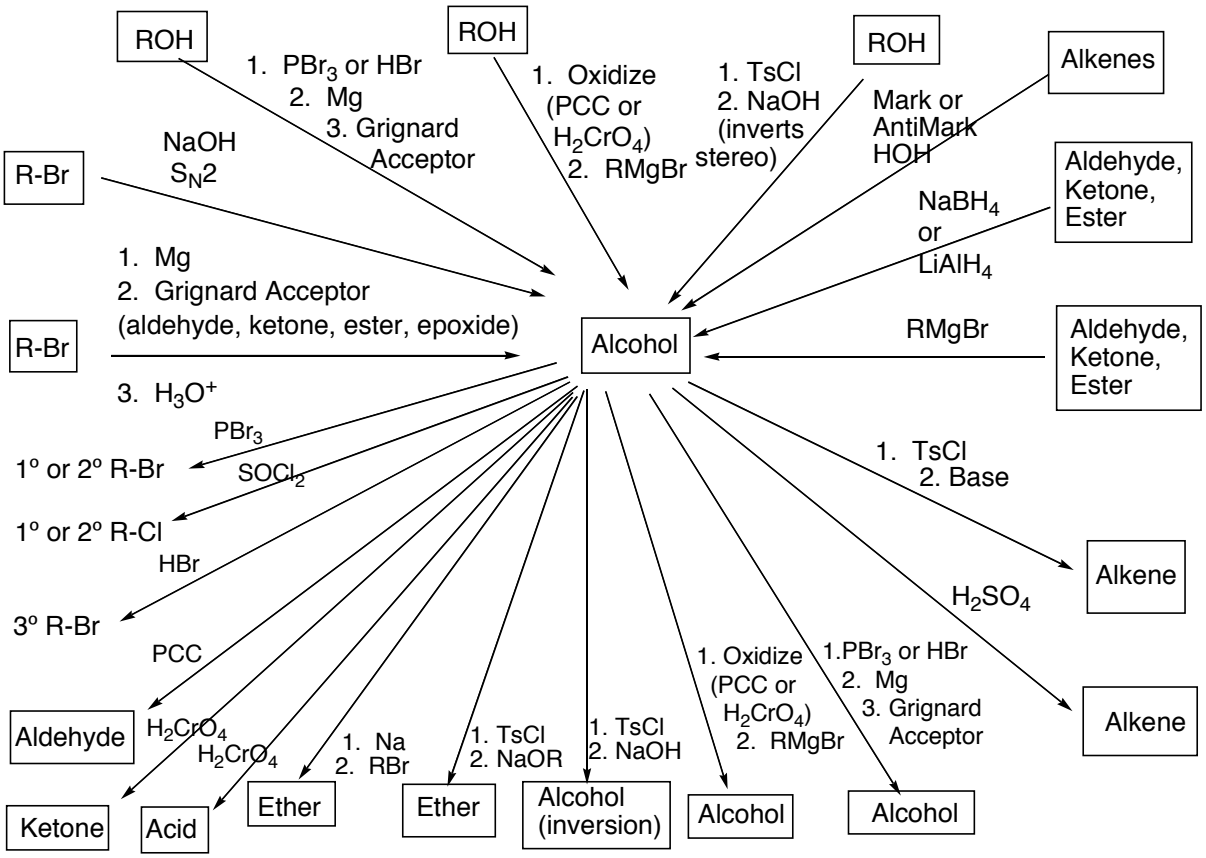
d.



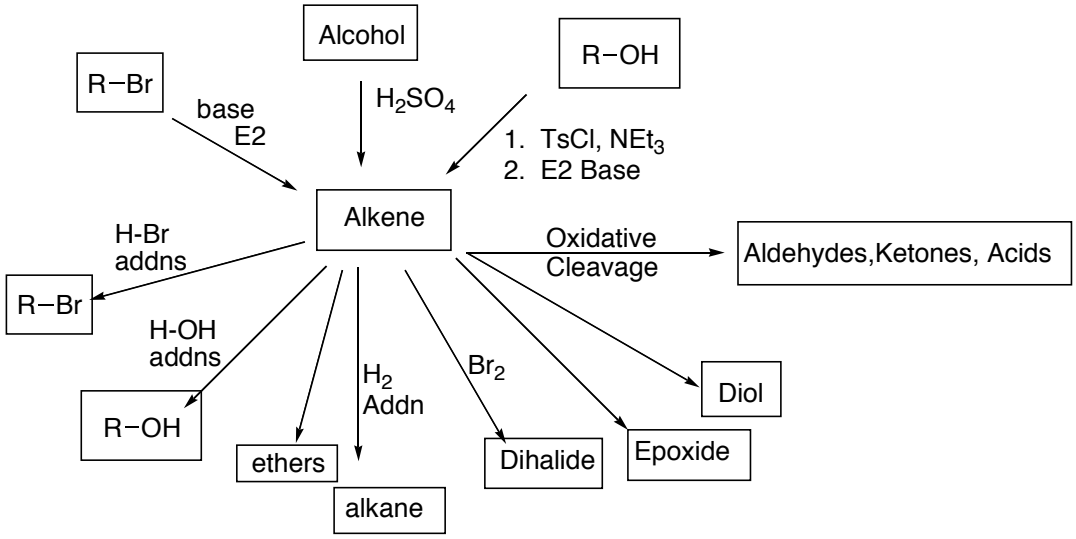
Bromoalkane Concept Map



Alcohol Concept Map



Alkene Concept Map



Ether Concept Map