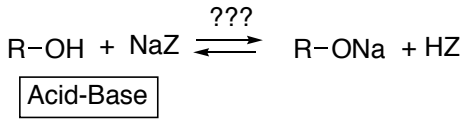
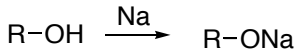
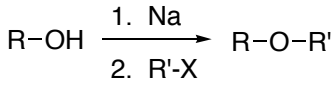
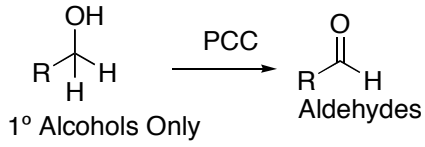
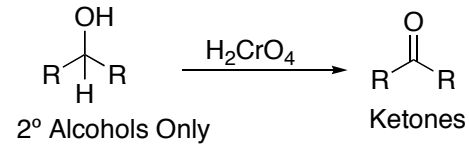
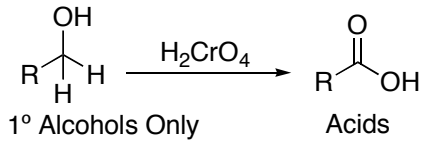
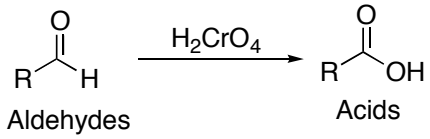
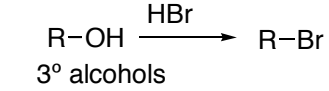
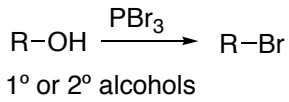
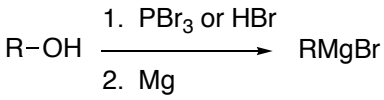
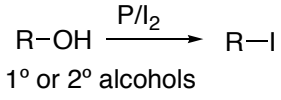
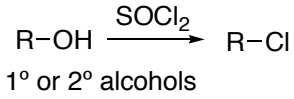
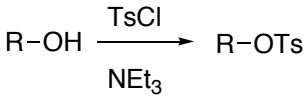
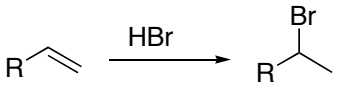
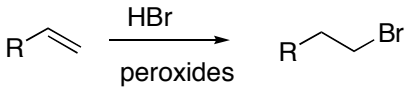
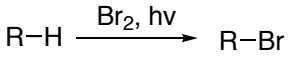
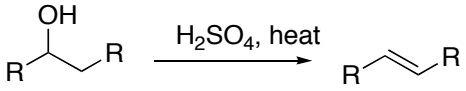
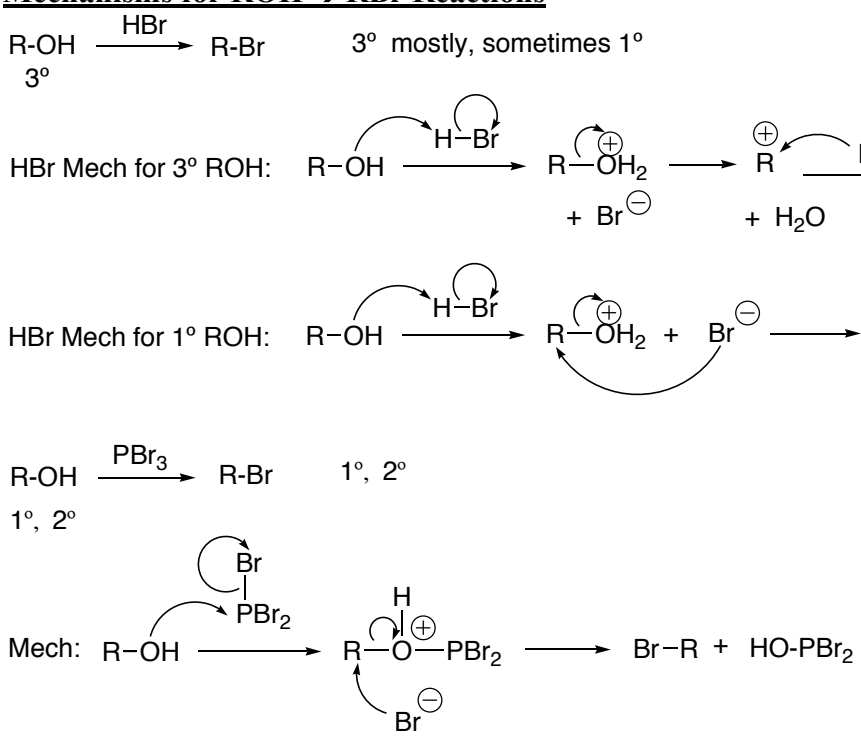
Summary of Alcohol Reactions, Ch. 11.

1		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.
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 3° alcohols
10		• Quick 2-step conversion of alcohol into a nucleophilic Grignard
11		• Via PI_3
12		• Retention of stereo!
13		• Tosylates are super leaving groups, better even than iodides. • Tosylates are well suited to S_N2 and E2 reactions.
14		• Markovnikov addition
15		• anti-Markovnikov addition
16		• Radical mechanism, 3° > 2° > 1°
17		• Zaytsev elimination

Mechanisms for ROH → RBr Reactions



Ch. 11 Reactions of Alcohols

A. Conversion to Alkoxides (Sections 11.14, 10.6)

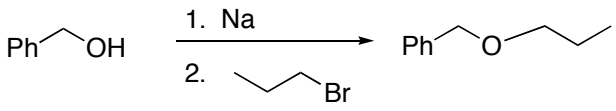
"alkoxide" = $RO^{\ominus}$ anion

1. By acid-base deprotonation (Section 10.6)
   - 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
2. By redox reaction with sodium or potassium (or some other metals)

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

B. Conversion to Ethers via Alkoxide (11-14)

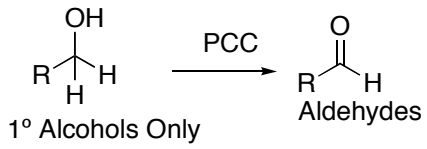
3	$R-OH \xrightarrow[2.\ R'-X]{1.\ Na} R-O-R'$	• Alkoxide formation-S_N2 route to ether • The electrophile R'-X must be S_N2 reactive, preferably 1º with a good leaving group



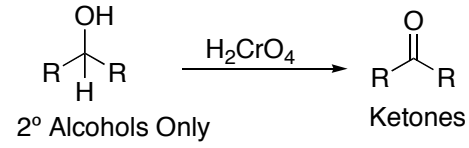
C. Oxidation of Alcohols to Carbonyl Compounds (11.1-4)

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

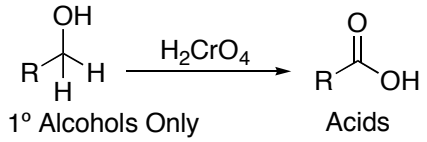
4 

- 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 

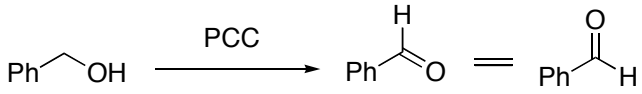
H_2CrO_4 = $Na_2Cr_2O_7$, H_2SO_4 or CrO_3/H_2O

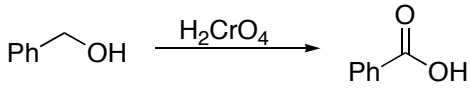
- Key access to ketones.
- PCC does not react very fast with 2º alcohols

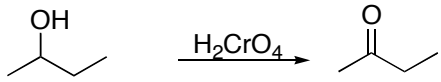
6 

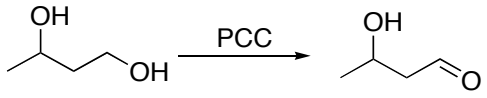
- Note difference between
- PCC and H_2CrO_4 when reacting with 1º alcohols.

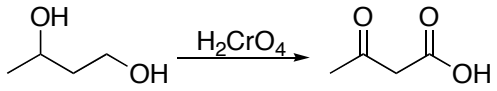
<u>Draw the products for the following oxidation reactions.</u>

1 

2 

3 

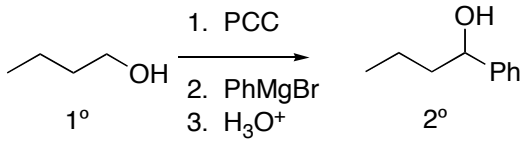
4 

5 

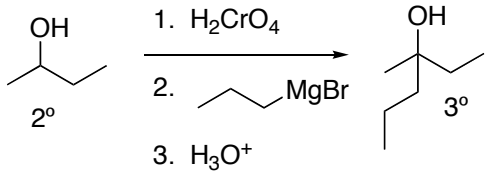
Oxidation Combined with Grignard Reactions (in either order): Indirectly Enables Substitution of Carbon for Hydrogen

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

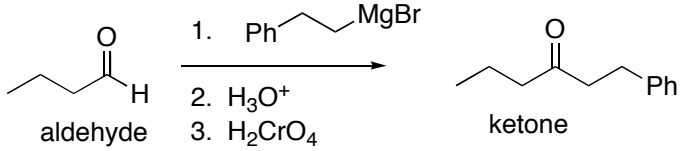
1



2



3



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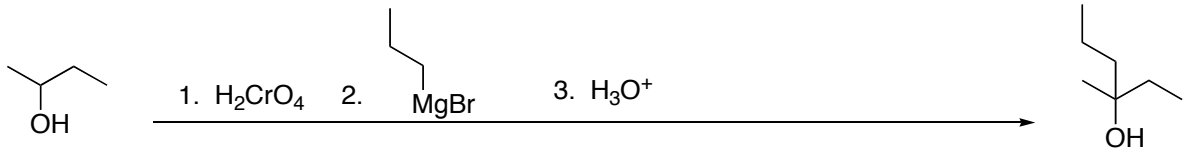

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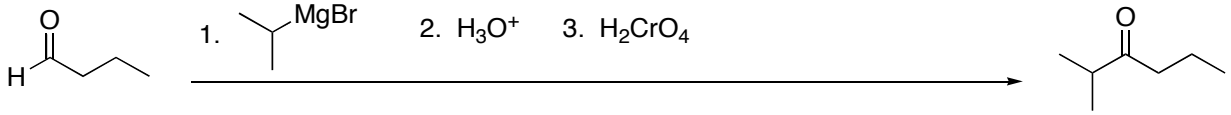

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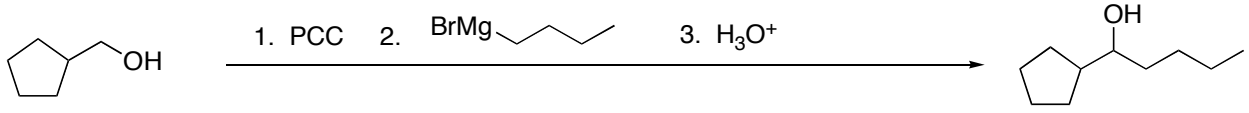
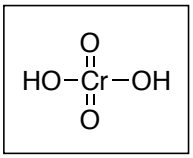
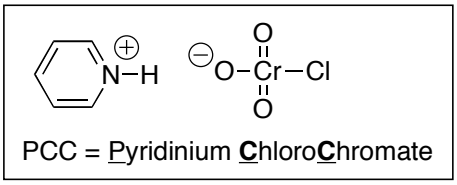


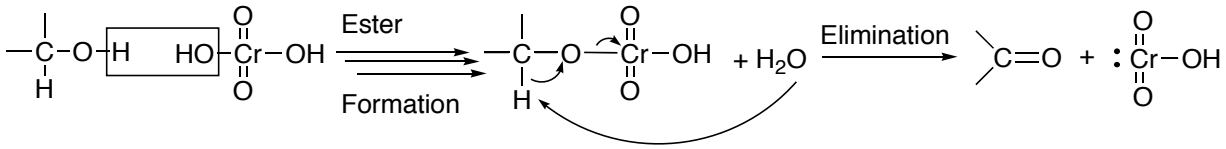
Jones Test H_2CrO_4 for Alcohols (11-2C) (test responsible)

- 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 **C**hloro**C**hromate

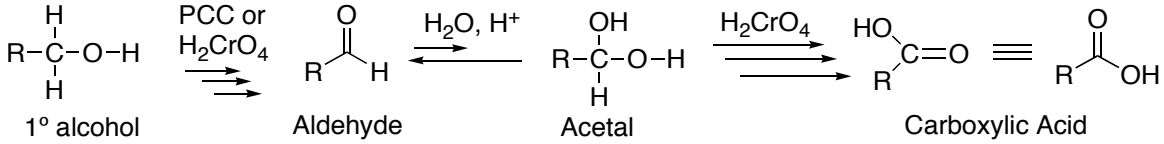
General Mechanism



- PCC operates analogously

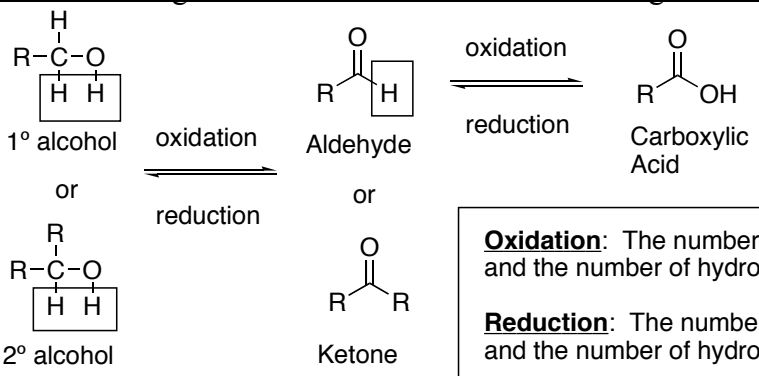
1º Alcohols, Aldehydes, and the Presence or Absence of Water:

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 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

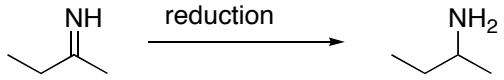


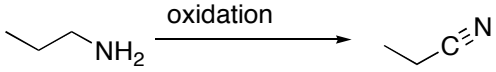
Oxidation: The number of oxygen bonds to a carbon increases, and the number of hydrogens bonded to a carbon decreases

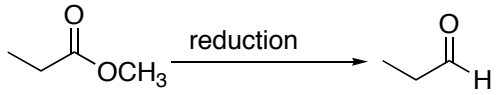
Reduction: The number of oxygen bonds to a carbon is reduced, and the number of hydrogens bonded to a carbon increases.

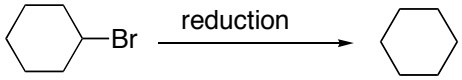
More General: # of bonds to heteroatoms versus to hydrogens

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

1. 

2. 

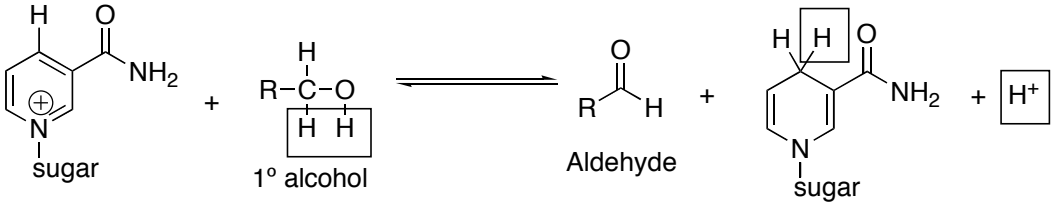
3. 

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)

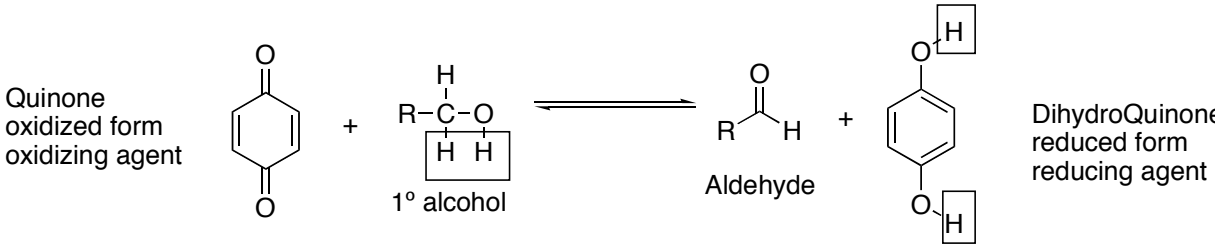
1. $KMnO_4$
2. CuO
3. "Jones": H_2CrO_4 with acetone added to temper reactivity
4. Collins: H_2CrO_4 with pyridine added to temper reactivity
5. "Swern": $(COCl)_2$ and $(CH_3)_2S{=}O$ then NEt_3
6. HNO_3
7. Biological Oxidant 1: "NAD^+" "nictonamide adenine dinucleotide"



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_4 (+6)
$H2CrO_4$ (+6)
HNO_4 (+5)
$H_2O_2 \rightarrow H_2O$
$RCO_3H \rightarrow RCO_2H$
$O_3 \rightarrow O_2$

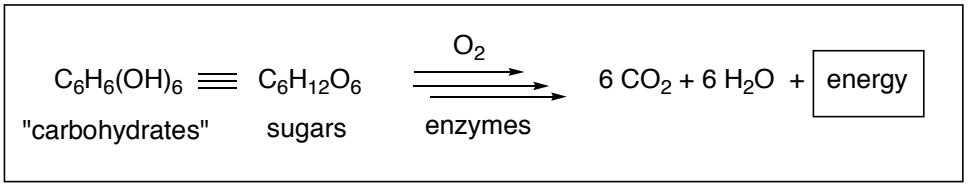
Reducing Agents: Often involve:
- Hydrides in Formulas
- Highly Reduced Metals
- Metals + H_2
- Metals + acid

$LiAlH_4$
$NaBH_4$
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

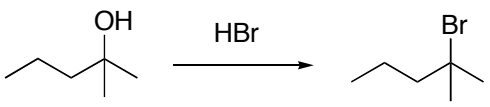
8	$R-OH \xrightarrow{HBr} R-Br$ (3º alcohols) Mech: Be able to draw!	• HI, HCl analogous • Converts alcohol into a bromide that can be used in Grignards, E2 reactions • Cation mechanism • Usually not method of choice for 1º, 2º alcohols
9	$R-OH \xrightarrow{PBr_3} R-Br$ (1º or 2º alcohols)	• Converts 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	$R-OH \xrightarrow{P/I_2} R-I$ (1º or 2º alcohols)	• Via PI_3
12	$R-OH \xrightarrow{SOCl_2} R-Cl$ (1º or 2º alcohols)	• Retention of stereo! • Section 11-9

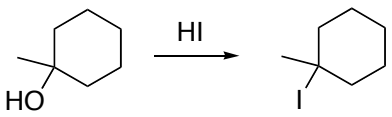
Summary:

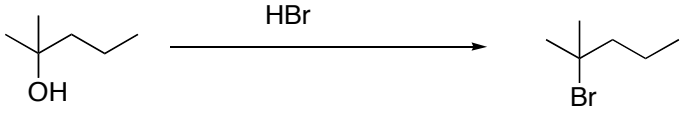
Class	**R-Br**	R-I	R-Cl
1º ROH	**PBr_3**	P/I_2	$SOCl_2$
2º ROH	**PBr_3**	P/I_2	$SOCl_2$
3º ROH	**HBr**	**HI**	**HCl**
Vinyl or Aryl	Nothing works	Nothing works	Nothing works

Straight Reaction with H-X (Section 11.7)

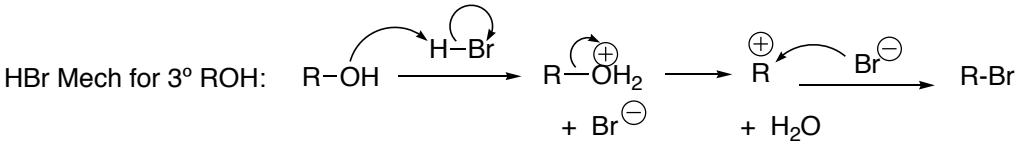
- Ideal only for 3º ROH,
- sometimes works with 1º alcohols, with a complex mechanism
- Only occasionally for 2º alcohols
- **Method of choice for 3º, but not for 1º or 2º**

1 

2 

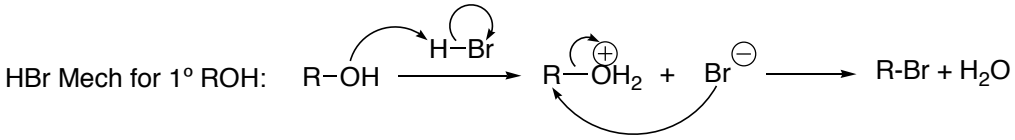
3 

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



Notes:

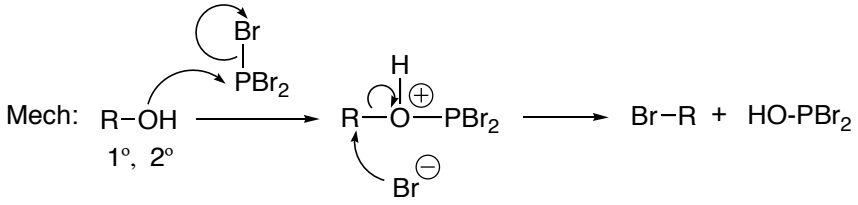
1. Memorize the 3º alcohol mechanism (test responsible)
   a. Protonate
   b. Leave to give Cation. This is the slow step for 3º alcohols
   c. Capture
2. Analogous with HI or HCl
   - HCl slower, normally enhanced with ZnCl2, which enhances rate of cation formation (Lucas test, see later)
   - Outside 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)



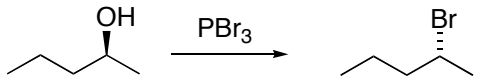
   - carbocation formation never occurs
   - bromide ion simply does S_N2 on the protonated alcohol, with water as an excellent leaving group
   - yields tend to be pretty inconsistent

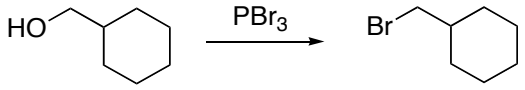
Reaction of 1º and 2º Alcohols with PBr_3 (Section 11-8)

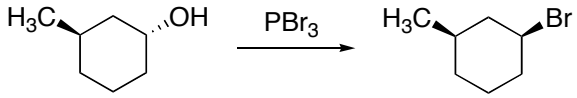
- Default recipe for 1º and 2º alcohols



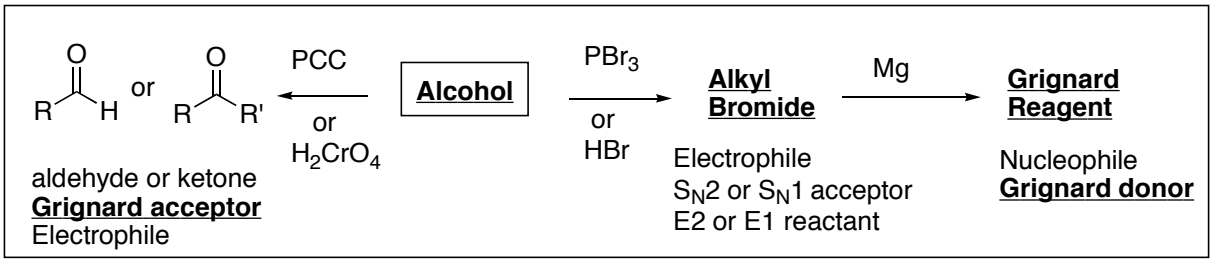
- PBr_3 is an exceptional electrophile, and reacts even with neutral alcohols
- The first step activates the oxygen as a leaving group.
- The second step involves an S_N2 substitution
  - **stereochemical inversion occurs chirality present (common for 2º alcohols)**
- Because the second step is an S_N2 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

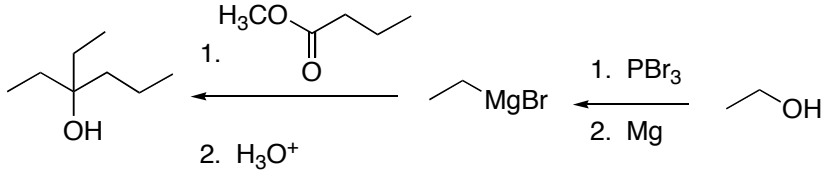


1. oxidation can convert an alcohol into a carbonyl = **Grignard acceptor (electrophile)**
2. PBr_3/Mg or HBr/Mg can convert an alcohol into RMgBr = **Grignard donor (nucleophile)**
3. PBr_3 or HBr can convert an alcohol into RBr, capable of normal substitution and elimination reactions.

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 

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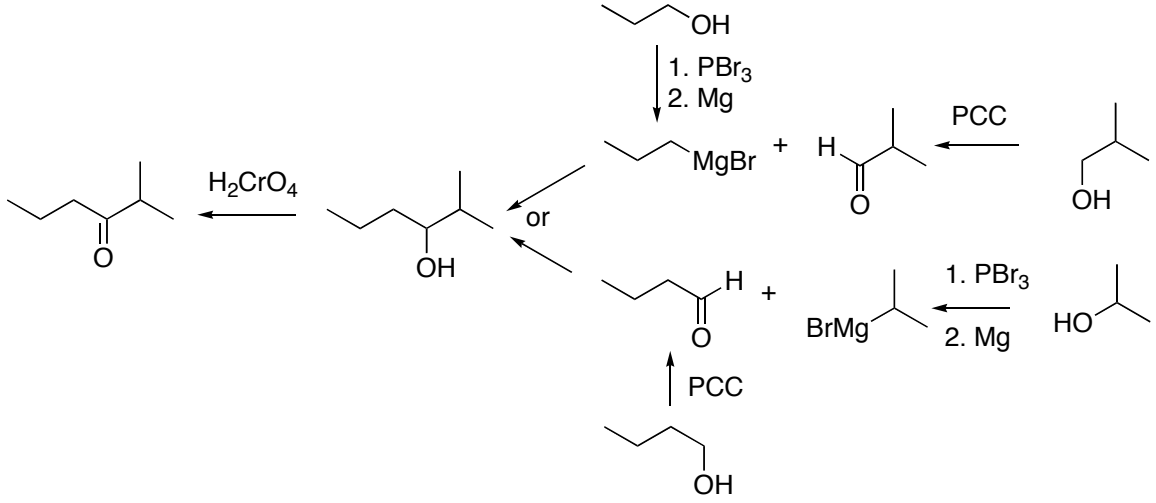
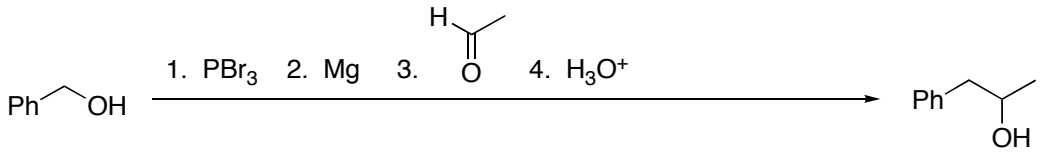


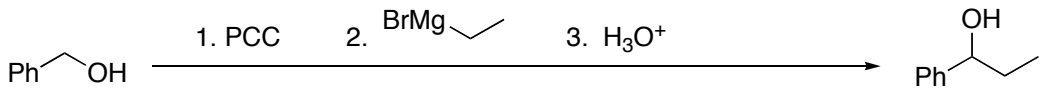
Normal Synthesis Design: In which you are given at least one of the starting Chemicals. Provide Reagents. You may use whatever reagents, including ketones or aldehydes or Grignards or esters, that you need. Tips:

- 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.

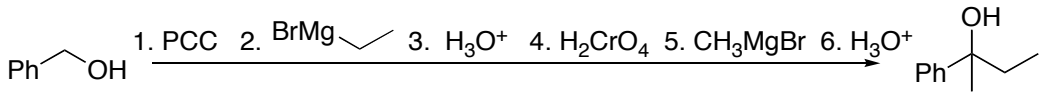
a.



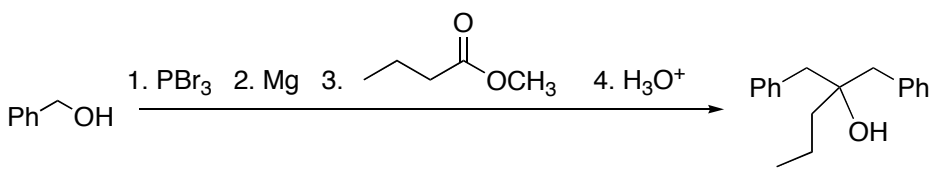
b.

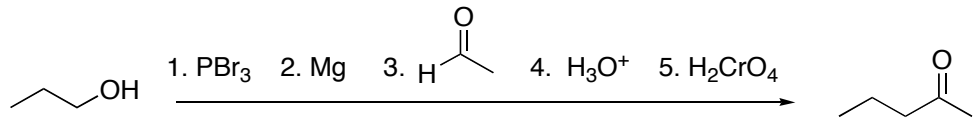


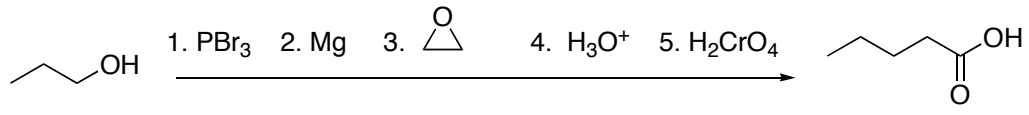
c.



d.



e. 

f. 

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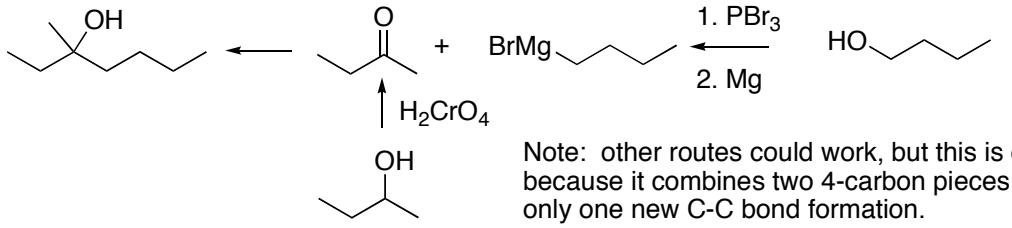
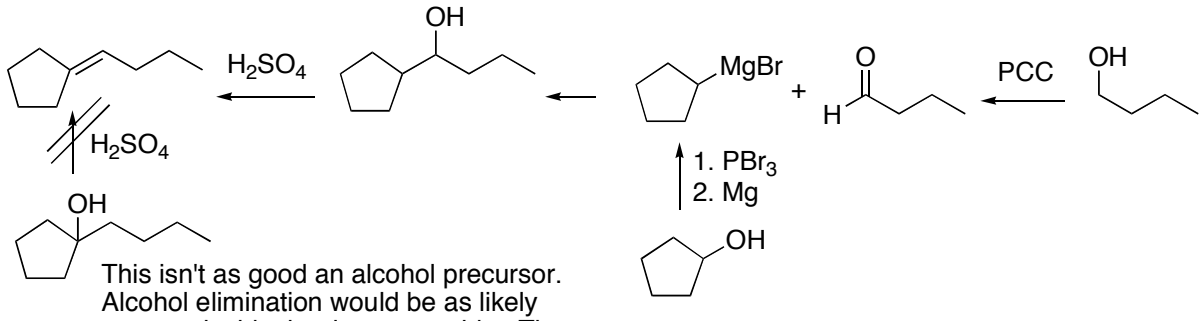
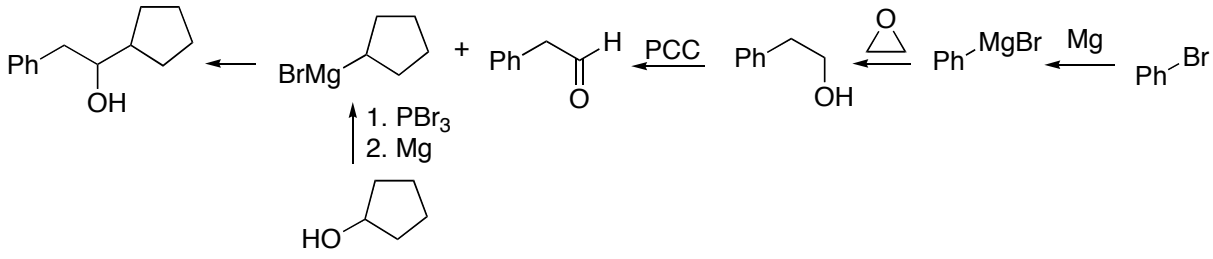
3 

Note: other routes could work, but this is cleanest because it combines two 4-carbon pieces, and requires only one new C-C bond formation.

4 

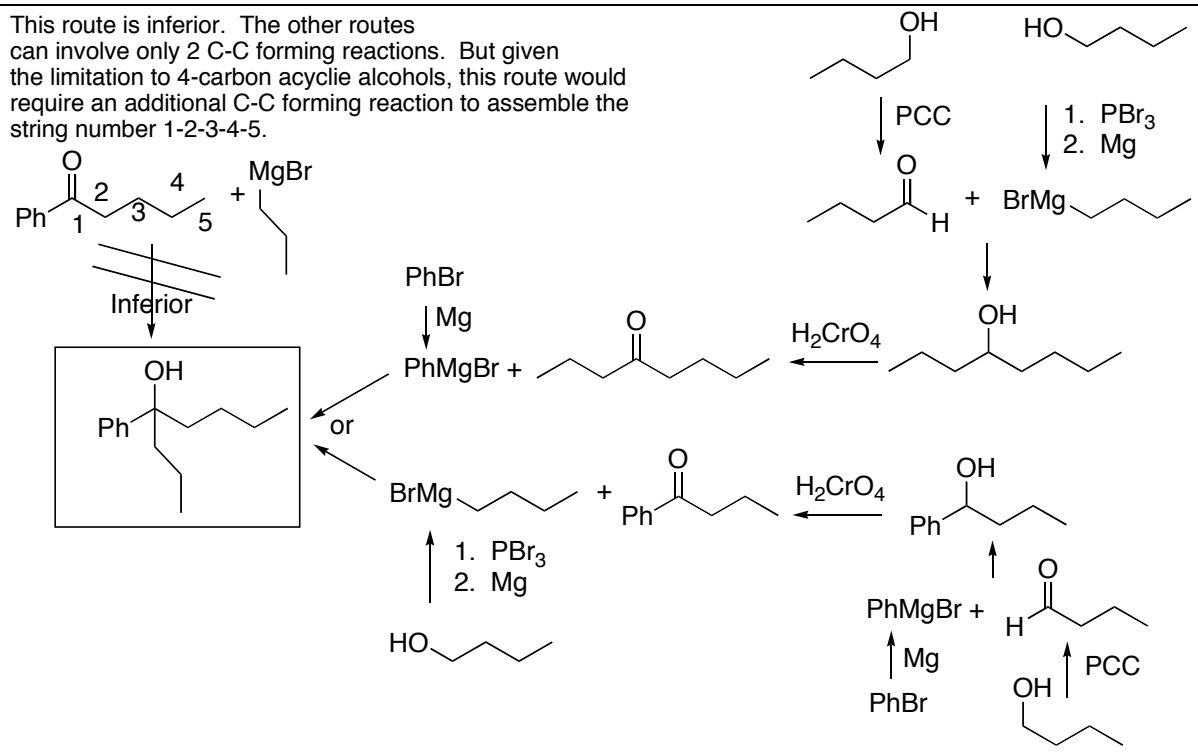
This isn't as good an alcohol precursor. Alcohol elimination would be as likely to occur inside the ring as outside. The better route involves an alcohol who should have a pretty clean Zaytsev elimination.

5



6

This route is inferior. The other routes can involve only 2 C-C forming reactions. But given the limitation to 4-carbon acyclie alcohols, this route would require an additional C-C forming reaction to assemble the string number 1-2-3-4-5.



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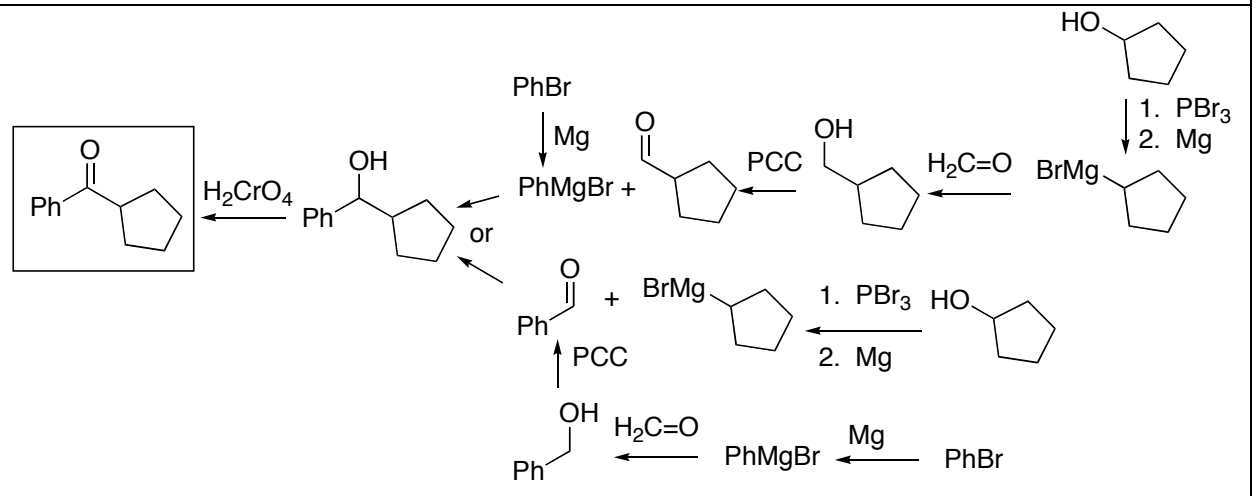

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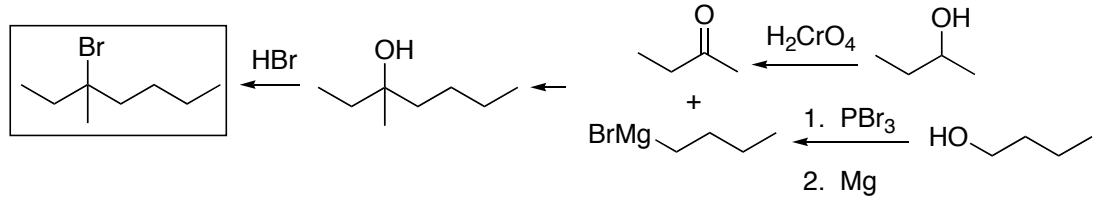


Unknowns and Chemical Tests (Sections 11-2C, 11-7)

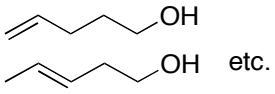
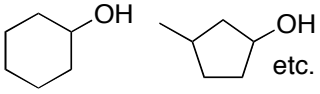
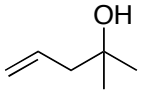
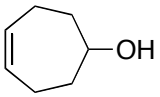
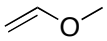
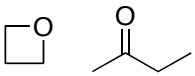
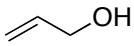
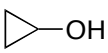
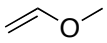
1. H_2/Pt test for alkenes
2. Br_2 test for alkenes
3. **Jones reagent (H_2CrO_4) Test for 1º or 2º alcohols**
   - 3º alcohols do not react
   - 2º alcohols keep the same number of oxygens but lose two hydrogens in the formula
   - 1º alcohols lose two H's but also add one oxygen
4. **Lucas Test: HCl/$ZnCl_2$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

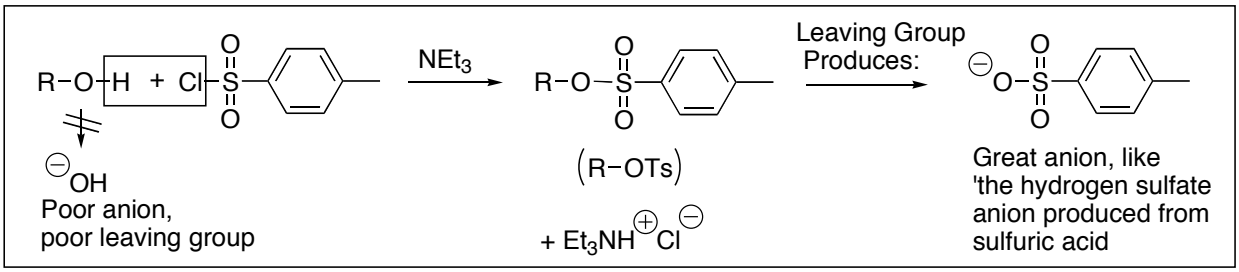
- 3º alcohols are fastest
- 1º alcohols don't react at all
- $R^{\oplus}$ stability is the key
- Test is based on **solubility**: The R-Cl product is nonpolar and water insoluble, so it separates out from water. Alcohols are quite soluble especially in highly acidic water.
- Test fails is useless for 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	1º ROH One Alkene	 etc.
2	$C_6H_{12}O$	Yes	Yes, 1-5 min	No	2º ROH One ring	 etc.
3	$C_6H_{12}O$	No	Yes	Yes	3º ROH One Alkene	 etc.
4	$C_7H_{12}O$	Yes	Yes	Yes, Produces $C_7H_{14}O$	2º ROH One Alkene One ring or carbonyl	 etc.
5	C_3H_6O	No	No	Yes	No ROH One alkene	
6	C_3H_6O	No	No	No	No ROH One ring or Carbonyl	 etc.
7	C_3H_6O	Yes, produces $C_3H_4O_2$	No	Yes	1º ROH One alkene	
8	C_3H_6O	Yes, produces C_3H_4O	Yes	No	2º ROH One ring	
9	C_3H_6O	No	No	Yes	No ROH One alkene	

Section 11-5 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.

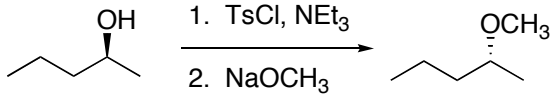
13 $R-OH \xrightarrow[NEt_3]{TsCl} R-OTs$

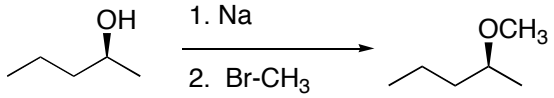


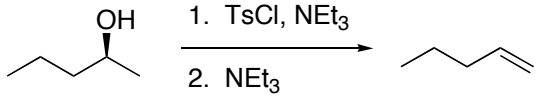
Notes:

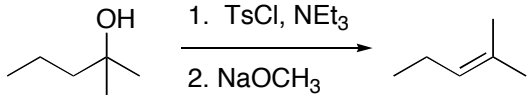
1. Tosylates are easy to form
2. "Toluene sulfonate"
3. Tosylate anion is really stable, comparable to the anion from sulfuric acid
   - Both the electronegative sulfur and the resonance/charge sharing with the other oxygens helps
4. Whereas a normal OH has a poor leaving group (hydroxide anion), conversion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

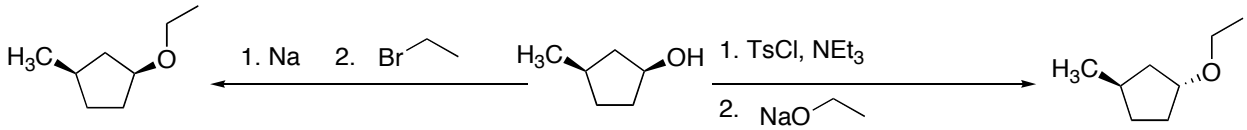
Draw Products

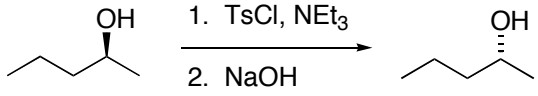
1 

2 

3 

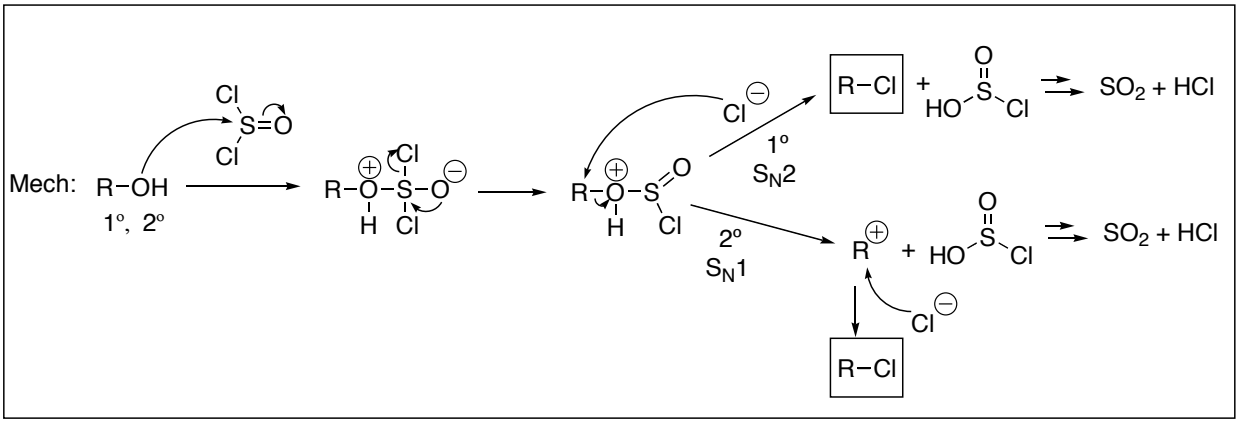
4 

5 

6 

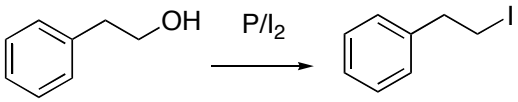
Reaction of 1º and 2º Alcohols with $SOCl_2$ (Section 11-9)

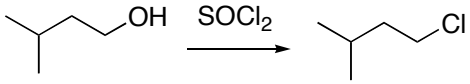
- Default recipe for 1º and 2º alcohols

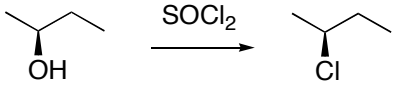


- Mechanism: Not for test responsibility
- Mechanism differs for 1º and 2º alcohols
- 1º involve an S_N2 substitution
- 2º involve an S_N1 type substitution
- The chloride that captures the cation is normally on the same side of the molecule on which the oxygen began, and often captures the cation very 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.

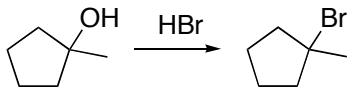
Draw Products or Provide Appropriate Reactants for the following Transformations

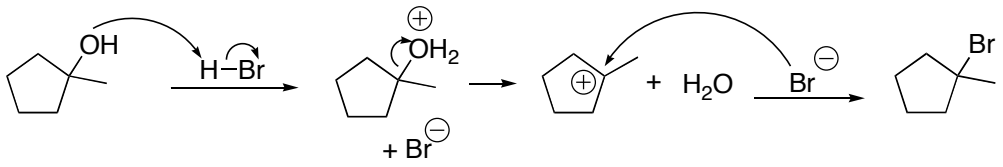
4 

5 

6 

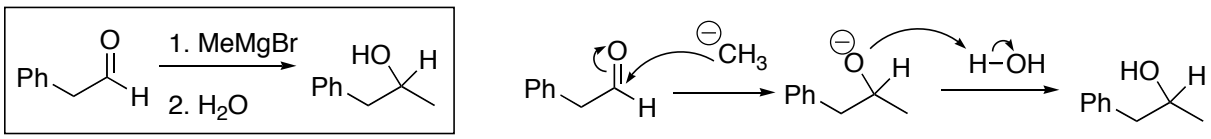
Draw the Mechanism:





Draw the mechanisms for the following reactions.

1



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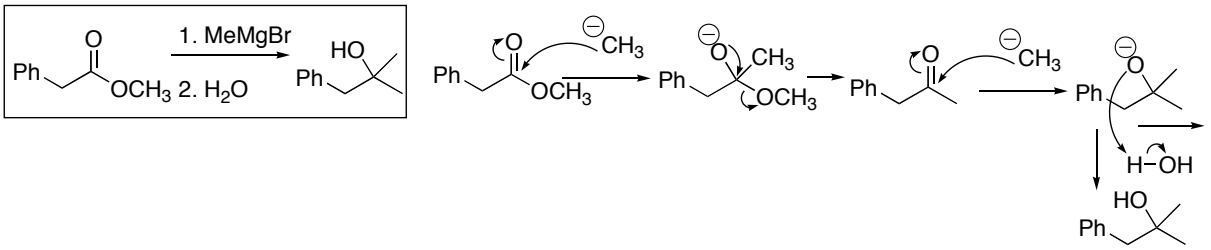

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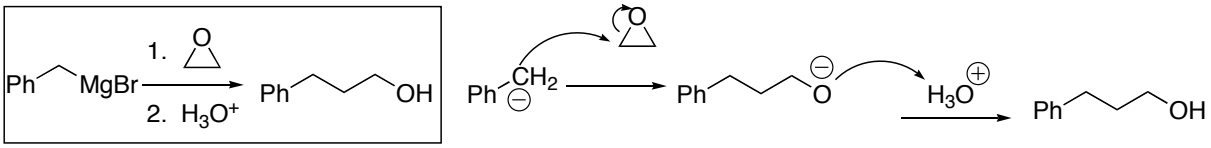

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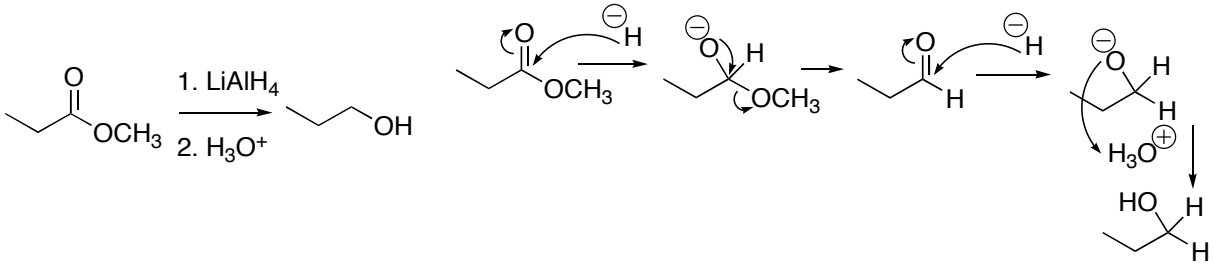

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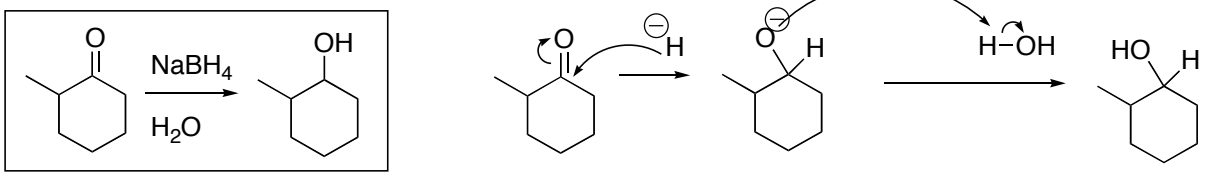

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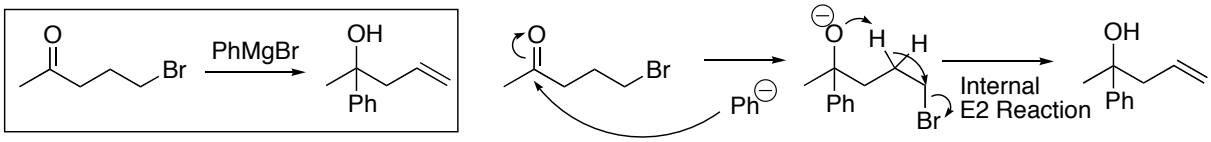

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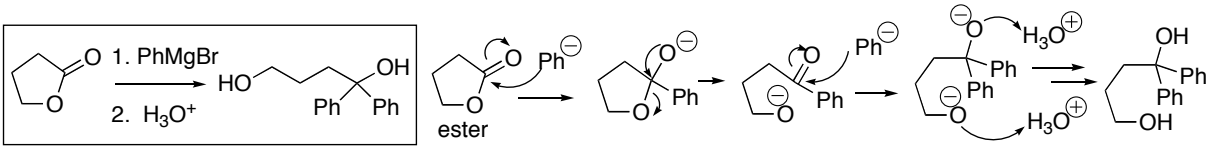

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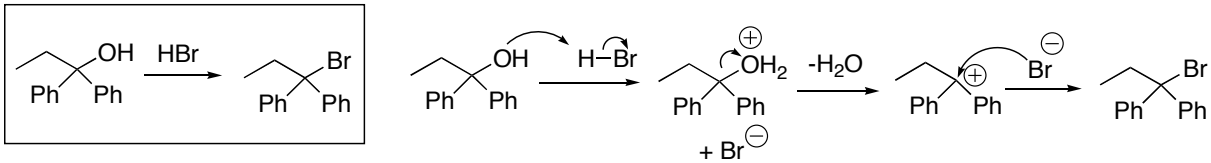
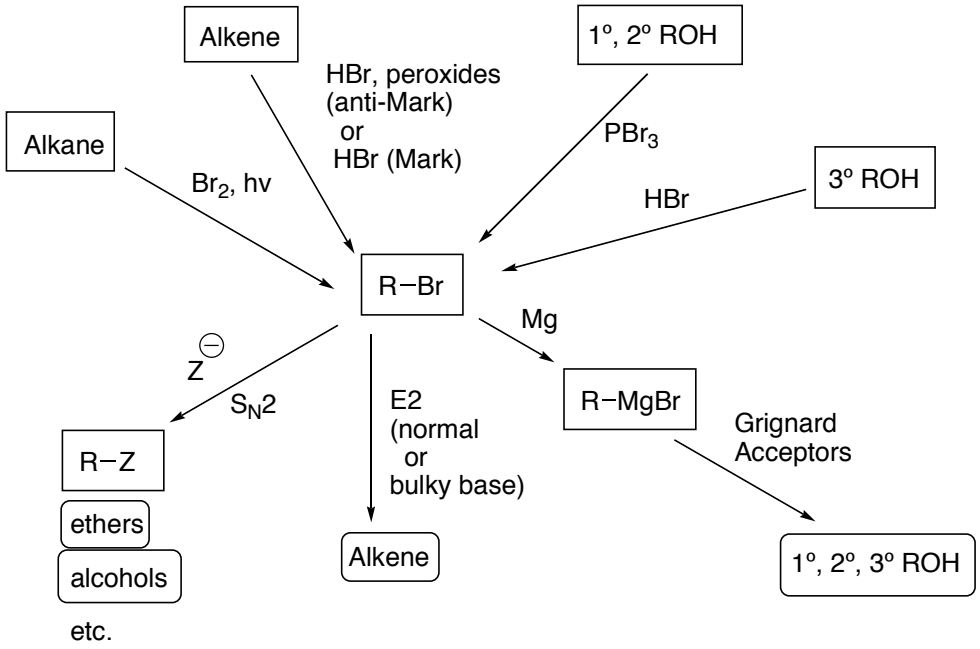
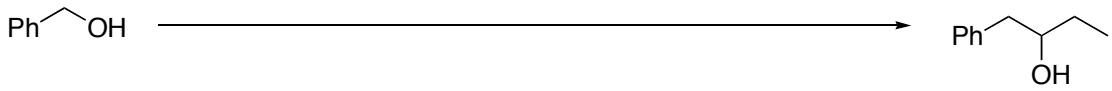


REVIEW. To make organometallic reagents, you must have RBr compounds (or RCl or RI).

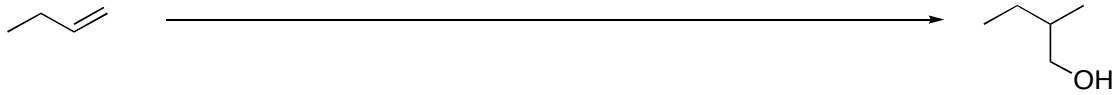


a.



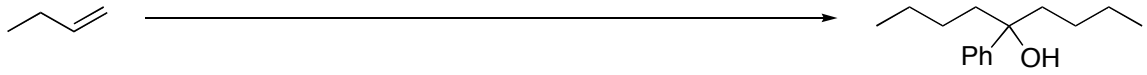
1. PBr_3 2. Mg 3. CH_3CH_2CHO 4. H^+

b.



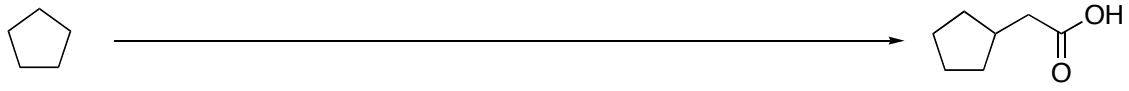
1. HBr 2. Mg 3. CH_2O 4. H^+

c.



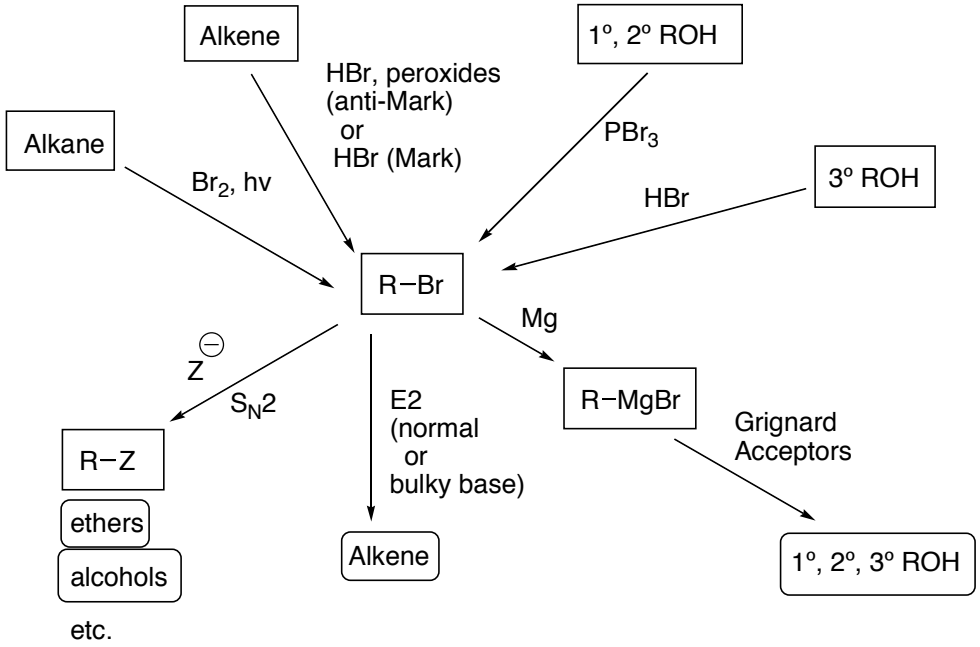
1. HBr (peroxides) 2. Mg 3. $PhCO_2CH_3$ 4. H^+

d.

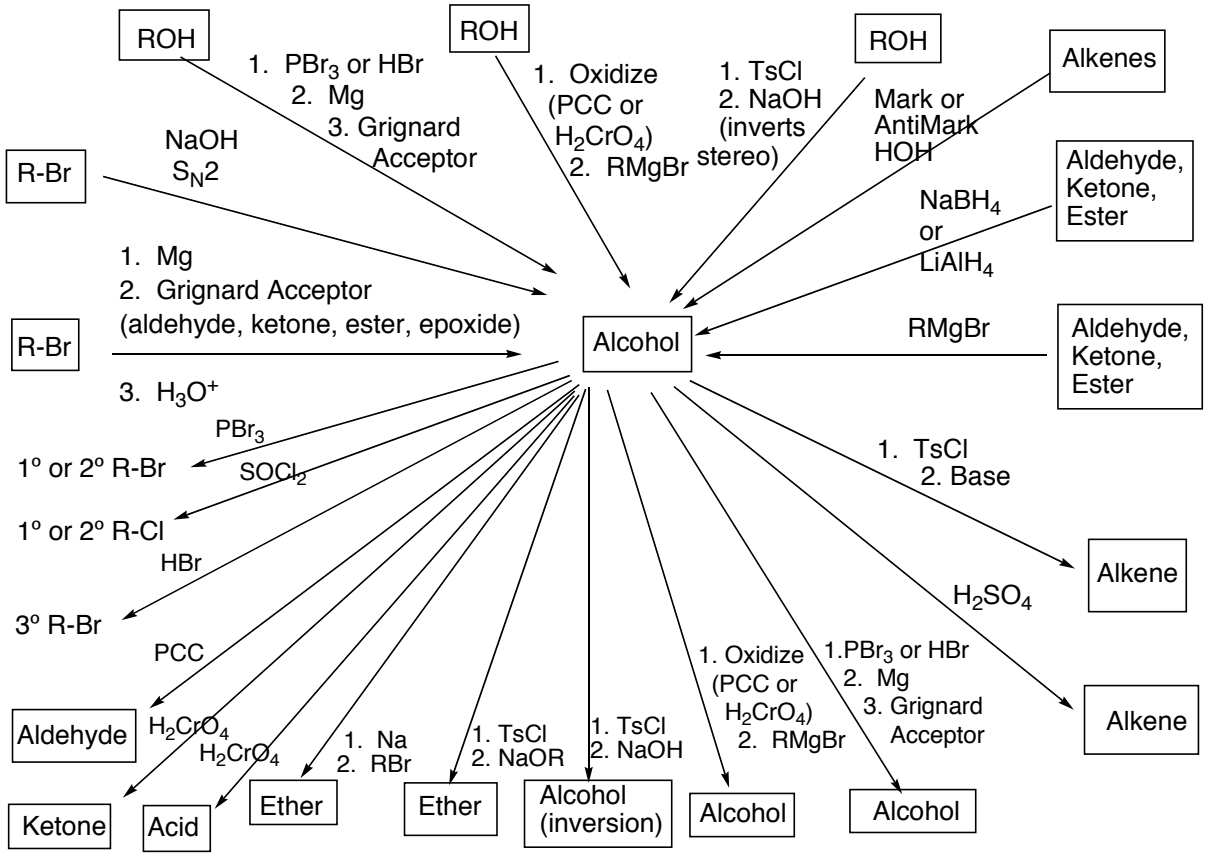


1. Br_2, hv 2. Mg 3. Ethylene oxide 4. H^+ 5. H_2CrO_4

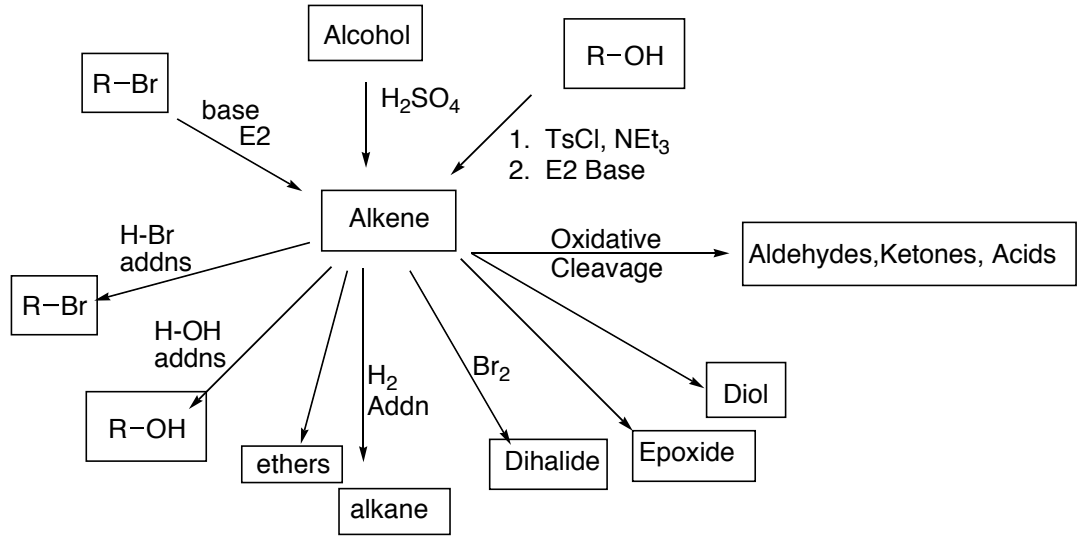
Bromoalkane Concept Map



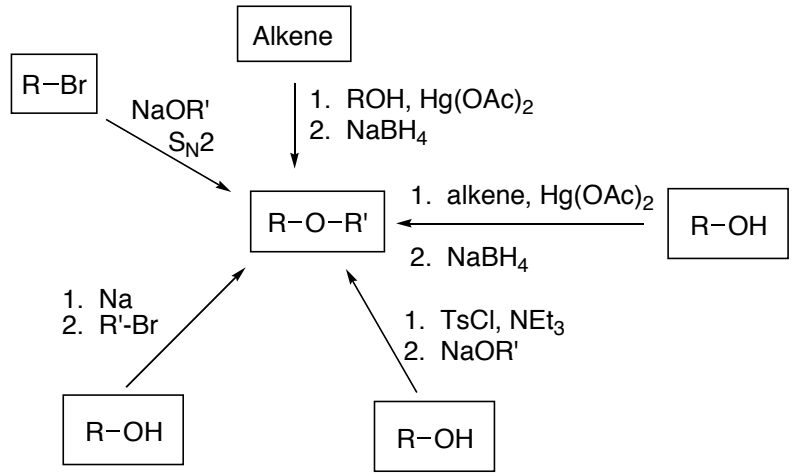
Alcohol Concept Map



Alkene Concept Map



Ether Concept Map



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