

Alcohols I

Reading: Wade chapter 10, sections 10-1- 10-12

Study Problems: 10-35, 10-37, 10-38, 10-39, 10-40, 10-42, 10-43

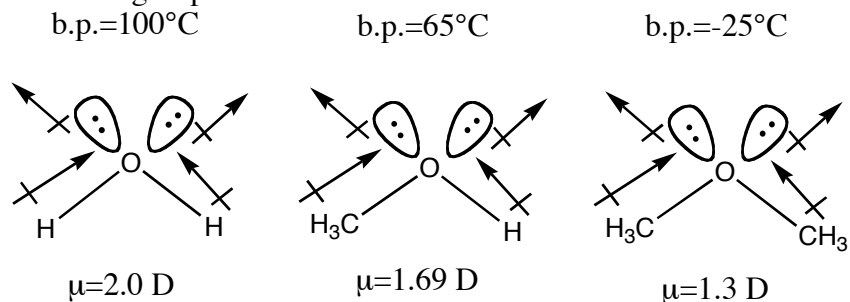
Key Concepts and Skills:

- Show how to convert alkenes, alkyl halides, and carbonyl compounds to alcohols.
- Use Grignard reagents and organolithium reagents for the synthesis of primary, secondary, and tertiary alcohols.
- Predict the relative acidities of alcohols and thiols

Lecture Topics:

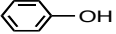
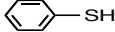
I. Alcohols-structure

Alcohols contain the hydroxyl functional group ($-\text{OH}$), which, like water, has a bent geometry and an overall dipole moment. The dipole moments of water, methanol, and dimethyl ether are similar, yet their boiling points are quite different; indicating the relative importance of hydrogen bonding as the intermolecular force for hydroxyl-containing functional groups.



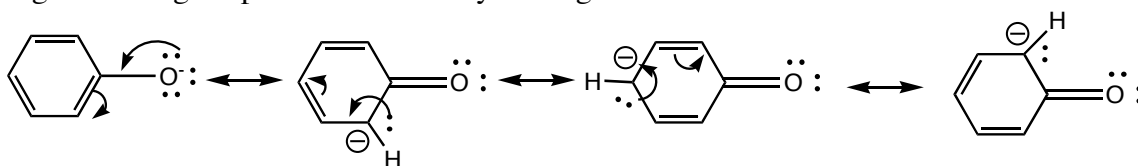
II. Acidity

Alcohols have similar acidity to water ($\text{pK}_a \sim 16$). Secondary and tertiary alcohols have higher pK_a values (making them less acidic) because steric hindrance around the alkoxide makes solvation difficult and thus raises the energy of the negatively charged species, shifting the equilibrium toward reactants.

$\text{R-OH} + \text{H}_2\text{O} \xrightleftharpoons{\text{K}_a} \text{R-O}^- + \text{H}_3\text{O}^+$	
	pK _a
H_2O	15.7
$\text{CH}_3\text{CH}_2\text{OH}$	15.9
$\text{CH}_3\text{CH}(\text{OH})\text{CH}_3$	16.5
$(\text{CH}_3)_3\text{C-OH}$	18.0
	
phenol	10
$\text{CH}_3\text{CH}_2\text{OH}$	16
$\text{ClCH}_2\text{CH}_2\text{OH}$	14.3
$\text{Cl}_3\text{CCH}_2\text{OH}$	12.2
$\text{CH}_2\text{CH}_2\text{SH}$	10.5
thiophenol	7.8
	

For the chlorinated derivatives of ethanol ($\text{ClCH}_2\text{CH}_2\text{OH}$, $\text{Cl}_3\text{CCH}_2\text{OH}$), the inductive electron-withdrawing effect of the local halogens enhances the acidity of the parent alcohols; this effect is additive, with trichloroethanol being more acidic than chloroethanol and ethanol.

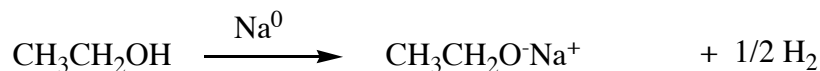
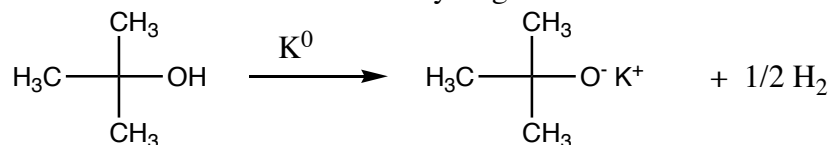
Phenol (an aromatic ring with an alcohol attached) is a relatively acidic alcohol because the corresponding **phenoxide** anion is stabilized by charge delocalization throughout the benzene ring. One can thus write multiple resonance forms for phenoxide in which the negative charge is placed successively on ring carbon atoms:



III. Formation of metal alkoxides

2 methods are available for accomplishing a formal deprotonation of alcohols:

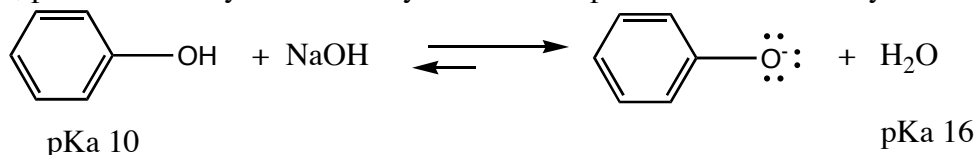
1. reaction of the alcohol with alkali metals such sodium and potassium. This is a redox reaction in which hydrogen is reduced and the metal is oxidized



2. reaction of the alcohol with sodium or potassium hydride:



In each case, hydrogen gas is given off as a by-product; because of the high acidity of phenols, phenoxides may be formed by treatment of phenol with sodium hydroxide:

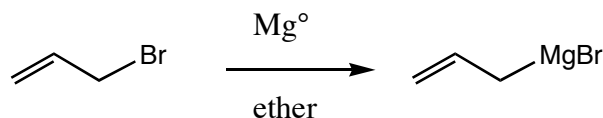
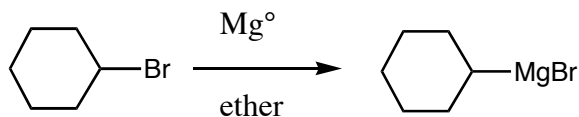
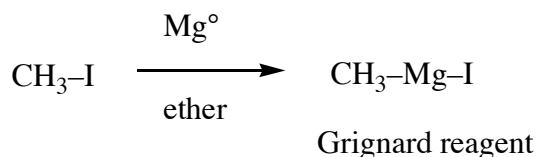


IV. Synthesis of alcohols

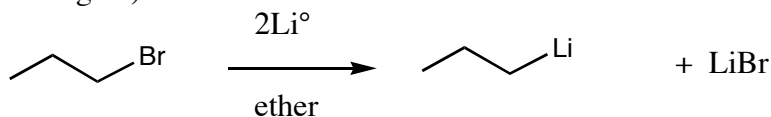
1. Organometallic reagents in the synthesis of alcohols

Organometallic compounds contain a highly polarized covalent bond between carbon and a metal atom ($\text{C}-\text{M}$, $\text{M}=\text{Li}$, Na , K , Mg). The $\text{C}-\text{M}$ bond is polarized so that most of the electron density resides on carbon, since it is the more electronegative atom of the pair. This makes carbon a good nucleophile (and also a good base).

Grignard reagents are organomagnesium compounds formed from alkyl halides and magnesium metal in ether. The reactivity of alkyl halides toward magnesium metal is ($\text{R}-\text{I} > \text{R}-\text{Br} > \text{R}-\text{Cl} >> \text{R}-\text{F}$):

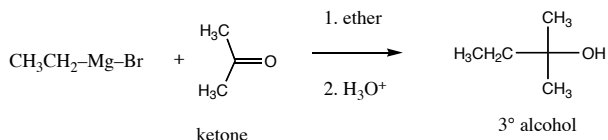
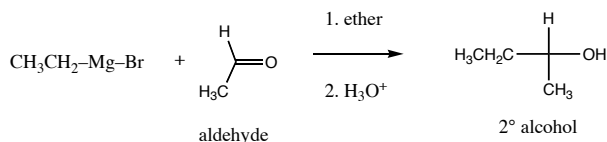
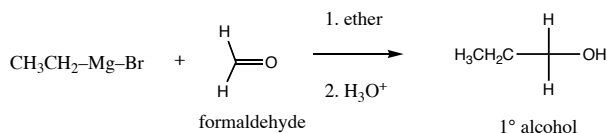
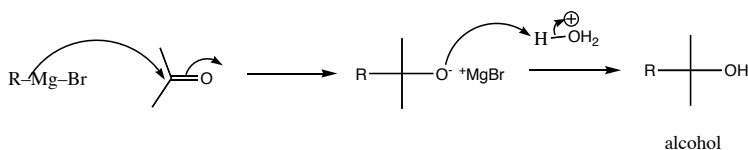


Formation of organolithium reagents requires 2 equivalents of lithium metal (which has only one electron to give):



2. Addition of organometallic reagents to carbonyl compounds

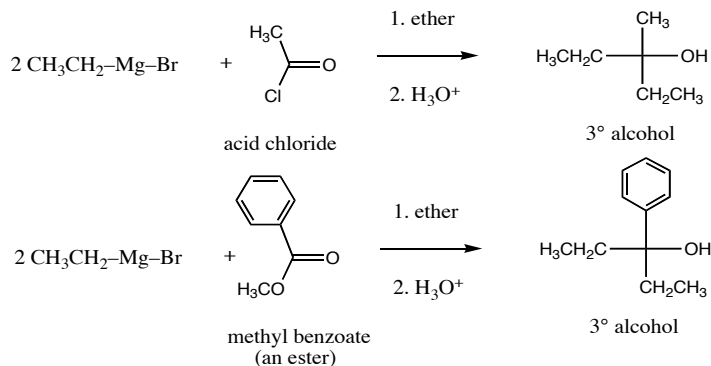
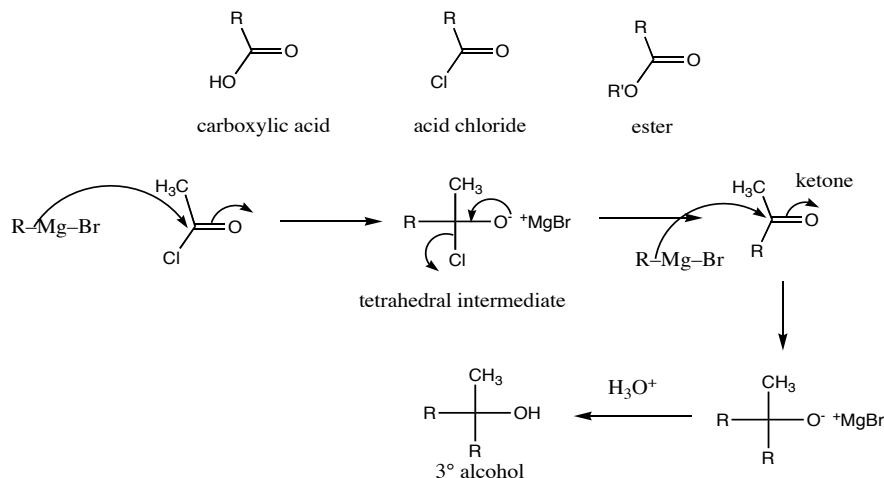
Grignards and organolithiums add to aldehydes and ketones efficiently. Reaction with formaldehyde generates primary alcohols after acidic hydrolysis of the metal alkoxide salt; reaction with aldehydes generates secondary alcohols after acidic hydrolysis of the metal alkoxide salt; reaction with ketones generates tertiary alcohols after acidic hydrolysis of the metal alkoxide salt.



Addition to carboxylic acid derivatives

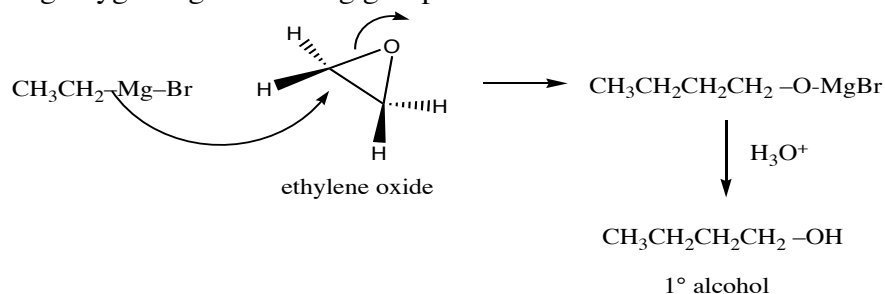
Grignard and organolithium reagents also add to esters and acid chlorides (derivatives of carboxylic acids) to form alcohols. Two equivalents are needed because the intermediate ketones are as reactive or more reactive than the carbonyl starting materials. Tertiary

alcohols are obtained as products. The reaction proceeds through an unstable tetrahedral intermediate which breaks down with loss of a leaving group to form the stable C=O unit of the ketone; addition of a second equivalent of Grignard reagent transforms the intermediate ketone to the tertiary alcohol as usual:



Synthesis of 1° alcohols by reaction with epoxides

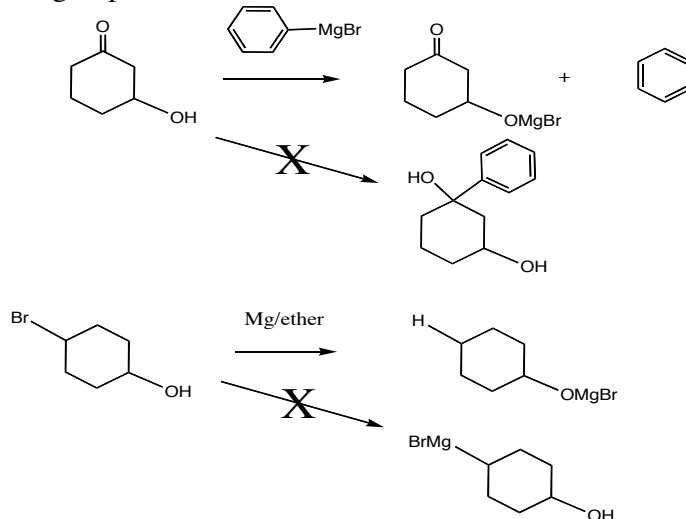
Grignard reagents add to ethylene oxide to afford 1° alcohols; the reaction proceeds by S_N2 backside attack on the terminal carbon of the epoxide. Ring strain in the epoxide makes the ring oxygen a good leaving group:



Grignard reagents and Organolithiums react with water and alcohols

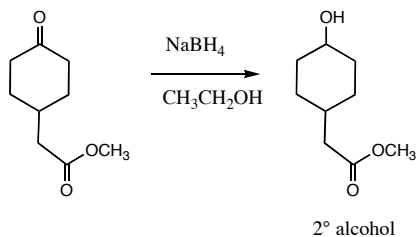
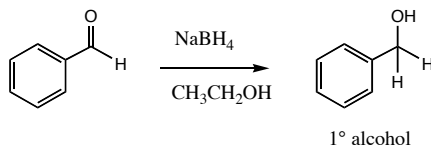
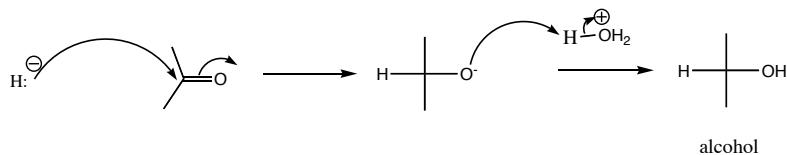
Organometallic reagents are very basic (pK_a's of alkanes ~50) and react rapidly with water and alcohols (pK_a's ~16) by deprotonation to generate alkanes. Thus, when

designing a synthesis, one must be careful to avoid moisture in the reaction or the use of substrates containing unprotected alcohols or amines.

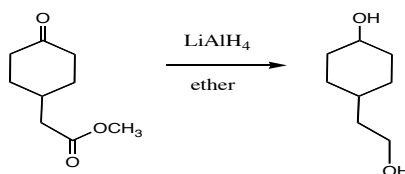


3. Reduction of Carbonyl Compounds

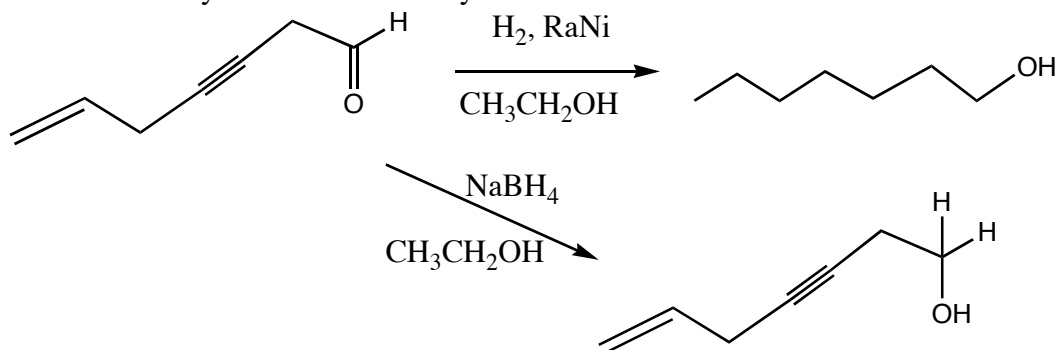
Sodium Borohydride is a complex metal hydride reagent that delivers an equivalent of H^- (hydride) to carbonyls. It reacts exclusively with aldehydes and ketones to give alcohols. Aldehydes give primary alcohols and ketones give secondary alcohols. Esters, acids do not react:



Lithium Aluminum Hydride (LiAlH_4) is a stronger reducing agent than sodium borohydride that can reduce all carbonyl compounds. Ketones are reduced to 2° alcohols; all other carbonyl compounds (aldehydes, esters, acids, acid chlorides) are reduced to primary alcohols.

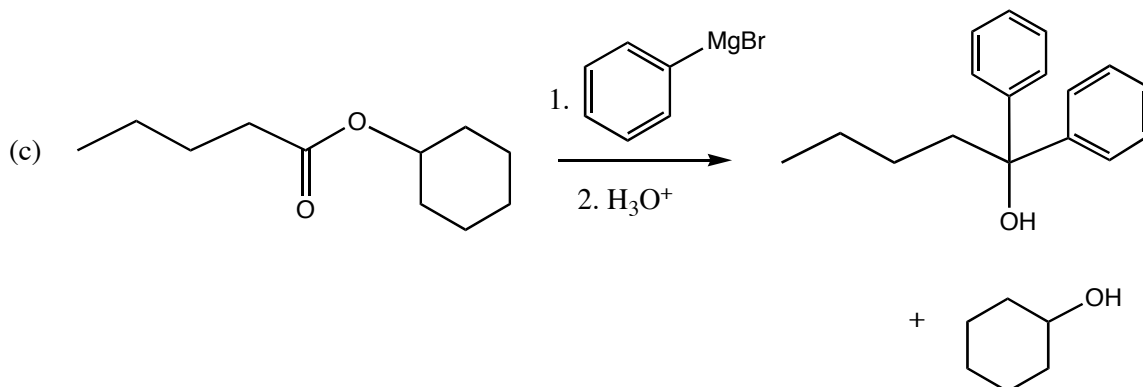
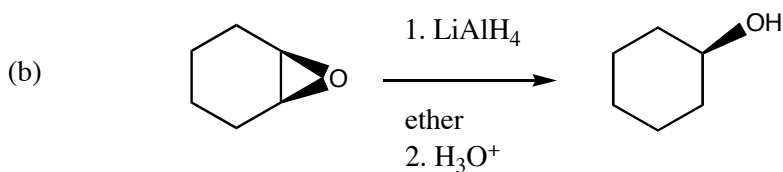
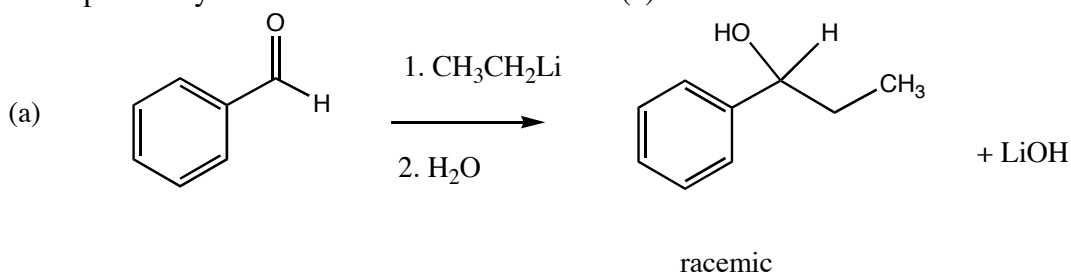


Catalytic hydrogenation with Raney Nickel allows one to directly deliver an equivalent of H_2 to a carbonyl to reduce it. Raney Nickel is an alloy of nickel and aluminum with hydrogen gas adsorbed on the surface; this reagent can reduce aldehydes, ketones, alkenes and alkynes indiscriminately.

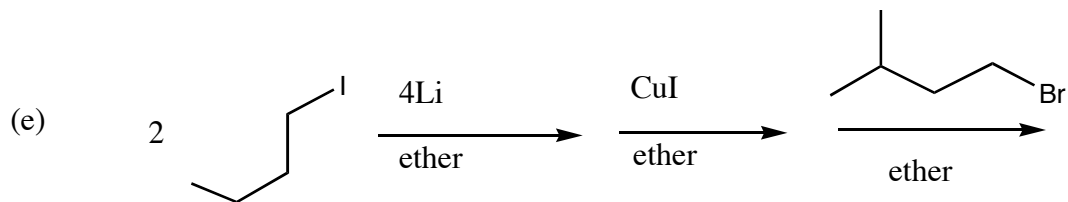
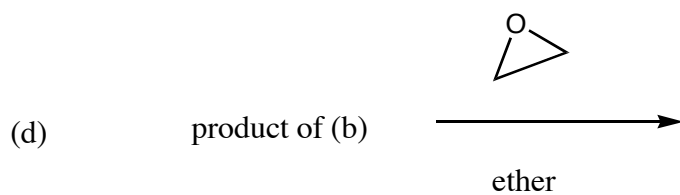
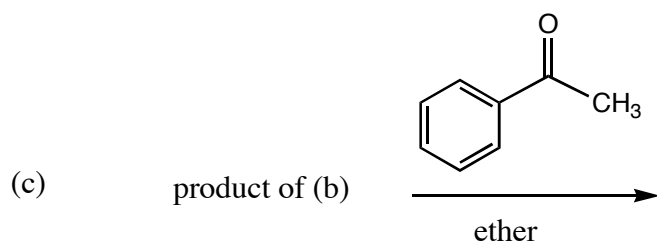
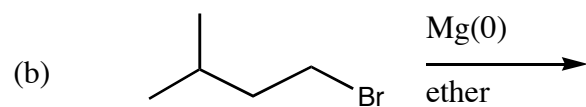
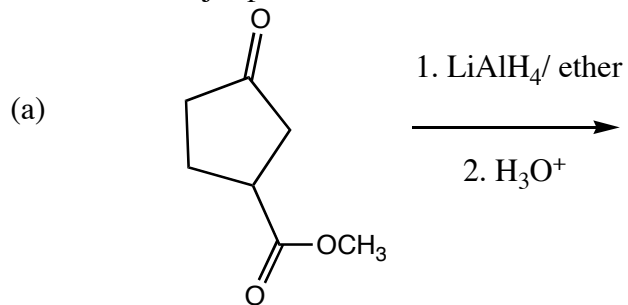


Additional Problems for practice:

1. Draw a mechanism for the following transformations, using the curved arrow notation to indicate the reorganization of electron density. Show all intermediates, unshared electrons, formal charges and countercharges where appropriate. Explain why a racemic mixture is formed in (a):



2. Write the major product of each of the following reactions:



3. Devise four different syntheses of 2-methyl-2-hexanol starting with each of the following compounds:

