

Alcohols

alcohol - any organic compound containing a hydroxyl (R-OH) group

uses:

alcoholic beverages

fuel

cosmetics

cleanser

synthetic intermediate

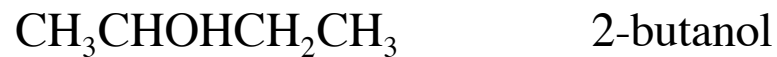
alcohols in short are an extremely important organic source

Nomenclature

- for an alcohol the longest continuous chain containing the hydroxy group determines the root name and then -ol is used as the suffix

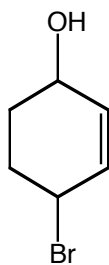


- to number the chain the hydroxy group takes priority to find the lowest number



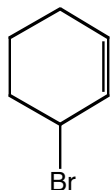
We have learned various substituents that can change priority in numbering

- alcohol has highest priority



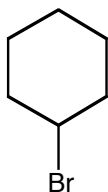
4-bromo-2-cyclohexen-1-ol

- alkenes have higher priority than halides



3-bromocyclohexene

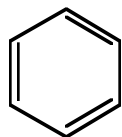
- if neither alcohol or alkene is present then substituent takes lowest number



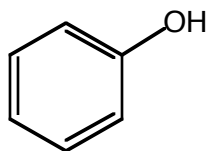
1-bromocyclohexane (1 is not required)

all other nomenclature is identical to that previously learned

- except when the hydroxy is attached to what is called an aromatic ring



benzene (called a phenyl group)



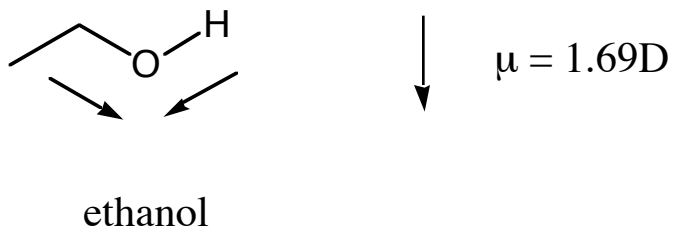
phenol (takes phenyl root with -ol suffix)

Physical Properties

there are two physical properties of alcohols that account for their behavior:
molecular dipole and hydrogen bonding ability

dipole

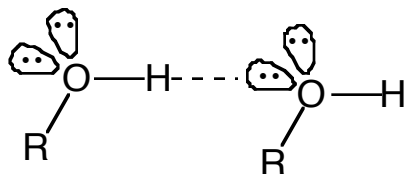
the electronegative oxygen causes the molecule to have a dipole moment



this high dipole-dipole interaction cause alcohols to have a higher affinity for states where
the dipoles can be aligned (therefore boiling point is higher)

dipole-dipole interactions are much weaker than hydrogen bonding interactions

a hydrogen bond is an interaction between a weakly acidic hydrogen and a lone pair of electrons on a different atom



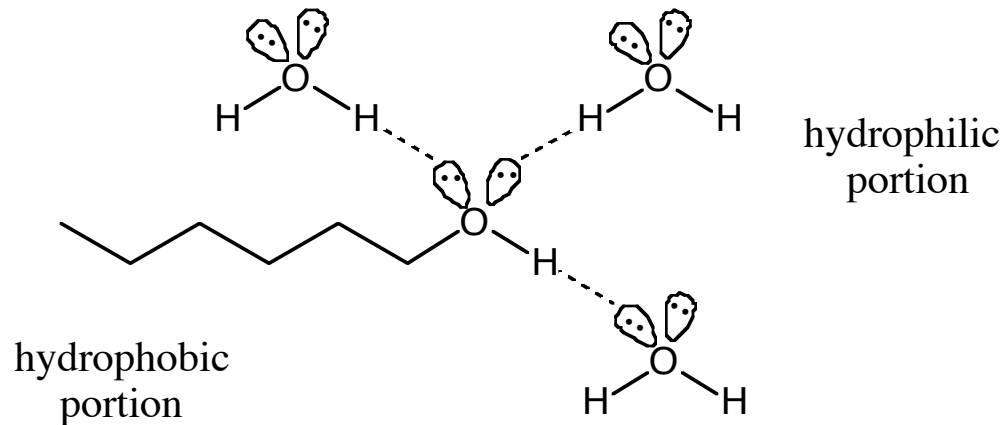
- each hydrogen bond has an energy of $\sim 4-5$ Kcal/mol

- this is much smaller than a covalent bond (O-H ~ 104 Kcal/mol) but a solution will have multiple hydrogen bonds that need to be broken to “escape” the liquid phase (i.e. causes a higher boiling point)

Due to this hydrogen bonding ability of alcohols they are both hydrophilic and hydrophobic

hydrophilic - “water loving”

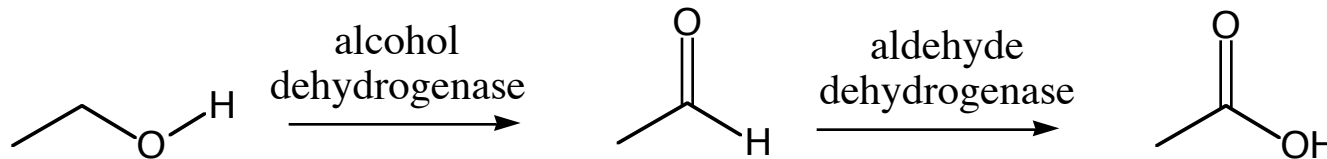
hydrophobic - “water hating”



due to this property alcohols have a high miscibility with water until the carbon chain becomes longer

Reasons why methanol is toxic yet ethanol is used for alcoholic beverages

ethanol (which is known to lower inhibitions and cause a lightheadedness)
is oxidized biochemically to acetaldehyde



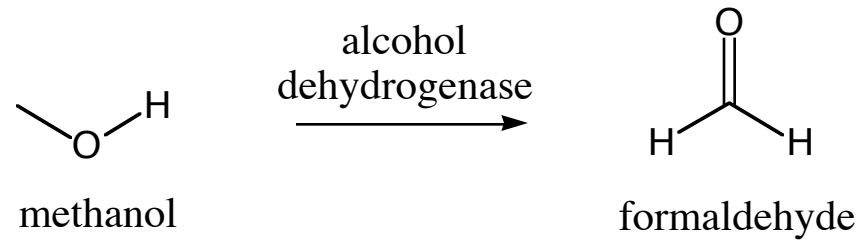
- the physiological side effects of consuming ethanol
are due to the buildup of acetaldehyde

(causes nausea, dizziness, sweating, headaches, lower blood pressure)

some people have a nonfunctioning aldehyde dehydrogenase enzyme

- these people experience the side effects of acetaldehyde with low ethanol consumption

Methanol also gets oxidized by the same enzyme



- but this oxidation creates formaldehyde NOT acetaldehyde

formaldehyde is toxic to the body because it disrupts other essential enzymes from working properly

- ethanol is consumed 25X faster than methanol by this enzyme

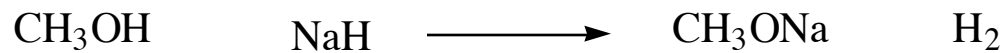
Acidity of Alcohols

- the alcohol O-H bond is weakly acidic

we have seen uses of alkoxides in substitution reactions

CH_3ONa sodium methoxide

the alkoxides can be generated by reaction of the alcohol with sodium hydride



the acidity of the alcohol changes depending upon substitution

- extending the alkyl chain raises the pKa

	pKa
CH ₃ OH	15.5
CH ₃ CH ₂ OH	15.9

also increasing the branching increases pKa

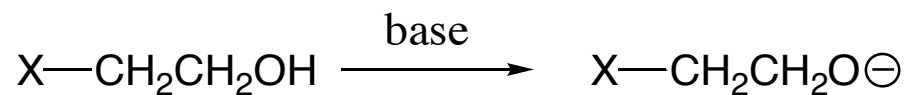
	pKa
(CH ₃) ₂ CHOH	17.1
(CH ₃) ₃ COH	18.0

both due to electron donating ability of methyl groups

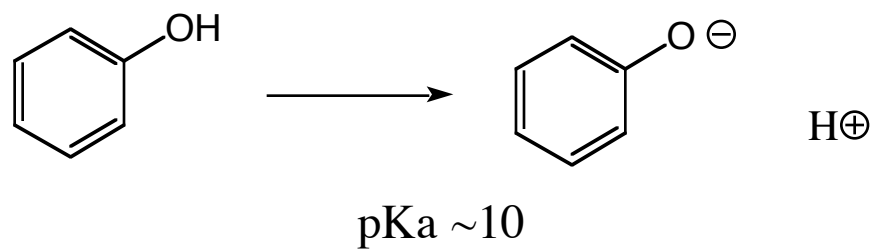
Placing an electron withdrawing group on alcohol will lower the pKa

	pKa
CH ₃ CH ₂ OH	15.9
ClCH ₂ CH ₂ OH	14.3
CF ₃ CH ₂ OH	12.4
CF ₃ CH ₂ CH ₂ OH	14.6
CF ₃ CH ₂ CH ₂ CH ₂ OH	15.4

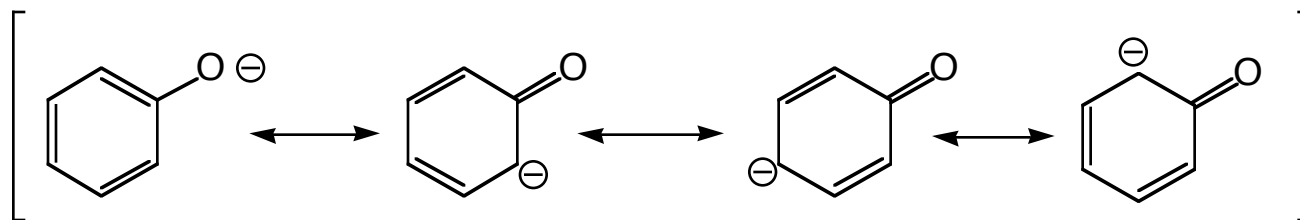
- again due to ability of electronegative atom to accommodate the increased electron density of the deprotonated form



Phenol is more acidic relative to other alcohols

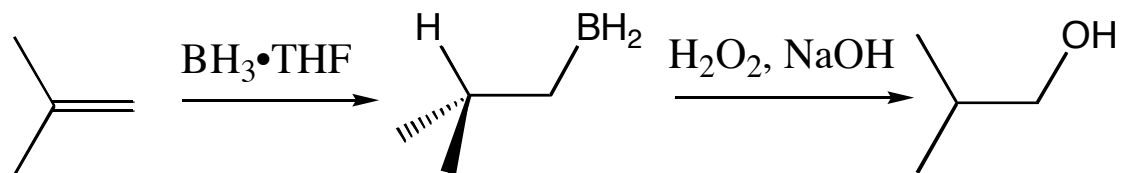
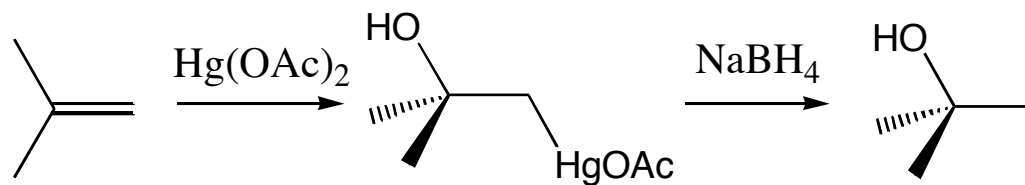
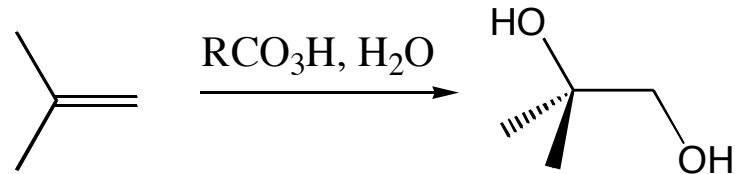
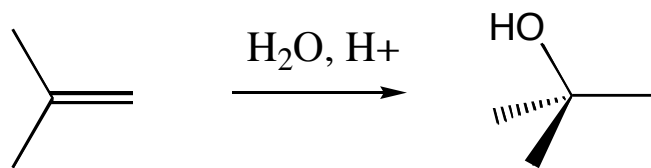
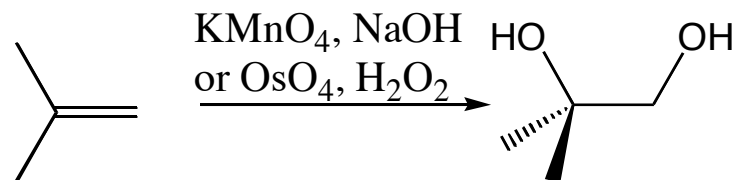
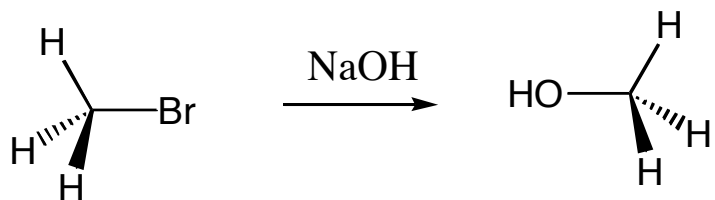


- due to the resonance forms of the phenolate which stabilizes the negative charge



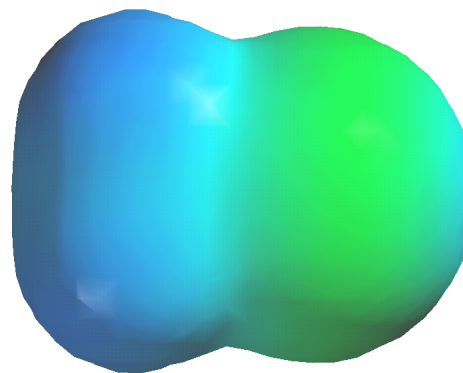
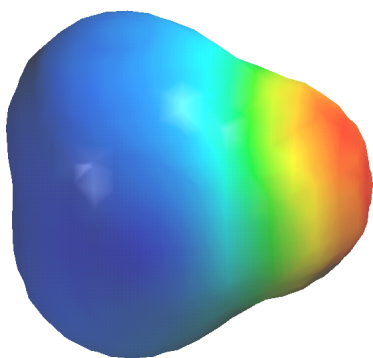
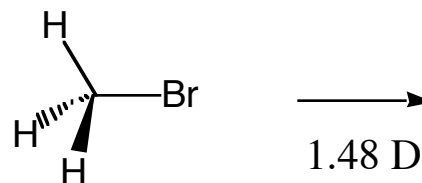
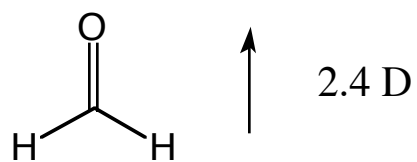
Synthesis of Alcohols

We have already learned many ways to synthesize an alcohol

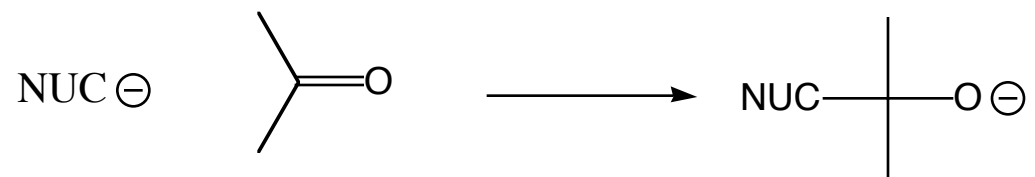


Another Route to Alcohols is an Addition to a Carbonyl Group

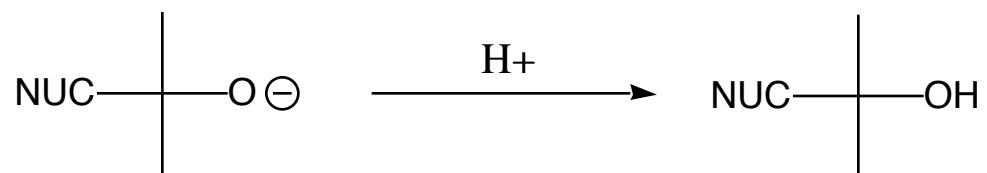
carbonyl carbons can act as an electrophilic site



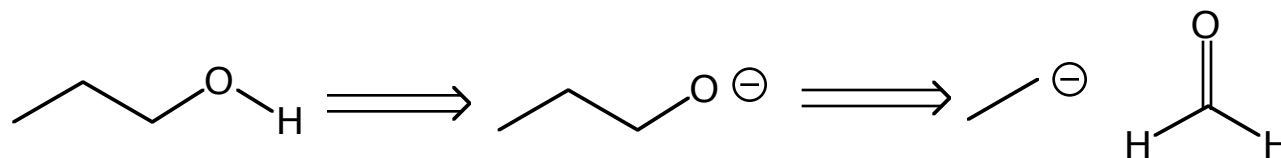
Addition to Carbonyl Creates an Alkoxide



work up in acidic medium will therefore create an alcohol



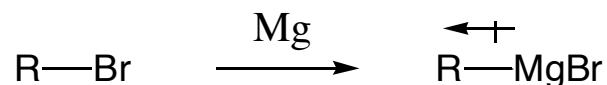
How do we create carbon based nucleophiles?



we need to create a polarized bond between carbon and another atom

there are two ways:

1) Grignard Reagents

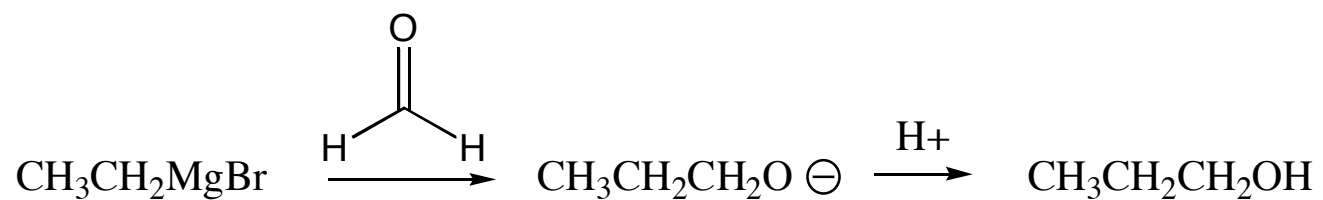
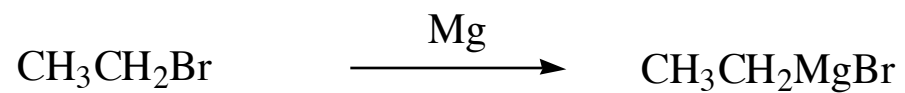


iodine is most reactive followed by bromine then chlorine
(fluorine is relatively nonreactive toward Grignards)

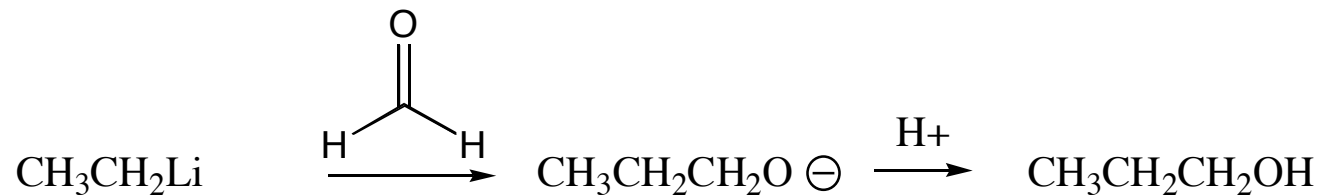
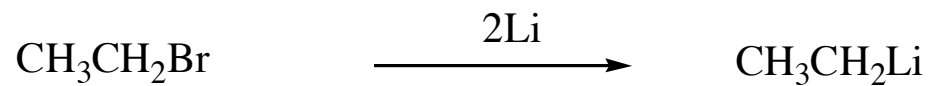
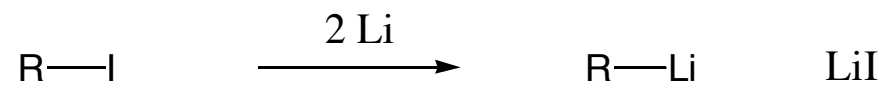
bond is polarized

acts like R⁻ +MgBr⁺

If a Grignard reagent reacts with a carbonyl then an alcohol is produced

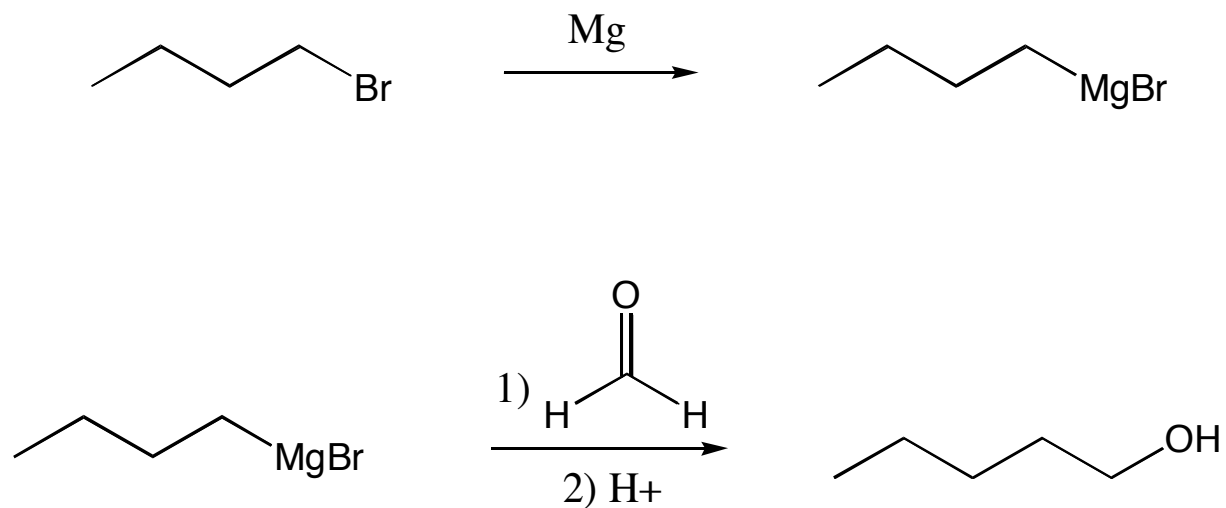


Second way to create polarized bond is to use an organolithium compound

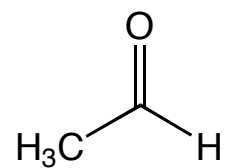


Grignard Reagents, or Organolithiums, to Create Alcohols

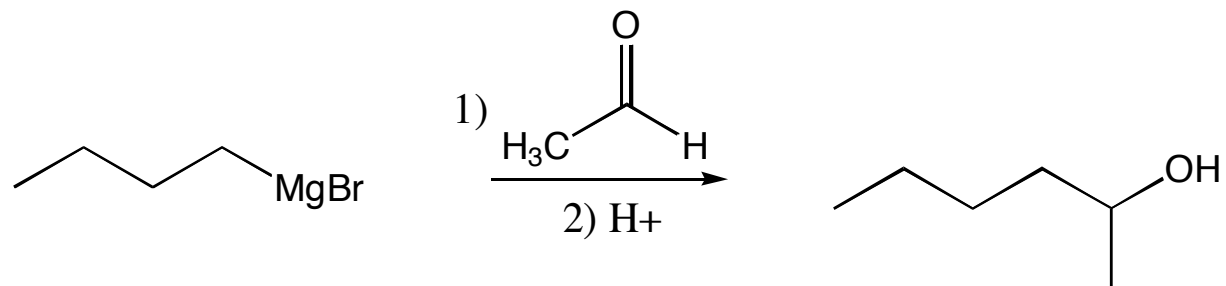
Already saw how reaction with formaldehyde will create a 1° alcohol that has one additional carbon than starting material



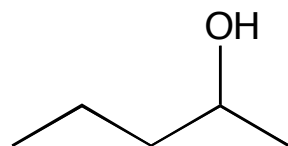
- if reaction is between a Grignard reagent and an aldehyde a 2° alcohol is obtained



acetaldehyde

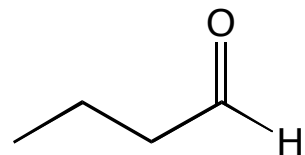
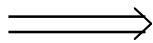
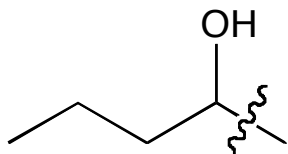
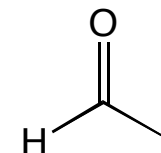
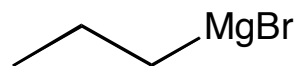
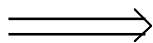
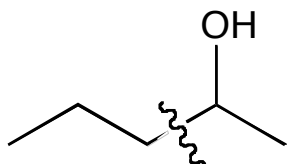


- a 2° alcohol can thus be prepared in two ways by a Grignard reagent



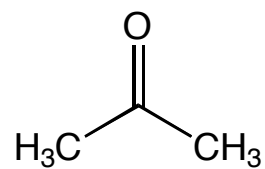
desired product
2-pentanol

the aldehyde can be used on either "halve" of the retrosynthetic analysis

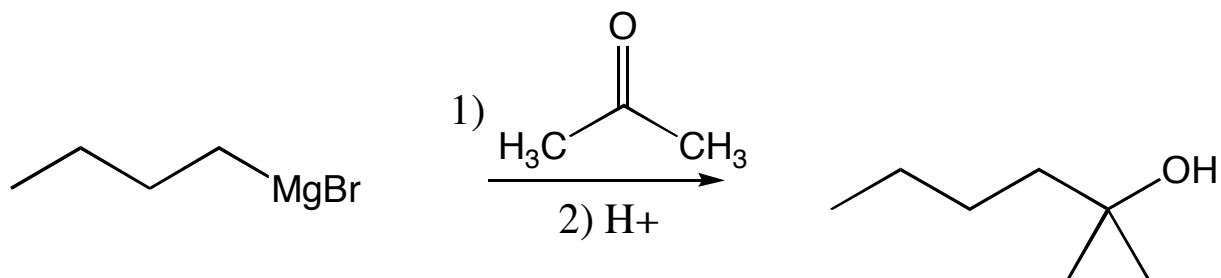


CH₃MgBr

Additionally, if Grignard reagent is reacted with a ketone a 3° alcohol is obtained

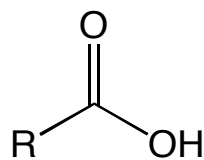


Acetone
(2-propanone)

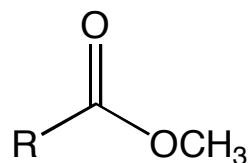


Acid Chlorides and Esters

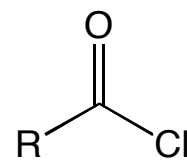
- if a carboxylic acid group is modified a Grignard reagent can react
(carboxylic acids will not react due to acid-base considerations)



carboxylic acid



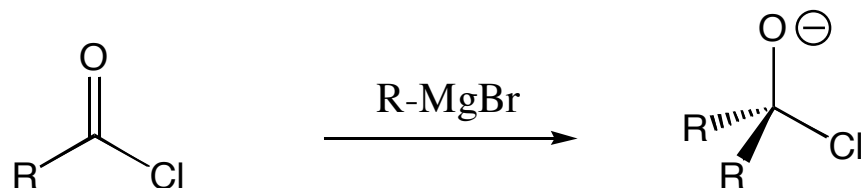
methyl ester



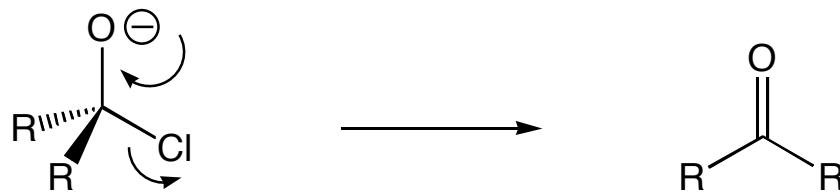
acid chloride

all three carbonyl derivatives can be interconverted
(will be covered in later chapter)

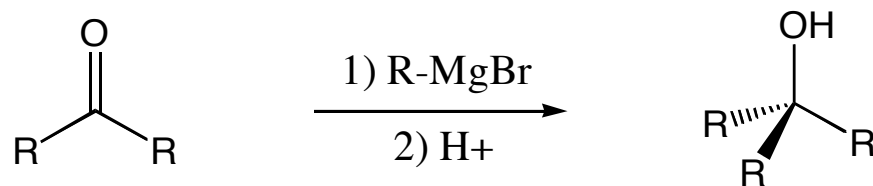
addition of one equivalent of Grignard reagent to an acid chloride (or ester)
creates a tetrahedral alkoxide with a good leaving group



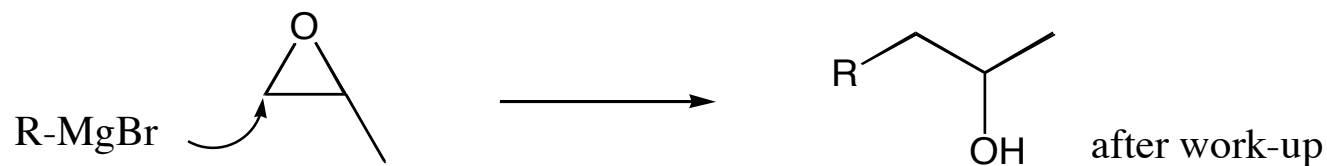
the chloride will leave to regenerate the carbonyl group



the generated ketone will react again with the Grignard reagent to create a 3° alcohol



Grignard reagents will also react with epoxides



the Grignard reacts in a S_N2 manner
therefore will react at least hindered carbon with inversion of configuration

generates an alcohol which is two carbons removed from Grignard

besides being good nucleophiles Grignard reagents and organolithiums
are STRONG bases

- carbon based anions (without resonance stabilization) have pKa values > 50

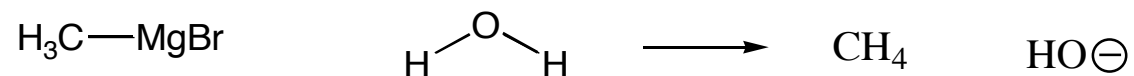
remember carboxylic acids have pKa of ~4 and alcohols ~16

follows directly from electronegativity trend

	$\text{H}_3\text{C}-\text{CH}_3$	$\text{H}_3\text{C}-\text{NH}_2$	$\text{H}_3\text{C}-\text{OH}$	$\text{F}-\text{H}$
pKa	~50	~36	~16	~3

due to this high basicity Grignard reagents CANNOT be used
with even weakly acidic compounds

equilibrium is driven by acid-base reaction



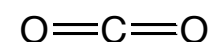
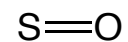
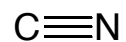
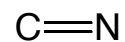
therefore NO alcohols or amines (or any labile hydrogens)
can be present anywhere in the molecule if a Grignard reaction is work

Another Problem: Grignard reagents are NOT selective

- since they are strong nucleophiles they will react with any electrophilic double bond
(reactivity versus selectivity)

this is good to react with carbonyl groups,
but if any other reactive groups are present they will also react

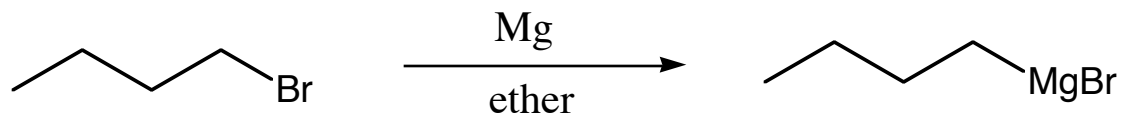
will react with various multiple bond structures



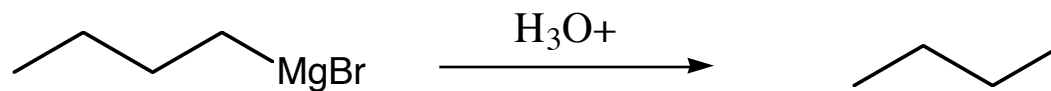
cannot react at one preferentially if more than one reactive site is present

One Effect of These Side Reactions:

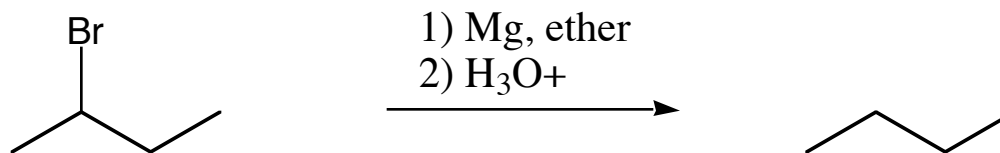
Grignard reactions can be used to reduce alkyl halides to alkanes



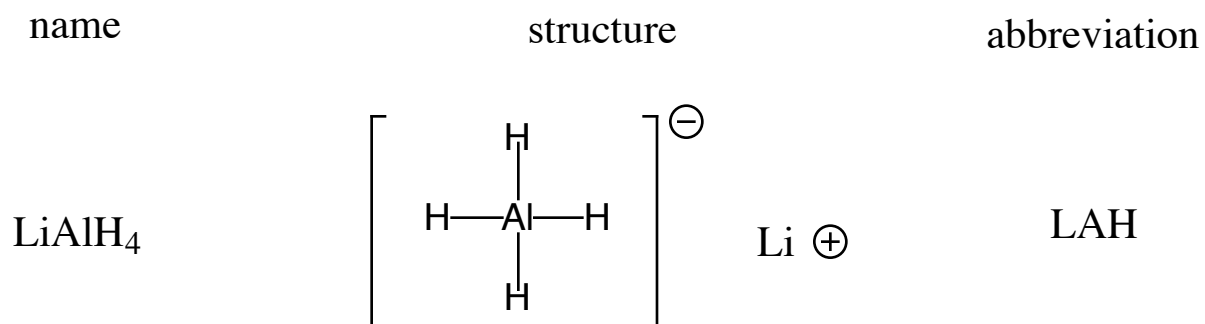
if an acidic hydrogen source is present an alkane is generated



therefore this represents a reduction of the alkyl halide

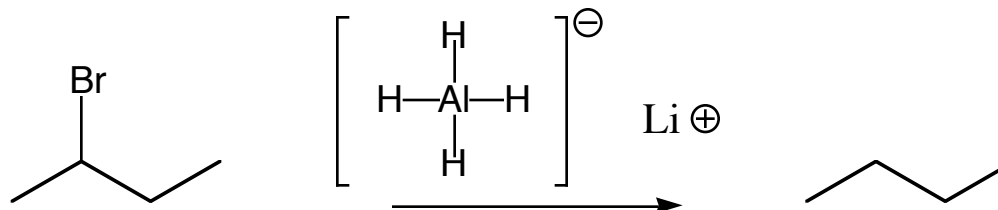


Another way to reduce alkyl halides is to use lithium aluminum hydride



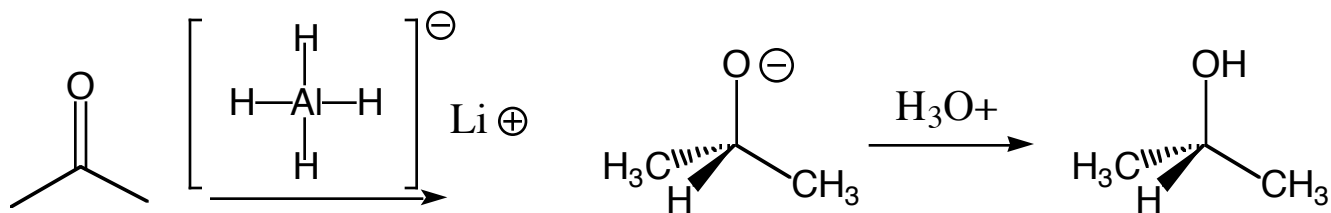
can consider LAH as a source of hydride (H^-) anions

- if LAH is reacted with an alkyl halide an alkane is formed



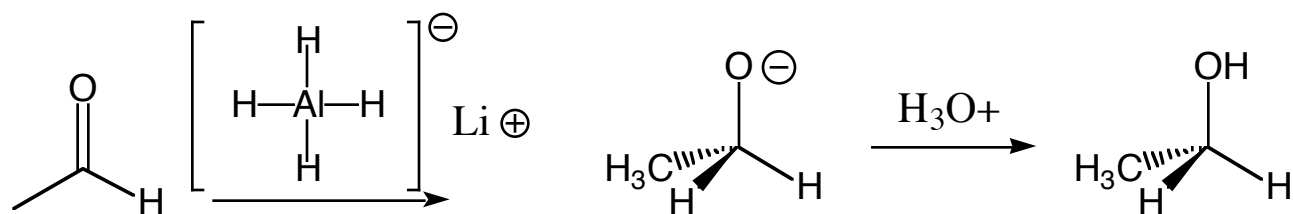
LAH can also be used to create alcohols

- the hydride anion can also act as a nucleophile with an electrophilic carbonyl group



therefore a ketone upon reaction with LAH creates a 2° alcohol

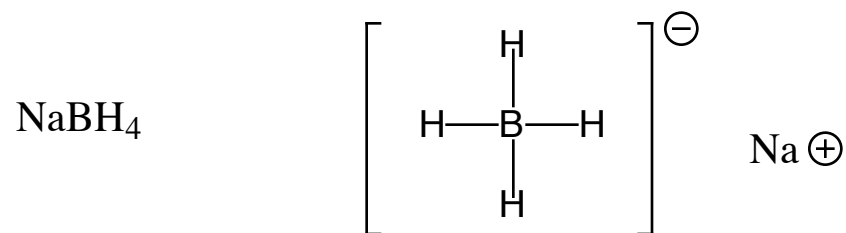
- likewise an aldehyde is reduced to a 1° alcohol with LAH



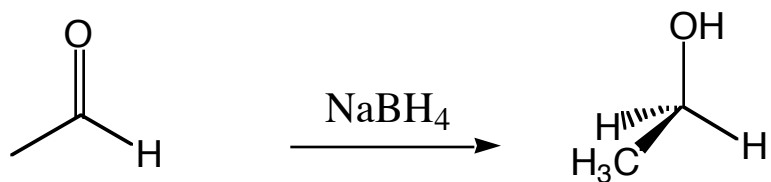
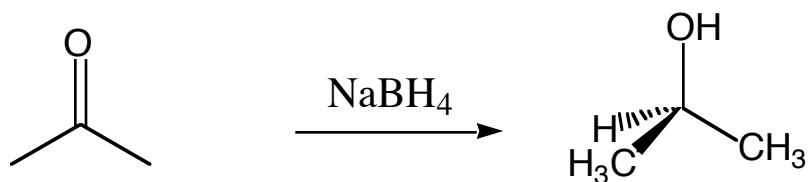
- in essence these reductions are adding hydrogen to both ends of the carbonyl bond
- both the carbon and oxygen of the original double bond are bonded to a new hydrogen

sodium borohydride will also reduce a ketone and aldehyde
to 2° and 1° alcohols, respectively

structure



since both boron and aluminum are in the same column of the periodic table
they share similar chemical properties

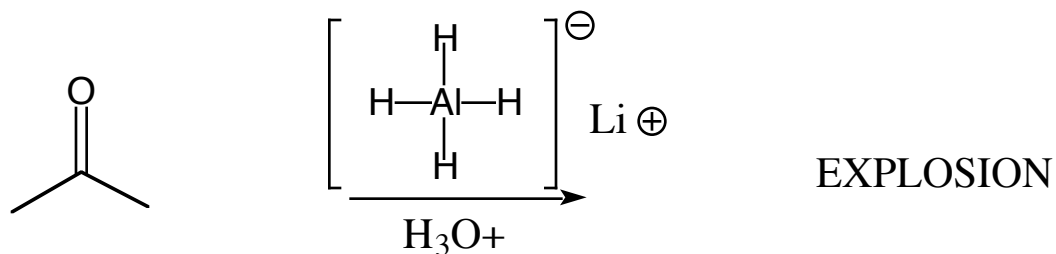


The reactivity increases down the periodic table

- therefore aluminum is more reactive than boron (LAH is more reactive than NaBH_4)

due to this increased reactivity LAH will not work in alcoholic or aqueous solvents

- it reacts with the solvent before reducing the carbonyl group

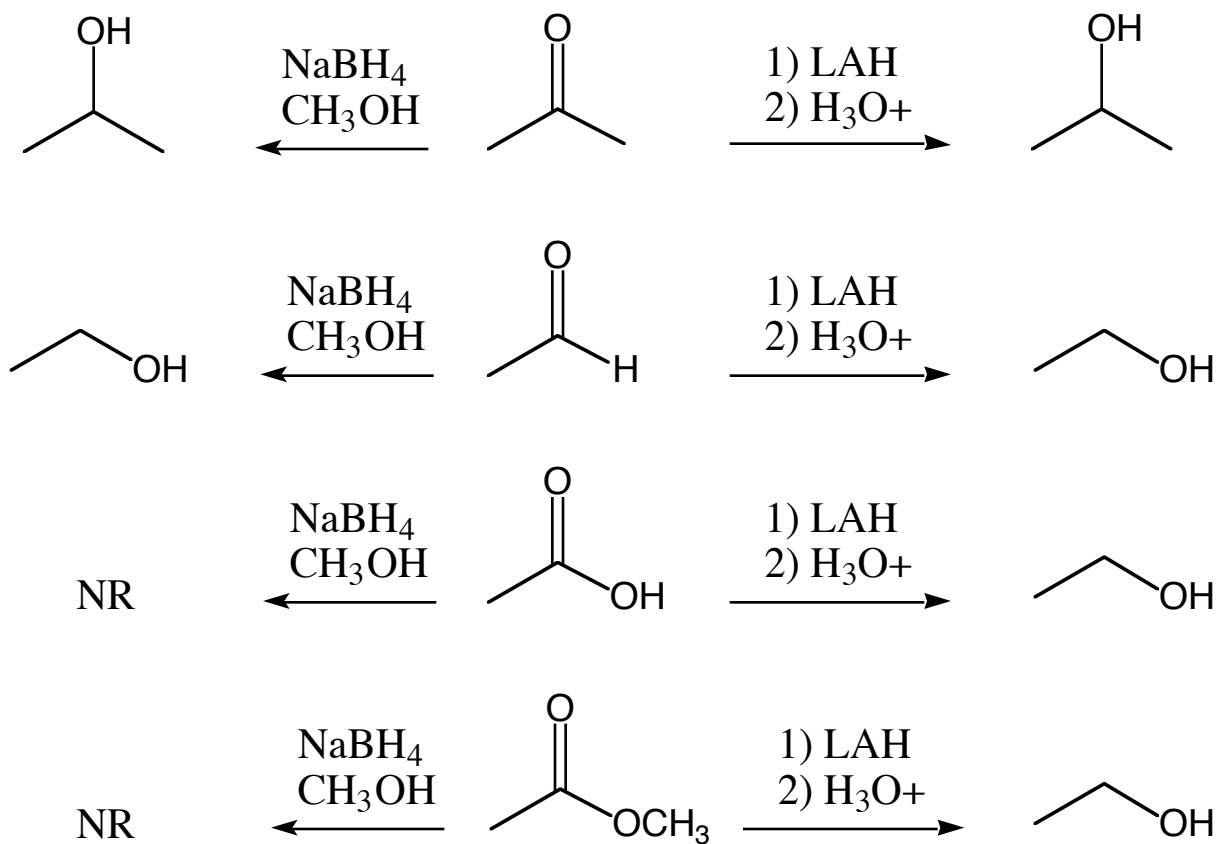


therefore need to work-up LAH reactions in a SECOND step

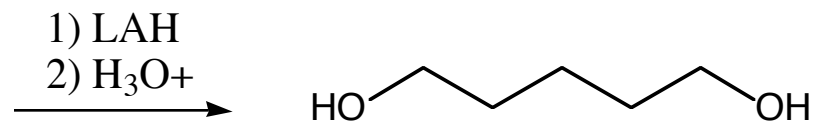
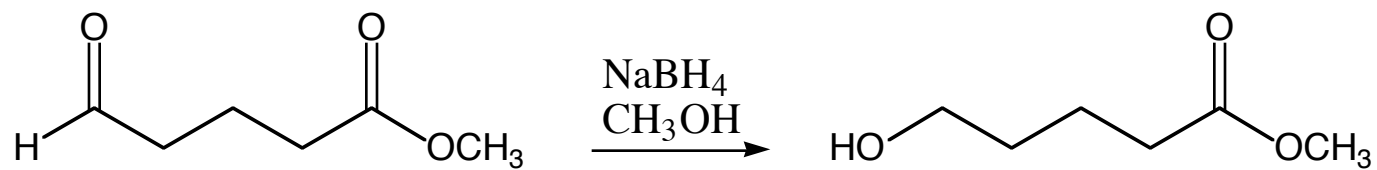
this is not true with NaBH_4

- these reactions CAN occur in alcoholic solvents

due to the increased reactivity LAH can reduce other carbonyl functional groups
which NaBH_4 cannot



Sodium Borohydride (NaBH_4) is thus more Selective than LAH

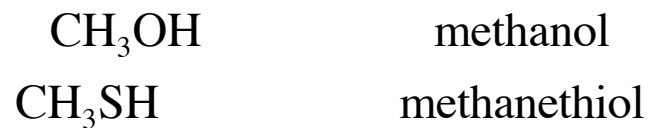


THIOLS

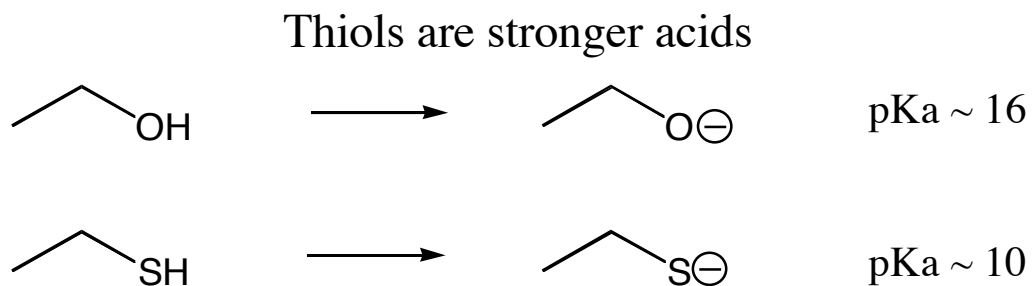
similar to the chemistry of alcohols
(sulfur is in the same column as oxygen)

- nomenclature

follow the same rules as learned for alcohols but use -thiol suffix instead of -ol

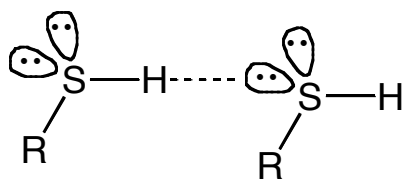


Differences Between Alcohols and Thiols



Due to charge being placed on more polarizable sulfur and a weaker S-H bond

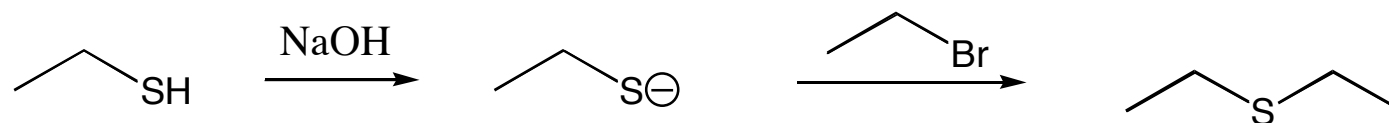
Thiols have less hydrogen bonding than alcohols



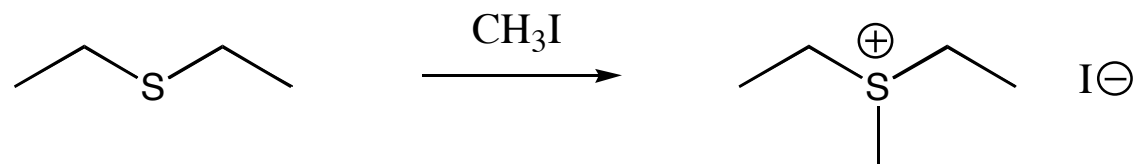
Due to sulfur being less electronegative than oxygen

Thiolate anions are more nucleophilic than alkoxide anions

Due to the more polarizable sulfur, and bigger atom which results in less solvation in protic solvents, the thiolate is more nucleophilic than an oxygen anion

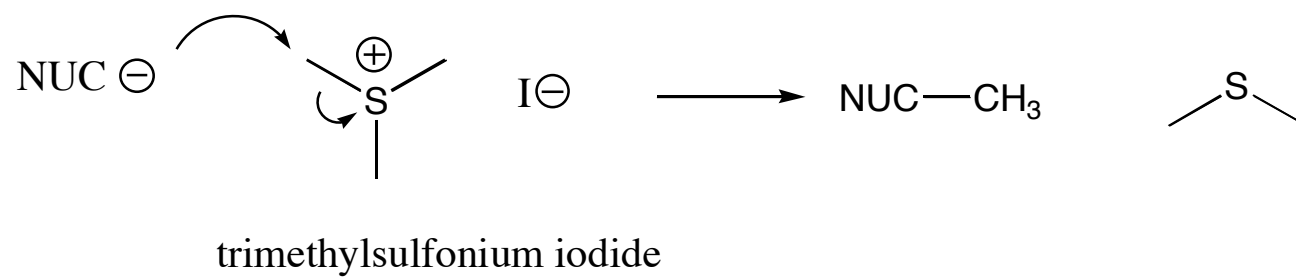


this increased nucleophilicity allows the formation of sulfonium salts

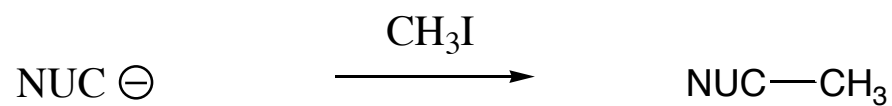


same process does not occur readily with ethers

Sulfonium salts are used as alkylating agents



similar to S_N2 reactions observed with methyl halides

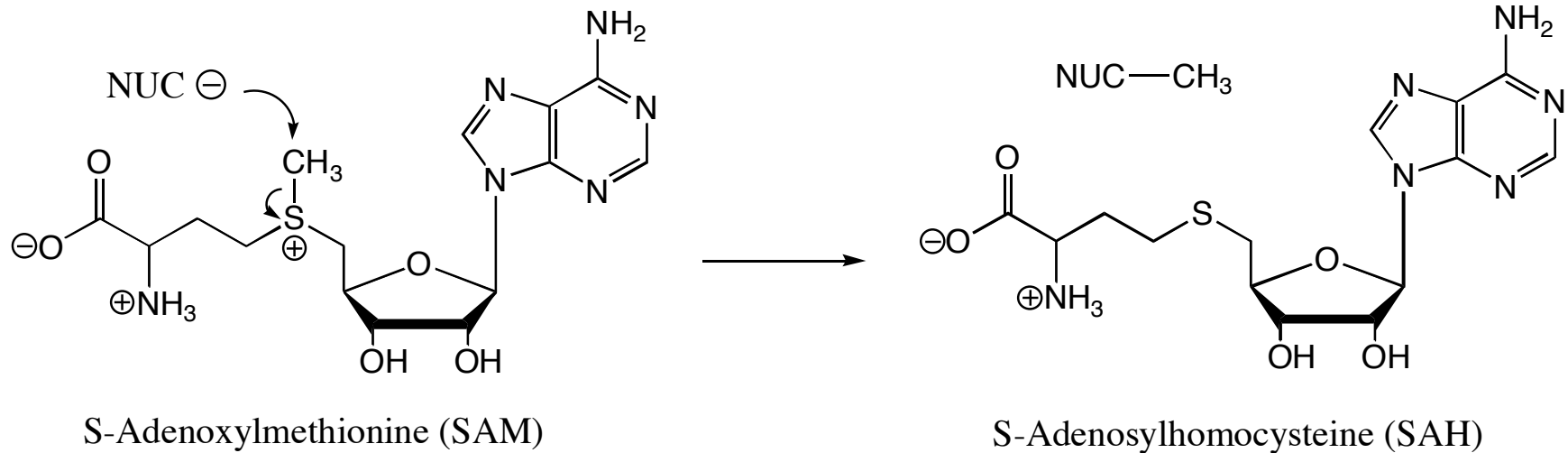


These sulfonium salts are used as methylating agents biologically

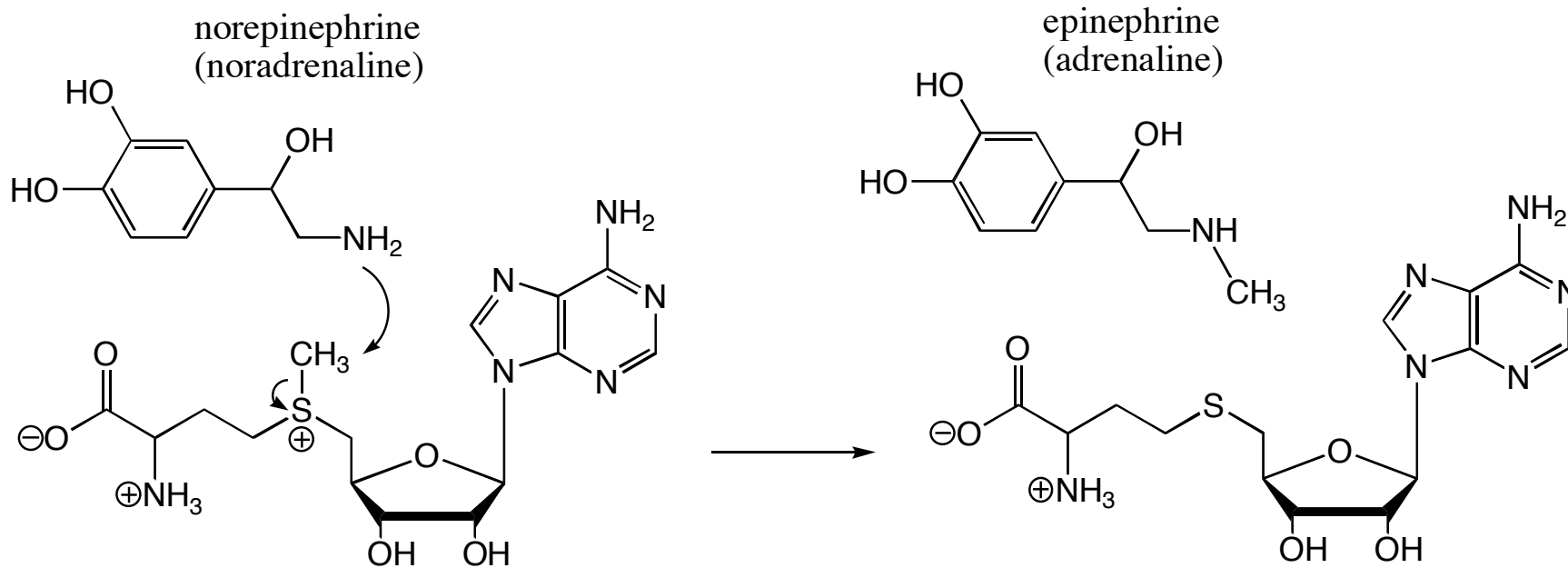
Methyl iodide cannot be used in living cells

-low water solubility and too reactive (will react nonselectively with amines)

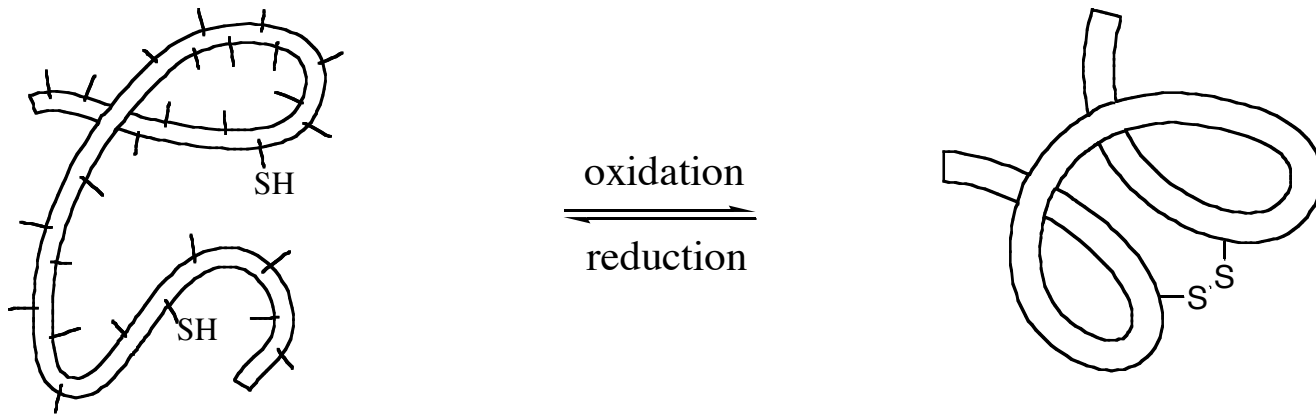
common methylating agent in living cells is S-Adenosyl methionine (SAM)



One example:
Conversion of norepinephrine to epinephrine



The formation of the disulfide bridge can change the properties of the protein



A cosmetic application of disulfide bridges

Human hair consists of a protein (keratin) that contains a large percentage of cysteine
(~ 4 times the amount found in other proteins)

The cysteine forms disulfide bonds to keep the hair in a particular shape

To change the shape:

A reducing agent is applied which breaks the disulfide bonds

The hair is rearranged into a desired shape (curlers or combing)

An oxidizer is added to maintain the new shape of the hair

To change straight hair to curly this is called a "permanent"

To change curly hair to straight this is called a "hair straightening"