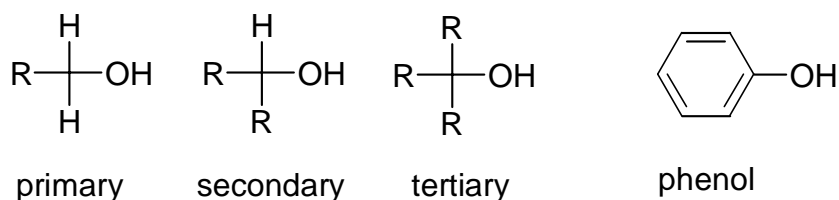


Synthesis and Structure of Alcohols

Alcohols can be considered organic analogues of water.



Alcohols are usually classified as primary, secondary and tertiary.



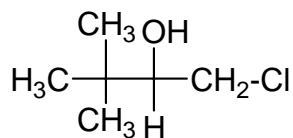
Alcohols with the hydroxyl bound directly to an aromatic (benzene) ring are called phenols.

Nomenclature of Alcohols

(Normally any compound's name which ends in -ol is an alcohol of some sort)

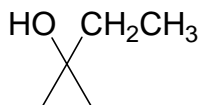
IUPAC rules that:

- (1) Name the longest carbon chain bearing the -OH group. Drop the last -e from the alkane name and add -ol to obtain the root name.
- (2) Number the longest chain starting at the end nearest the -OH group, and designate a number for the -OH group. (Hydroxyl has greater priority than carbon-carbon multiple bonds).
- (3) Name the remaining substituents and their numbers as for alkanes and alkenes.



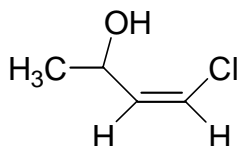
1-chloro-3,3-dimethyl-2-butanol

- (4) Cyclic alcohols have the prefix cyclo-, and the hydroxyl group is deemed to be on C-1.



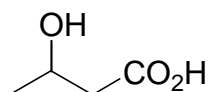
1-ethylcyclopropanol

- (5) Alcohols with double or triple bonds are named using the –ol suffix on the alkene or alkyne name. Numbering gives the hydroxyl group the lowest possible number. When numbers are also given for the multiple bond position, the position of the hydroxyl can be written immediately before the –ol prefix.



(Z)-4-chloro-3-buten-2-ol

- (6) If the hydroxyl group is only a minor part of the structure, it may be named as a hydroxy- substituent.

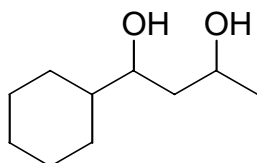


3-hydroxybutanoic acid

Nomenclature of Diols (Gycols)

Diols are compounds with two hydroxyl groups.

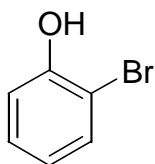
They are named as for alcohols except the suffix –diol is used and two numbers are required to locate the –OH's.



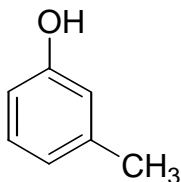
1-cyclohexyl-1,3-butanediol

Nomenclature of Phenols

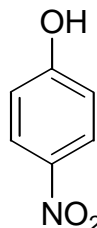
A phenol always involves a benzene (type) ring, and often the terms ortho, meta and para (meaning 1,2 disubstituted, 1,3 disubstituted and 1,4 disubstituted respectively) are used. These terms are non-IUPAC though.



2-bromophenol
ortho-bromophenol



3-methylphenol
meta-methylphenol



4-nitrophenol
para-nitrophenol

Solubility of Alcohols

The hydroxyl groups in alcohols can form hydrogen bonds with water, and many low molecular weight alcohols are miscible with water.

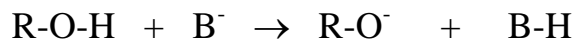
Alcohols are more polar than hydrocarbons, and are better solvents for polar substances. (E.g. NaCl is partially soluble in Ethanol).

The Hydroxyl group is said to be **hydrophilic** (water loving), whereas the alkyl (hydrocarbon) end is **hydrophobic** (water hating).

Alcohols will also dissolve in hydrocarbon solvents.

Acidity of Alcohols and Phenols

Just like water, the hydroxyl groups in alcohols are weakly acidic – strong bases can generate alkoxide ions.

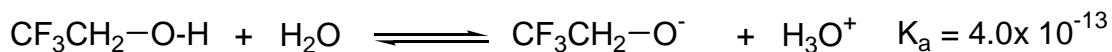
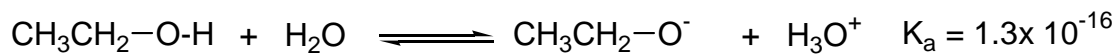


The acidities of alcohols vary greatly, depending on the substituents.

Alcohol		pK _a
Methanol	CH ₃ -OH	15.5
Ethanol	C ₂ H ₅ -OH	15.9
2-chloroethanol	Cl-C ₂ H ₄ -OH	14.3
2,2,2-trifluoroethanol	CF ₃ CH ₂ -OH	12.4
t-butylalcohol	(CH ₃) ₃ C-OH	19.0
cyclohexanol	C ₆ H ₁₁ -OH	18.0
phenol	C ₆ H ₅ -OH	10.0
water	H-OH	15.7
acetic acid	CH ₃ CO-OH	4.8
hydrochloric acid	H-Cl	-2.2

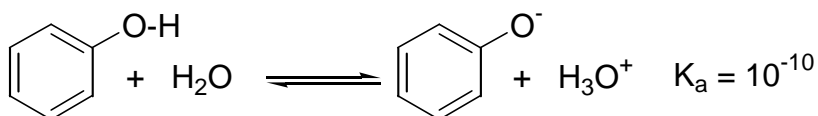
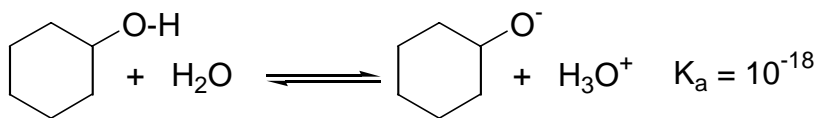
(Lower pK_a is stronger acid).

Notice that electron withdrawing groups on an alcohol increase the acidity by stabilizing the alkoxide formed.

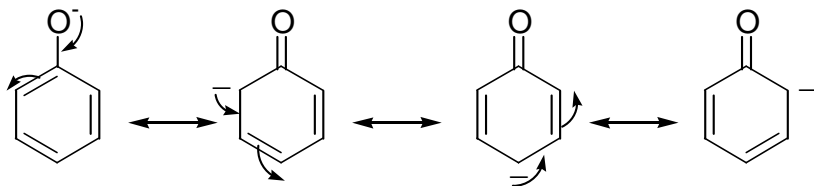


Acidity of Phenols

Cyclohexanol and phenol are similar in structure, yet their acidities are very different. (Phenol is 10⁸ more acidic).



The phenoxide ion has resonance stabilization since the negative charge can be delocalised over 4 atoms (3 carbons and 1 oxygen), making it more stable.



Phenols are **more acidic** than related alcohols.

Syntheses of Alcohols

Previously seen:

Nucleophilic substitution of alkyl halide with HO^-

Acid catalyzed hydration of alkenes

Oxymercuration-demercuration

Hydroboration-oxidation (anti-Markovnikov)

Hydroxylation gives diols (syn – OsO_4 : anti – epoxidation-hydrolysis)

Organometallic Reagents for Alcohol Synthesis

When a compound has a covalent bond between a carbon and a metal, it is called an **organometallic** compound.

The two most common types of organometallic are Grignard reagents and organolithium reagents (although there are a variety of others, Cu, Cd, Zn, Hg, etc).

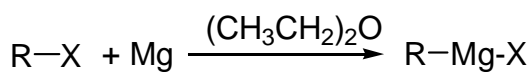


A carbon metal bond is polarized with significant negative charge on the carbon because metals are so **electropositive**.

These compounds will have nucleophilic carbon atoms.

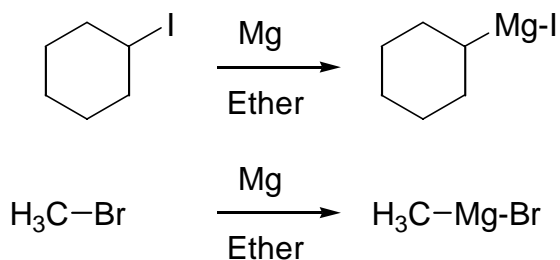
Grignard Reagents

These are of the formal type R-Mg-X where X is usually Br or I.



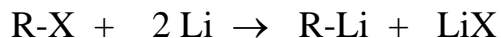
They are made via the reaction of metallic Mg with the corresponding alkyl halide, usually in ether type solvents.

This reaction is versatile; primary, secondary and tertiary alkyl halides can be used, and also vinyl, allyl and aryl halides.



Organolithium Reagents

These are also formed via action of the metal with an alkyl halide.

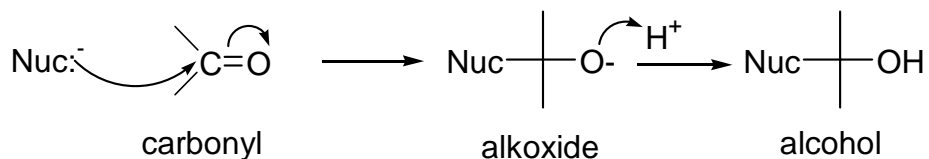


Unlike Grignard reagents, alkyl lithiums can be prepared and used in a variety of hydrocarbon solvents (hexane, pentane etc).

Reaction with Carbonyl Groups

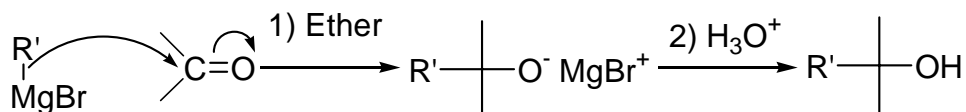
Nucleophilic addition of organometallics to the carbonyl (C=O) group is a versatile and useful synthetic reaction.

The carbonyl group is strongly polarized, with the oxygen bearing partial negative charge and the carbon bearing partial positive charge – the carbon is electrophilic, and therefore attacked by nucleophiles.



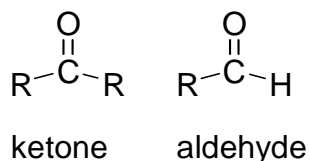
The attack of a nucleophile on a carbonyl group generates an alkoxide ion, which is usually protonated in a separate subsequent step.

A Grignard (or alkyl lithium) can function as this nucleophile.



The Grignard reagent adds to the carbonyl, and then is protonated in a separate step.

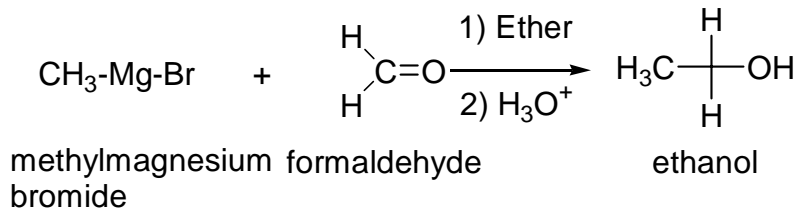
Ketones and Aldehydes



Ketones are compounds that have two alkyl groups bound to the carbonyl functionality.

Aldehydes have one alkyl group and one hydrogen bound to the carbonyl.

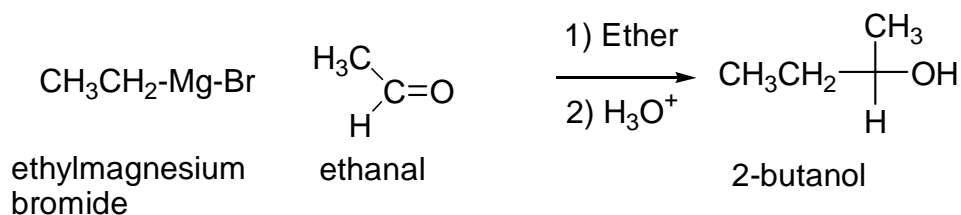
Formation of Primary Alcohols



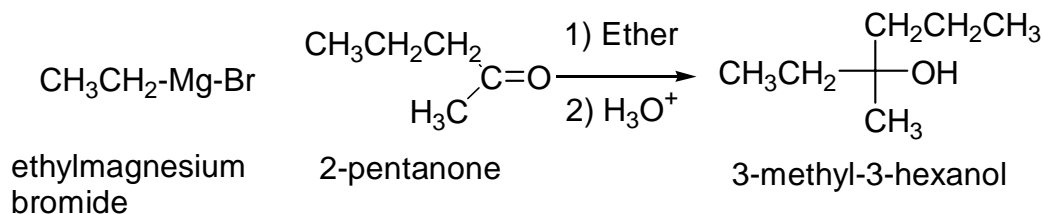
Formaldehyde is the simplest aldehyde, and reaction with a Grignard reagent generates a primary alcohol, which contains one more carbon atom than the original Grignard reagent.

Formation of Secondary Alcohols

Reaction of an **aldehyde** with a Grignard reagent generates a secondary alcohol.



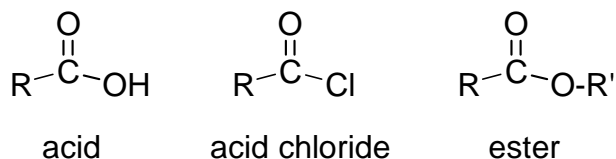
Formation of Tertiary Alcohols



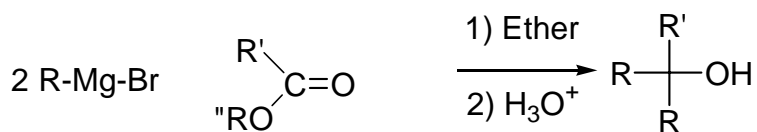
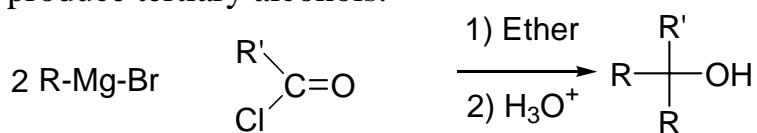
This can be achieved by reaction of a Grignard with a **ketone**.

Acid Derivatives

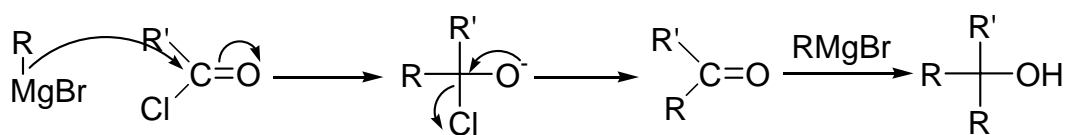
Acid chlorides and esters are derivatives of carboxylic acids, where the –OH group is replaced either by a chlorine atom or an alkoxy group.



Acid chlorides and esters react with two equivalents of Grignard reagents to produce tertiary alcohols.



The addition of the first Grignard produces a tetrahedral intermediate which is unstable.

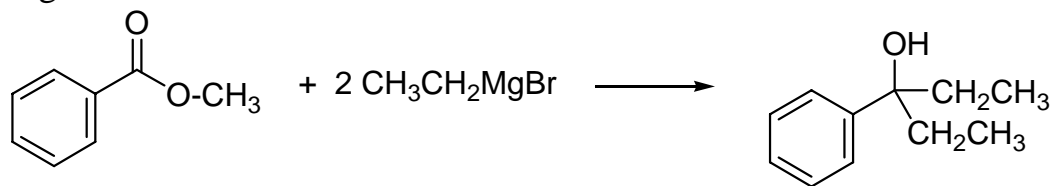


The leaving group is expelled (either chloride or alkoxide) as the carbonyl group is reformed, and a ketone is produced.

The ketone then reacts with the second equivalent of Grignard to give a tertiary alcohol (as before).

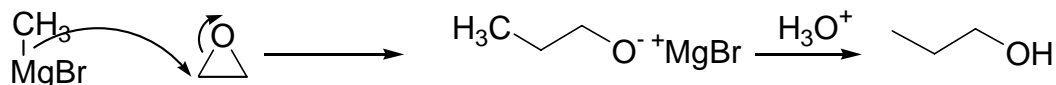
This is a good route to making tertiary alcohols with two identical alkyl substituents.

E.g.

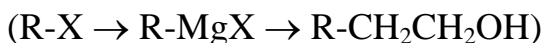


Addition to Ethylene Oxide

Normally ethers do not react with Grignards (use as solvents), but ethylene oxide is a strained ether (epoxide), and the epoxide ring is opened by Grignards.



After protonation, the final product is a primary alcohol with two additional carbon atoms.



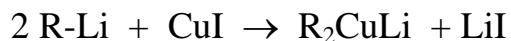
Other Selected Organometallic Reactions

Corey-House Reaction

This is a good synthetic way to join two alkyl groups together.



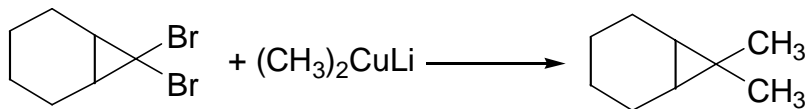
A lithium dialkylcuprate reacts with an alkyl halide.



The lithium dialkylcuprate is formed using the alkyllithium reagent and copper (I) iodide.

Coupling reactions of this type are very common (and useful) in organic synthesis.

E.g.

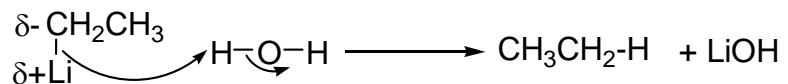


Reduction of Organometallic Reagents

Organometallics are generally strong nucleophiles and bases – this is both a blessing and a curse.

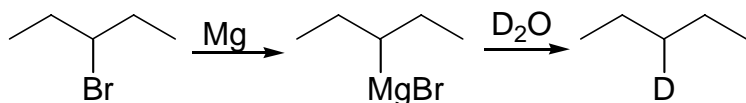
Acidic Compounds

Organometallic compounds react with water (moisture).



Ethyllithium reacts with water to form ethane and Lithium hydroxide. Often small amounts of water (humid air) can destroy hard earned organometallic compounds.

It is a convenient way to reduce an alkyl halide to an alkane. (R-X → R-H)

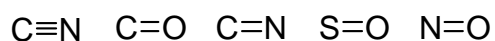


The use of Grignards and deuterium oxide (D₂O) is a useful way to incorporate Deuterium into an organic molecule. (R-X → R-D)

Besides –OH groups, other acidic groups like N-H and S-H cannot be tolerated by organometallics.

The terminal C-H of alkynes is also sufficiently acidic to be deprotonated by organometallics.

These groups are considered incompatible with organometallics.

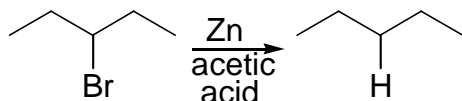


Other groups that are incompatible with Grignards have multiple bonds involving electronegative elements since these are also attacked by organometallics.

Other Reductions of Alkyl Halides

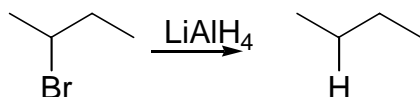
A combination of metals and acids can be used to reduce alkyl halides to alkanes.

E.g.



Hydride Reductions

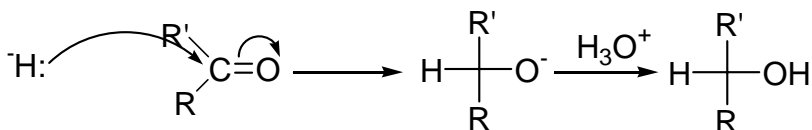
Lithium aluminum hydride (LiAlH_4) is a strong reducing agent, and will reduce alkyl halides to alkanes.



Essentially a hydride ion, ($:\text{H}^-$) acts as a nucleophile displacing the halide.

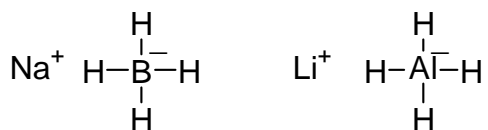
Syntheses of Primary and Secondary Alcohols (Carbonyl Reductions)

Hydride ions will attack carbonyl groups, generating alkoxide ions, and protonation furnishes alcohols.

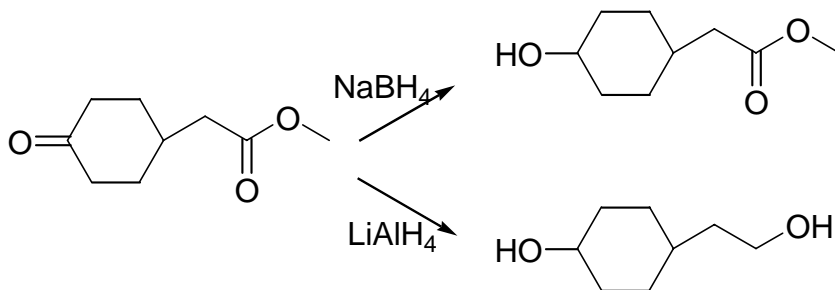


The conversion of ketones to alcohols involves the addition of H_2 across the $\text{C}=\text{O}$ bond – a reduction.

Complex hydrides are the source of hydride ions, and the two most commonly used reagents are sodium borohydride and lithium aluminum hydride.



Sodium borohydride is the gentler (more selective, safer) reagent of the two.



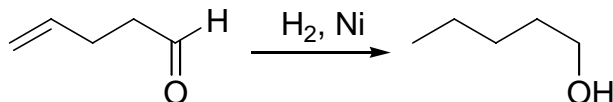
Sodium borohydride will not reduce esters or acids, whereas lithium aluminum hydride reduces esters and acids to primary alcohols.

These hydride sources do not reduce $\text{C}=\text{C}$ double bonds.

Catalytic Hydrogenation

Carbonyls can be reduced to alcohols by the addition of hydrogen across the double bond.

Usually a Raney Ni catalyst is employed.

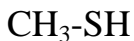


However, $\text{C}=\text{C}$ double bonds are reduced quicker than $\text{C}=\text{O}$ double bonds.

Thiols

Thiols are sulfur analogues of alcohols, they contain an $-\text{SH}$ group.

They are named using the suffix $-\text{thiol}$, and as a substituent as mercapto-.



Methanethiol



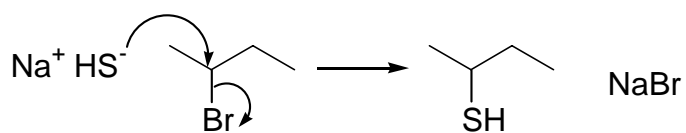
1-butanethiol



2-mercaptoethanol

Thiols stink, literally.

They are prepared by nucleophilic displacement of alkyl halides by the hydrosulfide ion.



Thiols (unlike alcohols) are easily oxidized to form disulfides. (Cysteine amino acid chemistry).

