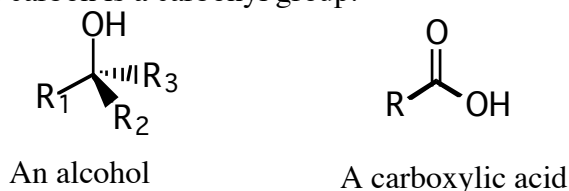


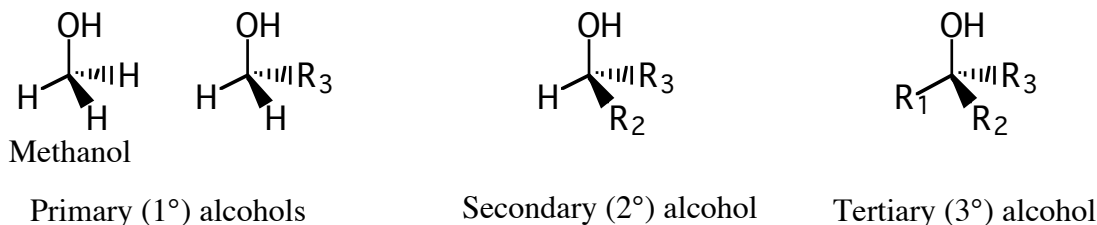
Alcohols and Thiols

Alcohols are one of the most important functional groups in Organic chemistry – alcohols can be easily converted to almost any other group by the application of the appropriate reagent(s).

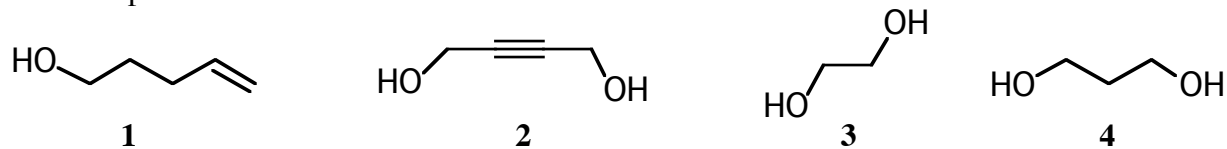
What is an alcohol? An alcohol is a hydroxyl group attached to carbon – the only exception being when that carbon is a carbonyl group:



Alcohols are often classified by the number of alkyl groups attached to the adjacent carbon. In other words (looking at the picture above), if $R_1=R_2=R_3=H$, or if $R_1=R_2=H$ and R_3 is alkyl, the alcohol is said to be primary. If $R_1=H$ and R_2 and R_3 are alkyl groups, the alcohol is secondary and if all the R groups are alkyl, the alcohol is tertiary:



The typical nomenclature rules apply to alcohols - where possible, the OH group should have the lowest number on the longest chain. Remember to keep *all* numbers as low as possible. For example:



Compound **1** is called 4-penten-1-ol, NOT 1-penten-5-ol.

In the case where there is more than one alcohol, you usually end the name with *diol*. Compound **2** is called 2-butyne-1,4-diol. Compound **3** *could* be called ethane-1,4-diol, and since it is derived from ethanol, it could also be called 2-hydroxyethanol (you'll actually find it named this way on some package labels - especially on cosmetics!). However, this compound has a common trivial name - ethylene glycol (yes, the main ingredient of antifreeze). Compound **4** is named in a similar way - propylene glycol. Can you guess the structure of butylene glycol?

Properties of Alcohols

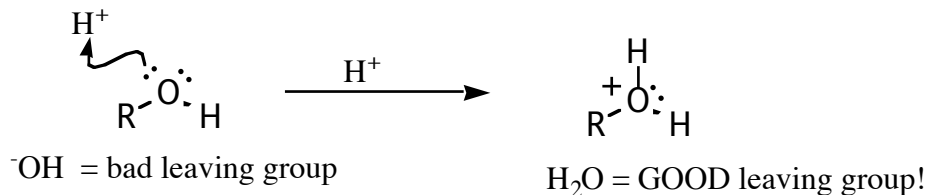
One of the most interesting properties of the alcohols is their ability to form a special kind of bond - the hydrogen bond.

Hydrogen bonds are not like normal covalent bonds (in fact, hydrogen bonding is called a noncovalent interaction) - these bonds are fairly easily broken, and re-formed. However, there is

a significant energy involved with this type of bonding, which causes the individual molecules to want to “stick” together. The most noticeable result is in the surprisingly high boiling points of small alcohols. Water, having *two* hydrogens on oxygen, is one of the simplest hydrogen-bonding molecules. If you splash a few drops of water on the countertop, and then splash some hexanes right next to it (in a hood! Actually, don't do this at all. Just imagine doing it. Yeah, that's it....), you'll notice that the hexanes will spread out evenly in a thin film, while the water “beads” on the surface. Why? The alkane feels no special attraction to other alkanes, and when put on a surface, it spreads to evenly cover the surface. Water, on the other hand, is much more attracted to other water molecules than any tabletop, and thus tries to *maximize* its contact with other water molecules, and *minimize* its contact with the tabletop *and* with the air. Thus, the spherical beads.

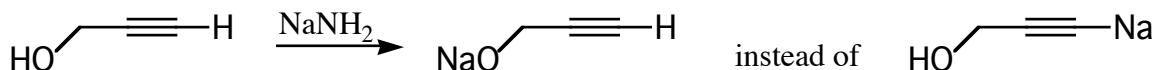
Alcohols also form these hydrogen bonds, although the interaction is not as strong as it is in water, and if the alkyl groups are significantly large, the hydrogen-bonding effect becomes negligible.

The oxygen of most alcohols is easily protonated in strong acids. This is a chemist's way of turning a bad leaving group (^-OH) into a good leaving group (H_2O).

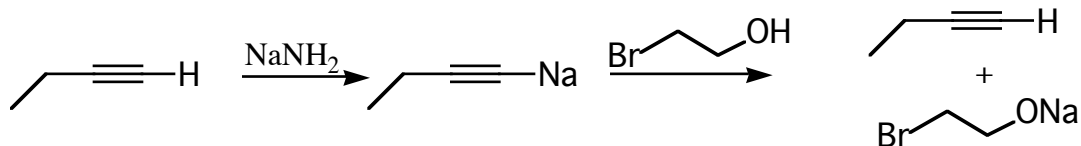


The alcoholic proton is also somewhat acidic. The pK_a for alcohols runs between 15 and 18 - certainly more acidic than your average alkyne! The general trend in acidity is $1^\circ > 2^\circ > 3^\circ$, with *t*-butanol being about the least acidic alcohol you'll find...this is why *t*-butoxide is used as a base in many of the reactions you've seen. Alcohols can be deprotonated by many of the strong bases you've seen, such as sodium hydride, sodamide, nearly *all* alkyl-metal compounds (e.g. methyl lithium, Grignard reagents, sodium acetylide). These are all good methods for the preparation of alkoxides (remember - chemical names ending in “ide” generally imply a negative charge. “oxide” thus means a negative charge on oxygen, “acetylide” means a negative charge on an acetylene, etc.). However, this also means that none of these reagents can be used for other purposes when there is an alcohol in the molecule. For example, you cannot deprotonate an acetylene with sodamide if there is an oxygen on the main molecule - alcoholic deprotonation will take place first! Some examples:

You cannot simply deprotonate the carbon of an alkyne containing an alcohol:



You cannot alkylate an alkyne with a compound containing an alcohol:

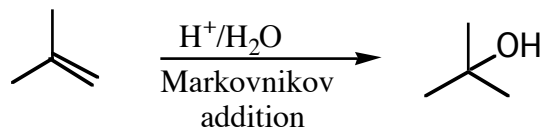


Preparation of Alcohols.

1) Alcohols from Alkenes

Hydration of an alkene:

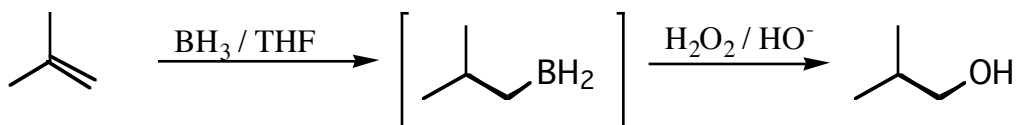
General Scheme: Water adds across a double bond in a Markovnikov fashion. Recall that a Markovnikov addition only applies when one of the alkene carbons has a hydrogen substituent. The carbon with the greater number of hydrogens is the one that picks up the proton! (i.e. them what gets, gets).



Hydroboration/Oxidation of an alkene:

Hydroboration/oxidation is a method for adding water to an alkene in an *anti*-Markovnikov fashion. This is complementary to the standard addition of water (and the outdated oxymercuration reaction):

General Scheme:

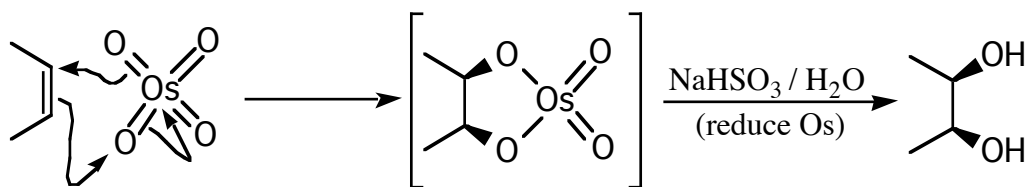


anti-Markovnikov addition

Syn-1,2-diols from Osmium Tetroxide.

Highly toxic osmium tetroxide (OsO₄) can be used to form a *syn* diol from an alkene. The diol ends-up *syn* because both of the oxygens come from the same metal, forming a 5-membered ring intermediate. Since the subsequent reduction (with bisulfite, NaHSO₃) occurs only on the metal, the resulting alcohols end up *syn*..

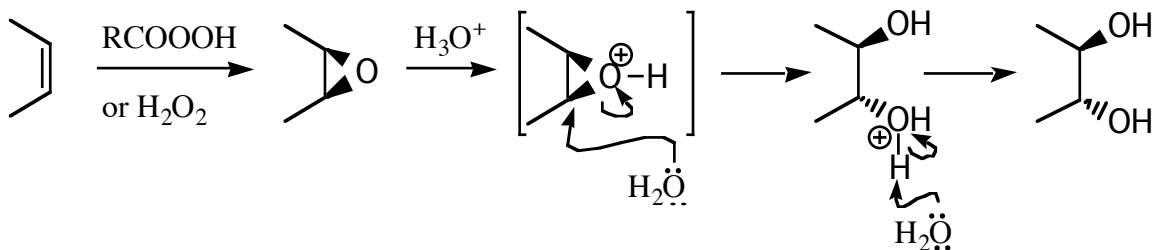
General Scheme:



Anti -1,2-diols from epoxides.

Later we will discuss the oxidation of alkenes to epoxides, a reaction cleanly performed by most *per*-acids or peroxides. Because of the nucleophile's requirement for backside attack, once this cyclic ether has been formed it is generally easy to open it to an *anti*-1,2-diol:

General Scheme:



2) Alcohols from Carbonyl Compounds:

Alcohols are more typically formed by the *reduction* of carbonyl compounds (and carbonyl compounds are formed by the *oxidation* of alcohols!) There are two main reagents used to reduce carbonyl groups. Sodium borohydride (NaBH_4) is a mild reagent, and can be used to reduce aldehydes and some ketones to the corresponding alcohol. Lithium Aluminum Hydride (LiAlH_4) is a much harsher reagent, but will take just about *any* carbonyl compound (aldehyde, acid, ester, ketone) to the corresponding alcohol.

The General "rule of thumb" is:

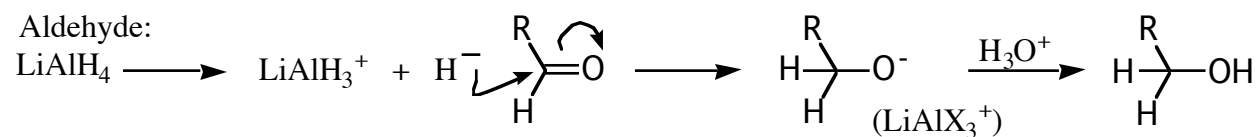
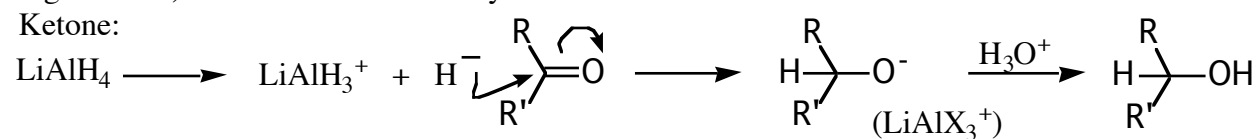
Aldehydes, Esters, and Acids reduce to *primary alcohols*.

Ketones reduce to *secondary alcohols*

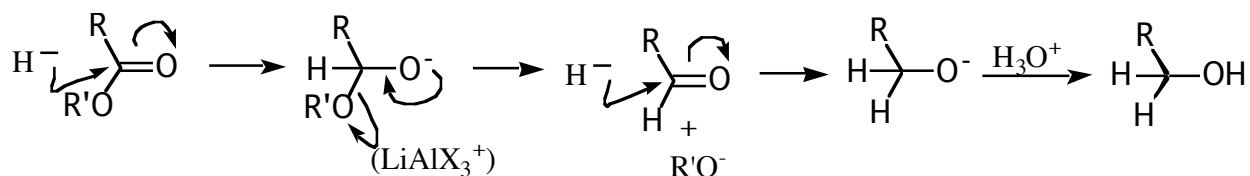
YOU CANNOT GET A TERTIARY ALCOHOL BY REDUCTION!!!!!!

Mechanism:

Although it is a little more complex than this, you can think of these reductions as a simple addition of hydride to the carbonyl (note - both reagents above have PLENTY of hydride to get rid of!). For ketones and aldehydes:

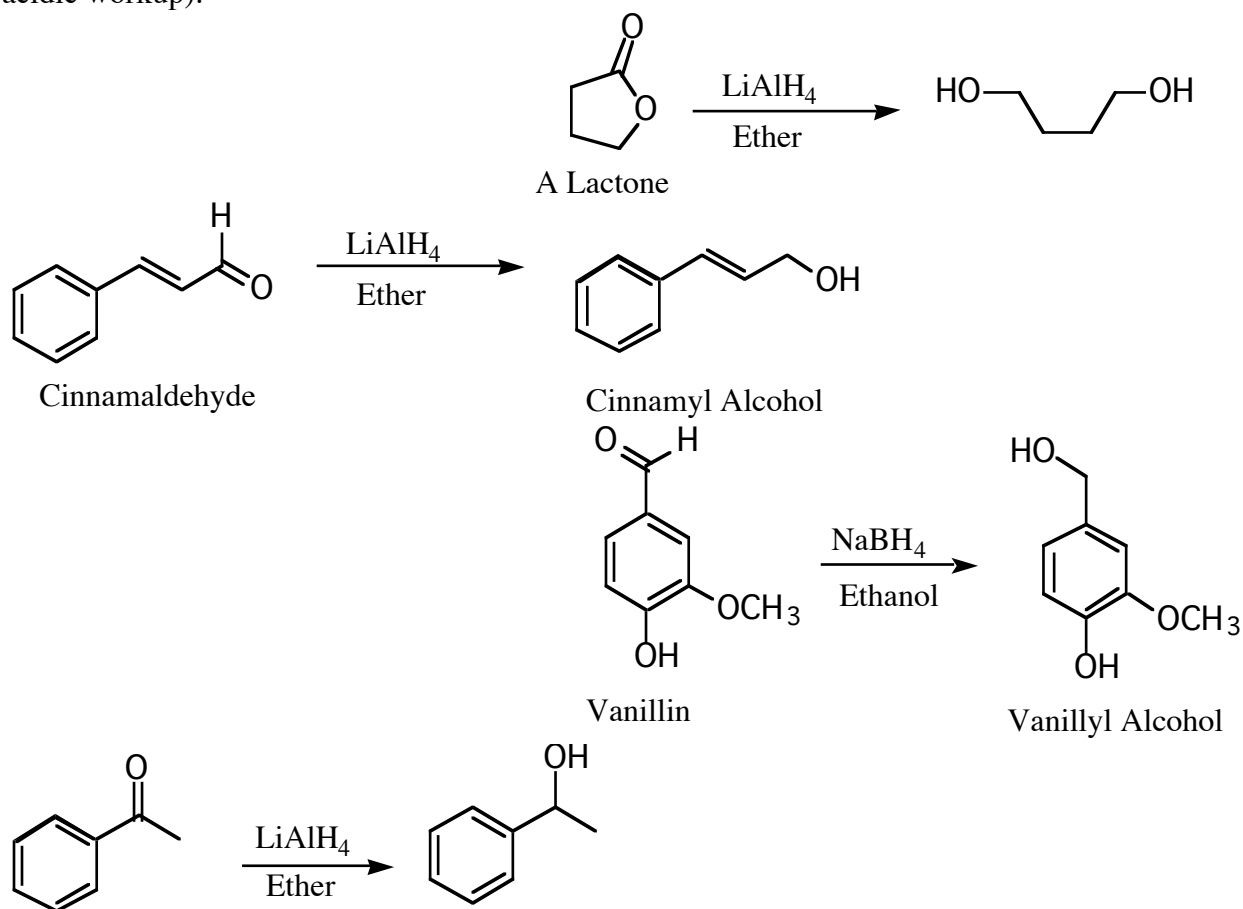


And for esters:



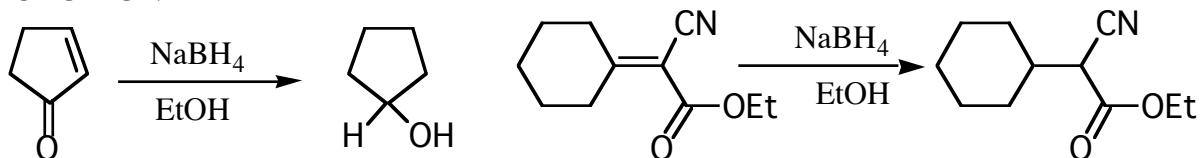
The Ester is first reduced to the ion of a *hemi-acetal* (we'll see more of this in a later chapter). This anion then boots out an alkoxide to form an aldehyde, which is then further reduced to a primary alcohol.

Some examples of whatcha can do by reduction (note - always assume an aqueous or acidic workup):



A word of warning at this point - with *conjugated* ketones, aldehydes or esters, sodium borohydride usually reduces the double bond (!) either alone, or along with the carbonyl group:

CAUTION:



3) Alcohols arising from Carbon-Carbon Bond Forming Reactions:

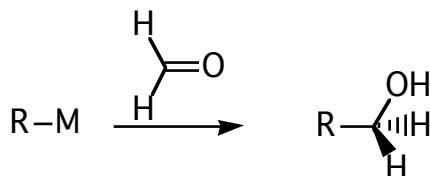
The addition of Grignard reagents, alkyllithiums, vinylolithium or acetylides (which I will designate as **RM**) to carbonyl groups forms alcohols, in addition to new carbon-carbon bonds. These sorts of reactions can be classified both by the type of reagent added (which we will not do), and by the type of alcohol formed (which we will).

Routes to Primary Alcohols:

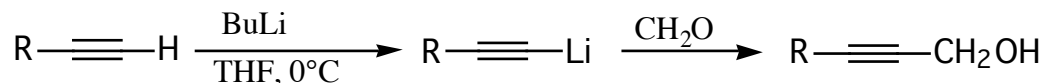
Primary alcohols can be the most difficult to form by the simple addition of **RM**. For the most part, there are only two ways to do this:

1) Addition of formaldehyde:

In General:



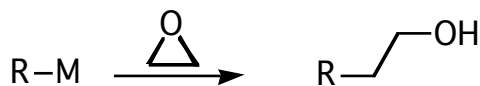
An Example:



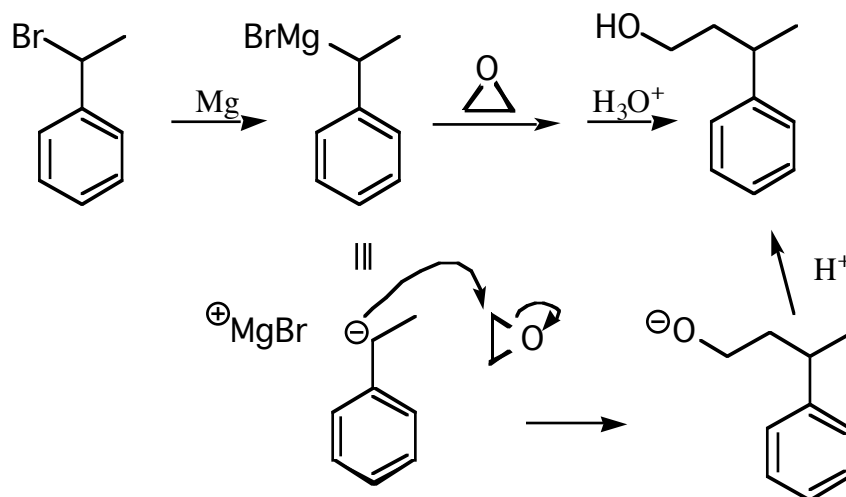
2) Addition of an epoxide:

Yes, those pesky 3-membered ring epoxides I introduced earlier can be used to form primary alcohols. Remember, the nucleophile (from **RM**) does a back-side attack to spring open the 3-membered ring, leading to a 2-carbon extension:

In General:



An Example (WITH MECHANISM!!! LOOK!!!! WHAT A BONUS!!!!):

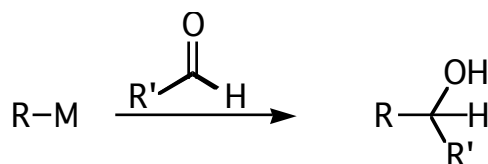


For the most part, these are the only ways to form primary alcohols by addition of **RM** to a carbonyl compound.

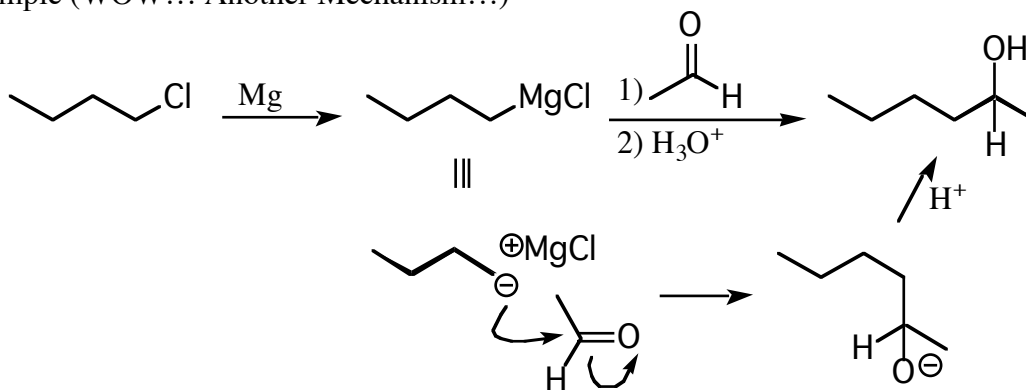
Routes to Secondary Alcohols:

Generally, the only method for the preparation of a secondary alcohol by **RM** addition is addition to an aldehyde:

In General:



An Example (WOW!!! Another Mechanism!!!)

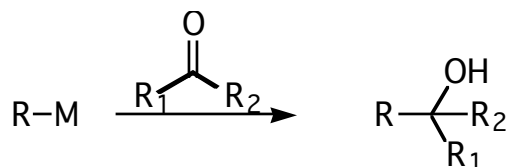


Routes to Tertiary Alcohols:

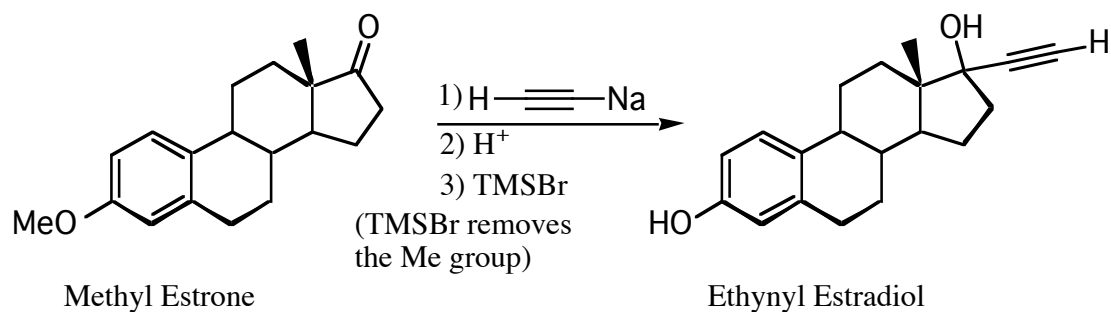
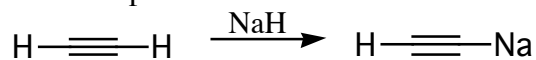
Okay, here is where things get a *little* bit more complicated. There are actually a number of ways to get to tertiary alcohols.

1) **RM** attack on a ketone. Any ketone. Really:

In General:

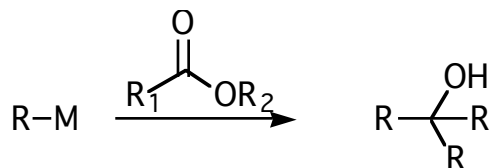


An Example:

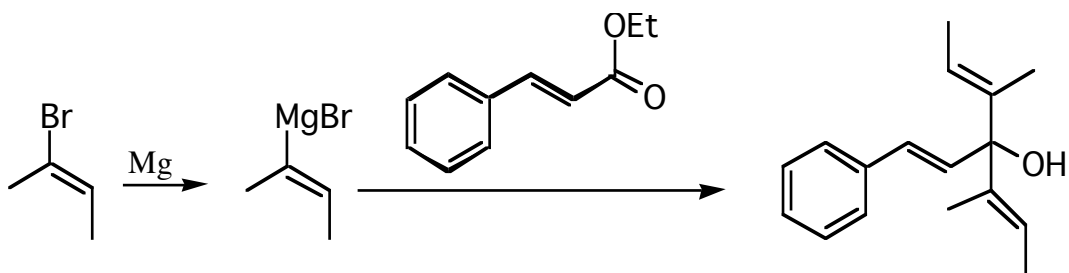


Another way to end up with a tertiary alcohol is to add **RM** to a carboxylic ester. Similar to the hydride reductions, the anion adds once, then kicks out alkoxide, and adds again. Yes, you do end up adding *two* equivalents of **RM**:

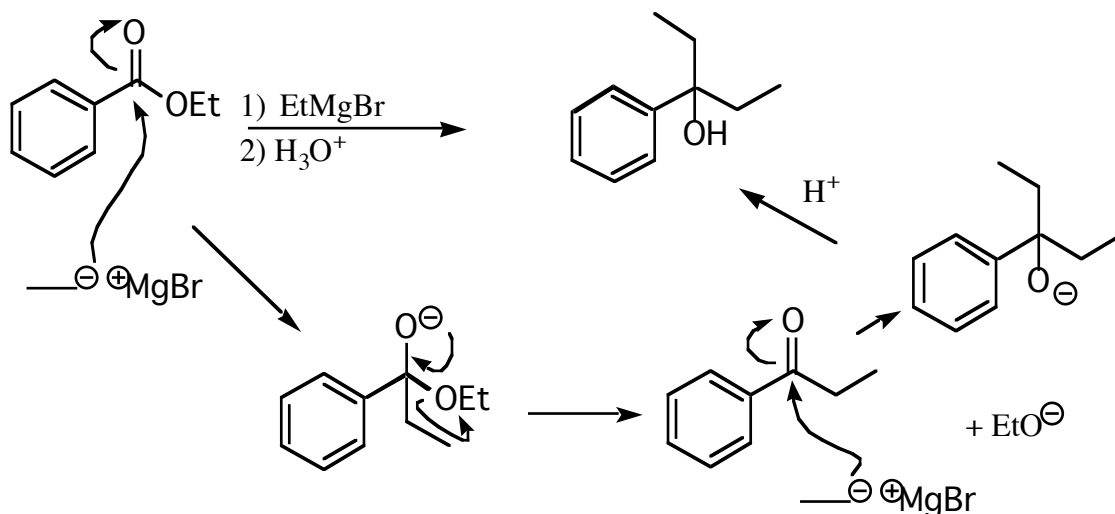
In General:



An Example (remember - you can always assume an aqueous or acidic workup!):



Okay, I know that one looked a little ugly. Here's a simpler one (+ Mechanism):

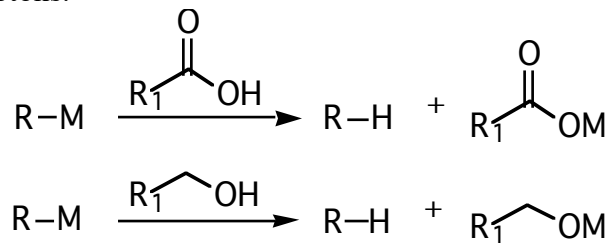


Other RM-type reagents:

One of the more unusual **RM** type reagents are the alkali-cyanides. Potassium cyanide, for example, adds irreversibly to aldehydes to give what is called a *cyanohydrin*. These compounds are valuable synthetic intermediates – the cyanide can be reduced (with lithium aluminum hydride) to an amine, or hydrolyzed (under basic or acidic conditions) to a carboxylic acid.

Restrictions (i.e. Stuff You Can't Do™)

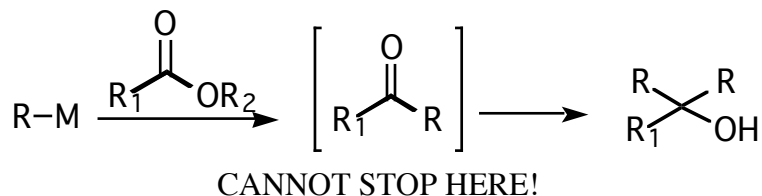
1) **RM** reagents will destroy themselves on carboxylic acids, alcohols, thiols, and amines, because of the acidic protons:



2) Your Metallated Compound (**RM**) *cannot* contain any of the groups just described (i.e. acids, alcohols, or ketones, aldehydes, etc.) - otherwise, it will just react with itself, forming a sticky, gooey polymeric sludge. Yech!

These problems can be avoided by the use of “protecting groups” - we will discuss this more later.

3) Even though it is an intermediate in the reaction of **RM** with an ester, it is very difficult to stop an **RM** from reacting with a ketone: Thus, it is nearly impossible to form a ketone from a reaction between **RM** and an ester:

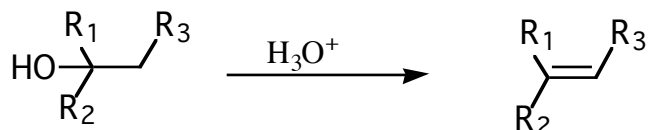


Reactions of Alcohols.

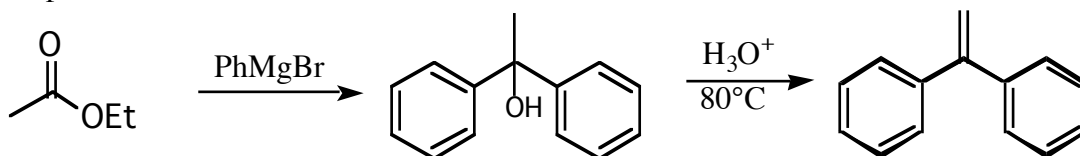
1) Dehydration to alkenes.

Just as alkenes can be hydrated to form alcohols, alcohols can be *dehydrated* to form alkenes (and generally, the most highly substituted alkene is formed):

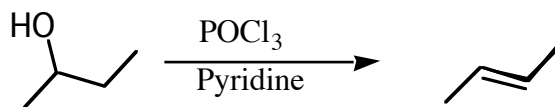
In General:



An Example:



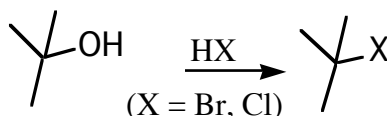
These dehydrations proceed via a E1 mechanism, and thus are *only* effective with tertiary systems. In order to dehydrate secondary alcohols (primary alcohols are a real bear to dehydrate!), we need to find a way to “activate” the system – this is generally done with phosphorous oxychloride and a base (E2 mechanism, see your text):



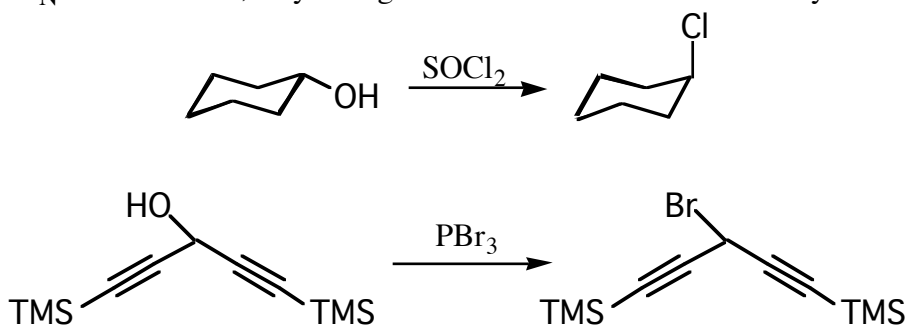
2) Halogenation.

It is quite a straightforward matter to turn an OH group into a halogen. Why would we want to do this? Well, alkyl halides are great precursors for Grignard reagents (remember what you can do with **RM**?)

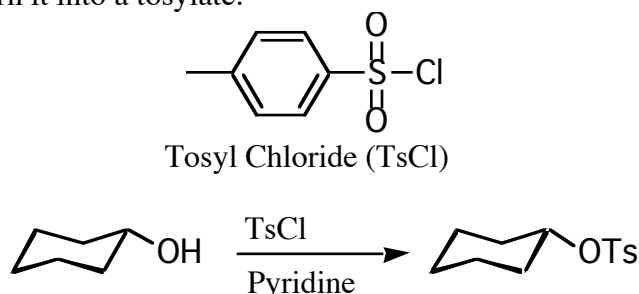
For tertiary alcohols, conversion to the halide is done via treatment with the corresponding acid (HCl or HBr):



Primary and Secondary alcohols require special reagents: Thionyl Chloride (SOCl_2) for chlorination, and Phosphorous Tribromide (PBr_3) for bromination. Remember, these reactions take place via $\text{S}_{\text{N}}2$ mechanisms, so you'll get an inversion of stereochemistry!:



One way to turn an alcohol into a good leaving group *without* messing with the stereochemistry is to turn it into a tosylate:

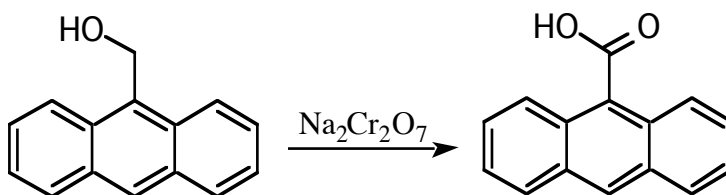
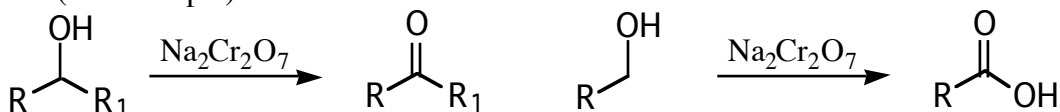


3) Oxidation.

Remember how we reduced carbonyl compounds to get alcohols? Well, we can *oxidize* alcohols to get carbonyl compounds!!!!

Just as with reducing agents, there are basically two oxidizing agents most commonly used – a harsh one and a mild one. The harsh one, sodium dichromate, will oxidize nearly anything (well, it isn't as bad as KMnO_4 , but pretty close). In particular, it takes secondary alcohols to ketones and primary alcohols to carboxylic acids:

In General (+ 1 example)

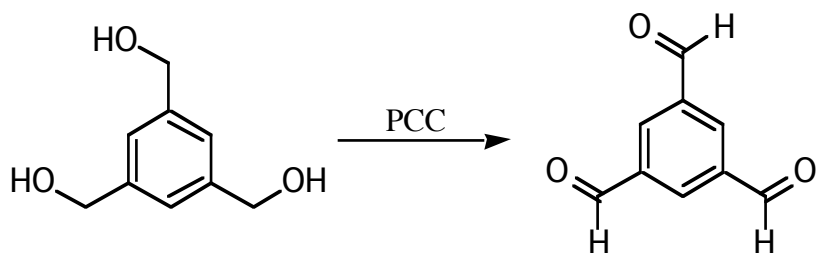
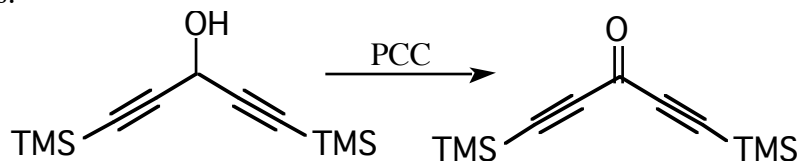


For the most part, organic chemists work with rather delicate molecules - so we use the milder reagents whenever possible. The more commonly used system is Pyridinium Chlorochromate (PCC). It oxidizes secondary alcohols to ketones, and PRIMARY ALCOHOLS TO ALDEHYDES:

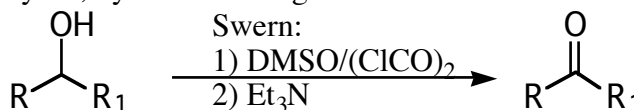
In General:

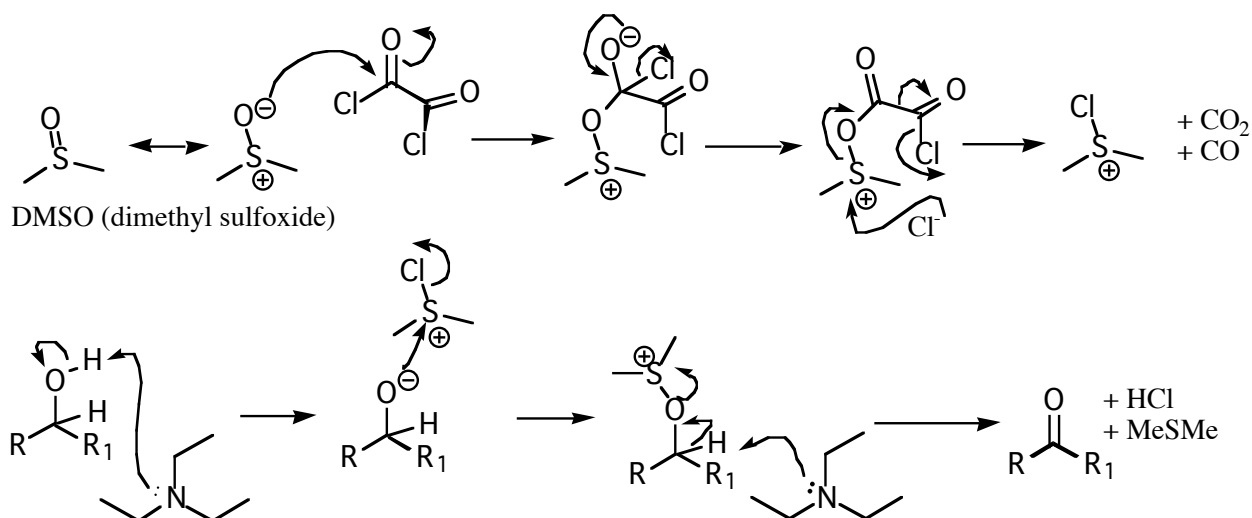


Some Examples:



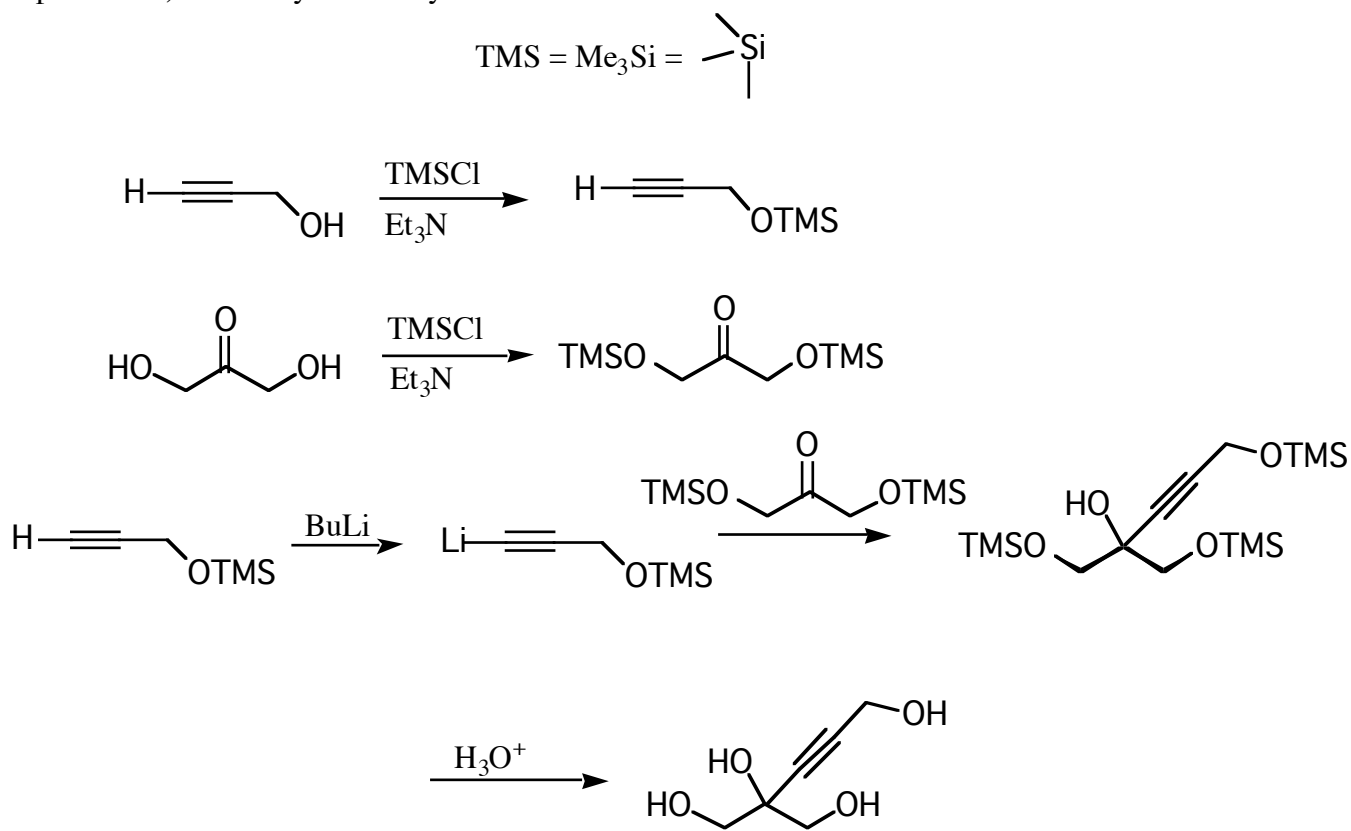
A big problem with all of these reagents is that they rely on chromium - a toxic heavy metal that is difficult to dispose of safely. An alternate mild oxidizing agent is the Swern. The Swern oxidation uses environmentally safe reagents to oxidize secondary alcohols to ketones and primary alcohols to aldehydes, by the following mechanism:





Protection of Alcohols

Alcohols are not stable to the action of Grignard reagents, alkyllithiums etc. (i.e. all **RM**). We thus need a way to mask the reactive (acidic) proton. Just as with acetylene chemistry, we use the trimethylsilyl group to perform this function. Alcohols are easily silylated under mild conditions, to form silyl ethers. These ethers are stable to most reactions, and are easily removed by treatment with mild acid. Below is a full example of how this type of protection (and deprotection) is used synthetically:



The Final Stretch: Thiols.

Thiols are simply the sulfur analogs of alcohols. Their main distinction is their horrible smell - guaranteed to empty a room in a hurry. Thiols are generally prepared by attack of sodium hydrogen sulfide on an organic halide. The only real point of interest for you folks would be that thiols can be easily oxidatively dimerized (sorta like a Hay coupling) to disulfides - this is the whole basis of hair permanents! The disulfide bridge is important in protein cross-linking (and causing hair to go curly is one of the less significant aspects of this...)

