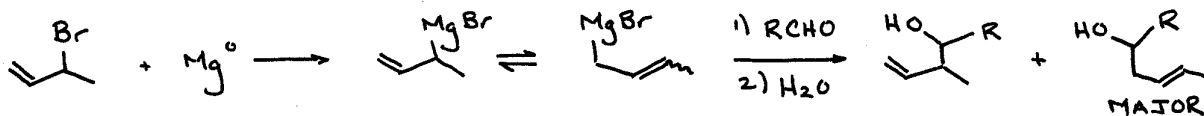
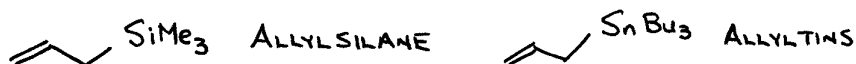


## Allylsilanes

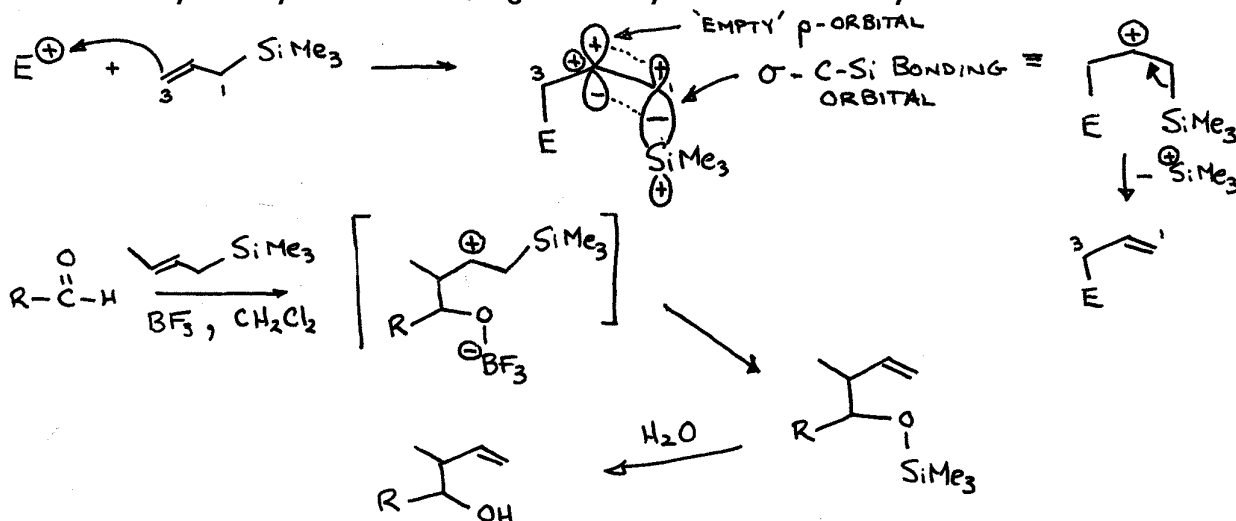
One particular problem which we have not addressed at all is the problem of (substituted) allyl Grignards/lithiums. The problem with these reagents is that they rearrange rapidly, and the site of attack of these can either be at the C bearing the metal, or the site allylic to it (often called  $S_N2'$  attack). As a result, one has very little control over regiochemistry of attack of these reagents.



Therefore, when one wants to attack, say carbonyls, by an organometallic allyl function, allylic silanes (or the more reactive allylic tins) are usually employed. These are certainly not as reactive as organolithiums/Grignards; they are stable isolable, distillable compounds. In the presence of an aldehyde, ketone, or epoxide, and a Lewis acid, the carbocation will react with allylsilanes.



The allylsilane always attacks the carbocation at the allylic terminus remote from Si; this gives a  $\beta$ -silyl cation intermediate, which is stabilized by the overlap of the empty p orbital of the carbocation with the C-Si  $\sigma$ -bonding orbital. This is often called the silicon  $\beta$ -effect. Silicon is then lost from the cation, to give the allylated alcohol after addition of water. The point here is that since the initial site of reactivity is always remote to Si, regiochemistry of reaction is always known.

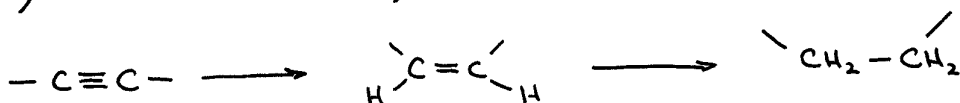
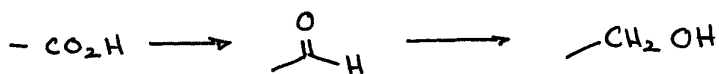


## Functional Group Manipulation

To date, we've been considering construction of the carbon skeleton of any molecule we wish to make. Having established a number of good ways of doing that, it's now useful to look at what we've missed; the modification of functional groups into ones we want.

The most common type (and simplest) of functional group modification reactions are **oxidation** and **reduction**. First, in organic terms, here's what is meant by the two terms.

**Reduction:** either the addition of H atoms, or  
 The removal of O atoms (yes this could be N atoms, too)  
 So common reductions would be.....



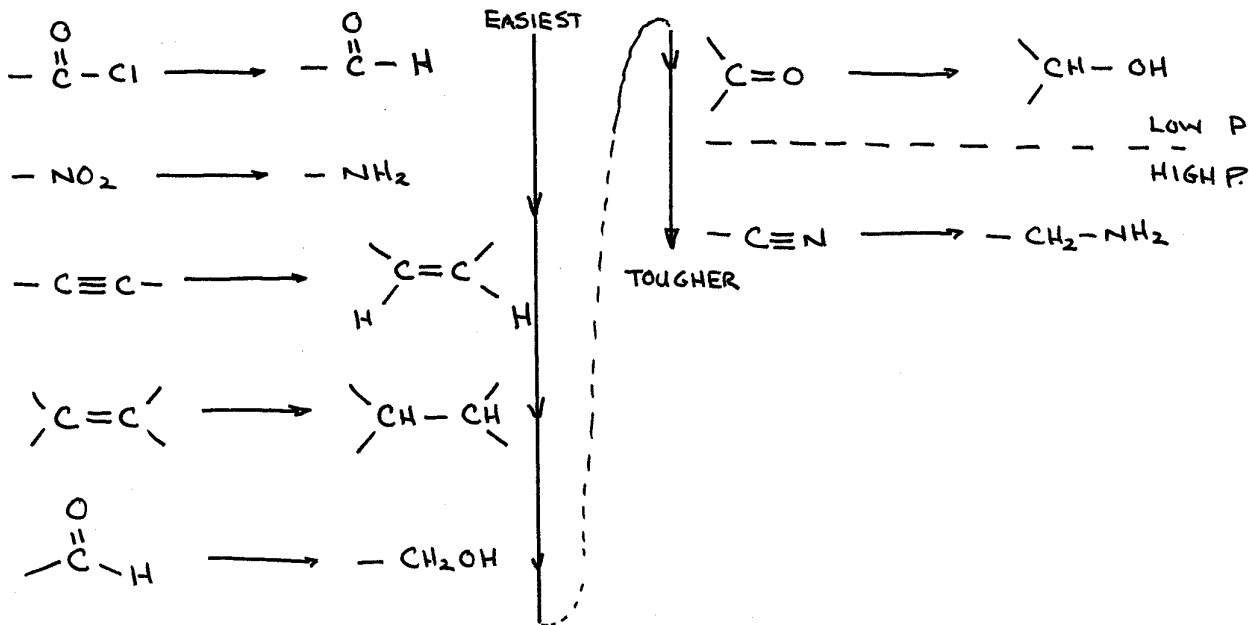
The simplest way of doing this is generally the use of H<sub>2</sub> gas and a catalyst. Here, the catalyst dictates which groups are reduced and how easily.

The most common catalysts are:

- finely divided metal i.e., Pd, Pt, Ni
- or coated on an inert support i.e., Pt/C

The solvents for reaction tend to be ones that are inert to reduction themselves, so solvents such as H<sub>2</sub>O, EtOH, ethyl acetate, and acetic acid are common.

**Reactivity:** It's obviously harder to get a more *non-polar* molecule than H<sub>2</sub>, so a general trend with functional groups is that the less polar they are, the more easily that they are reduced by catalytic hydrogenation. More specifically, the order of ease for reduction (from easiest to hardest) is as follows:



Note: At low pressure of H<sub>2</sub>, esters, amides, acids, and aromatics are generally inert.

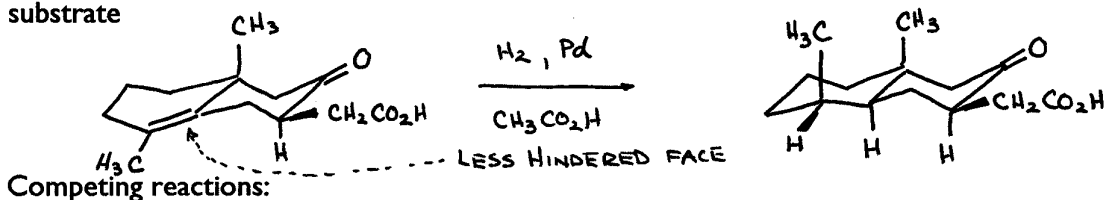
Which catalysts you would use for each of these can be also divided into three general groups.

- 1) Pd, Pd/C, Ni (usually denoted as Raney Nickel, RaNi),  $\text{CIRh}(\text{PPh}_3)_3$   
-these reduce  $\text{C}=\text{C}$ 's rapidly,  $\text{C}=\text{O}$  much more slowly, and aromatics not at all
- 2) Pt, Ru  
-these reduce  $\text{C}=\text{C}$  and  $\text{C}=\text{O}$  (or aldehydes and ketones) rapidly, but aromatics only very slowly
- 3) RaNi, Pt at high pressure of  $\text{H}_2$   
-these reduce  $\text{C}=\text{C}$ ,  $\text{C}=\text{O}$ , and aromatics pretty easily

Other general considerations

Stereochemistry:

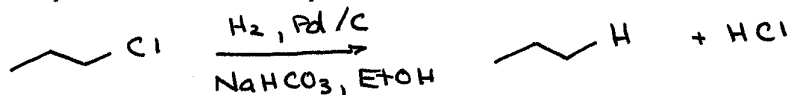
The H atoms are normally added in a cis fashion and from the less hindered face of the substrate



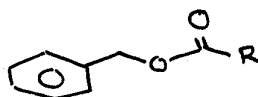
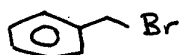
Competing reactions:

Hydrogenolysis is often a reaction which can compete with hydrogenation. This means that the  $\text{C}-\text{X}$  single bond (where X is a good leaving group) can also occur under hydrogenation conditions. This can be a nuisance, or it can be useful.

It tends to be a significant side reaction, when the R group bearing the X can form a relatively stable  $\text{C}^+$ , i.e., benzylic substrates.

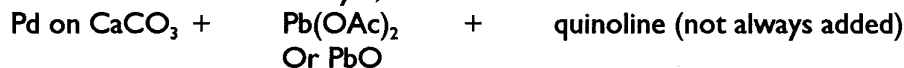


PROBLEM CASES

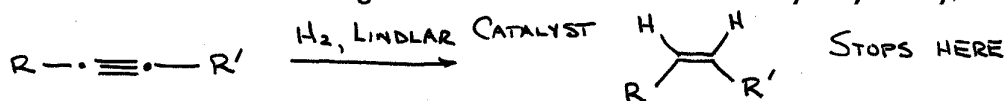


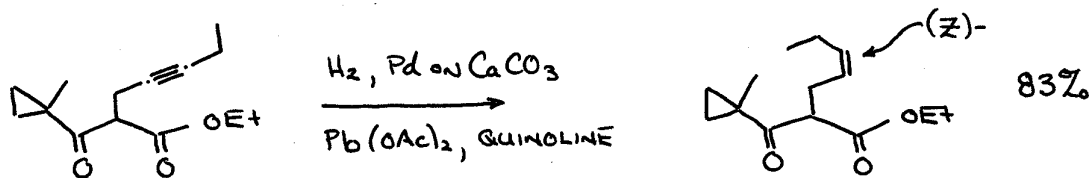
Alkynes:

The problem with alkynes is not that they can't be reduced, but the initial product of reduction (an alkene) is also easily reduced by catalytic hydrogenation. As a result, one has to poison the catalyst to get a catalytic hydrogenation of an alkyne to stop at the alkene stage. The most common method for this is to use the Lindlar catalyst, which is



This is deactivated enough so that it will reduce alkenes only very slowly, and so....

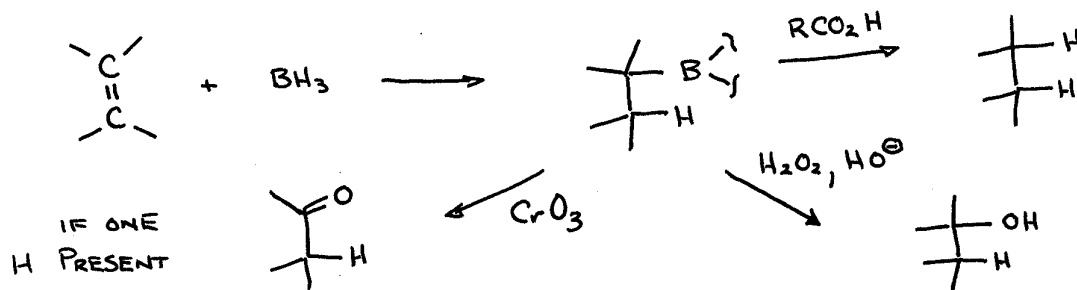




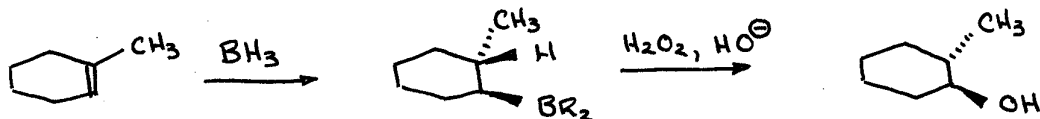
## Hydroboration

Hydroboration is a method of reduction which employs borane (or a more complicated borane) to reduce an alkene (or other substrate). Borane adds across a double bond in an unusual way; since B-H bonds are polarized  $\text{B}^{\delta+} - \text{H}^{\delta-}$ , the boron ends up on the **less substituted** end of the product. Furthermore, not only can these organoborane intermediates be converted to alkanes (with a carboxylic acid such as acetic acid), but they may also be oxidized into alcohols (most common) or even ketones (less common, and assumes the presence of an  $\alpha$ -H atom).

*Note:  $\text{BH}_3$  can add across three different alkene molecules, depend on how much is added, so I've left the other two groups on B deliberately undefined.*

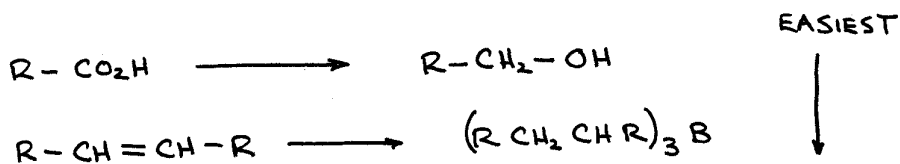


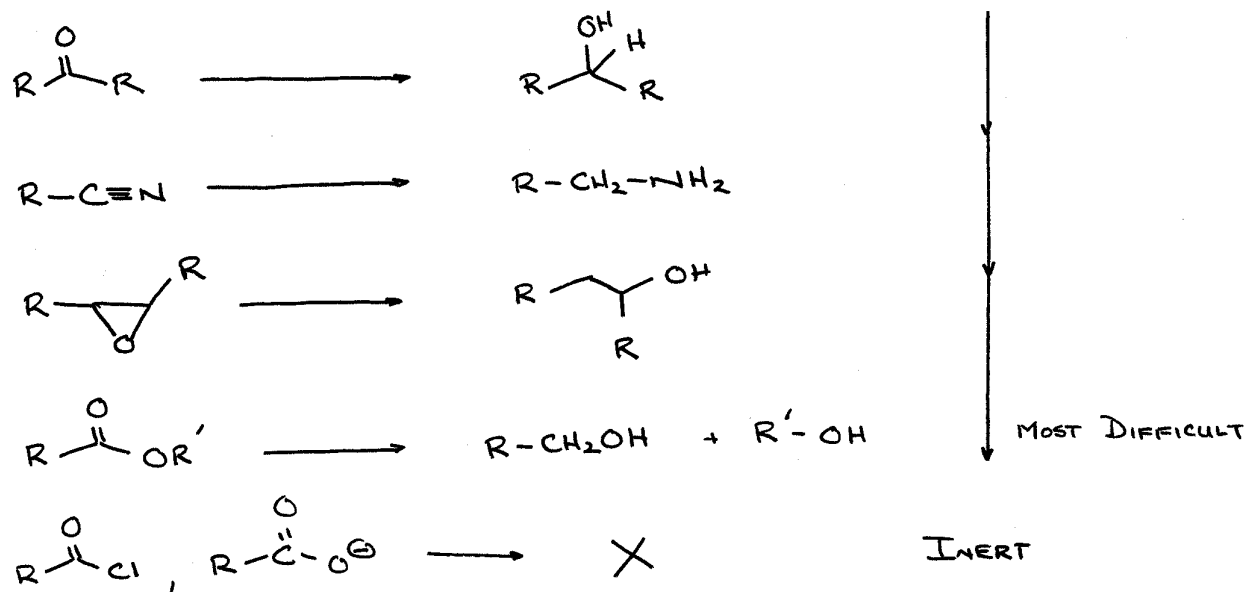
**Stereochemistry:** The addition of borane to an alkene is also *cis* across the double bond. Notably though, when one oxidizes these organoborane intermediates to alcohols, the replacement of B by OH occurs with retention of configuration. Therefore:



**Chemoselectivity:** As you'll see below, the order of ease of reduction of functional groups by  $\text{BH}_3$  is somewhat similar to catalytic hydrogenation. There is one important exception, however: carboxylic acids are reduced (to alcohols) significantly faster than anything else. The reason for this is the initial formation of a 'boroester', so that transfer of H is intramolecular here. This is particularly useful, since by almost all other reduction methods, carboxylic acids are just about the hardest things to reduce. This reversal is very useful.

For completions sake, the overall ease of reduction of functional groups (again easiest to hardest) is as follows.





### Reduction by Hydrides

In contrast to the non-polar  $H_2$  and the polar covalent B-H, hydride ion ( $H^-$ ) is very nucleophilic, much like, say, a Grignard reagent.

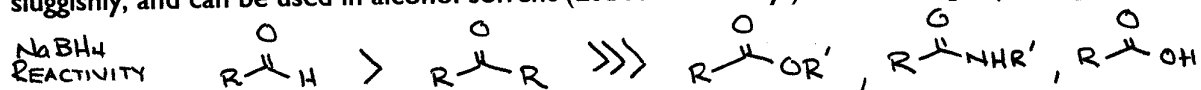
Since  $C=O$ 's are attacked by nucleophiles, but not  $C=C$ 's, metal hydrides will attack aldehydes, ketones, esters, and even acids, but not alkenes. This is almost the exact inverse of catalytic hydrogenation.

The most common metal hydrides are  **$NaBH_4$**  (sodium borohydride)

and  **$LiAlH_4$**  (lithium aluminum hydride)

**$NaBH_4$**  is the weaker, but more selective hydride source. It will reduce aldehydes (fastest), ketones (more slowly), and little else (esters, amides, acids are inert to it).

Although it is potentially a base (all nucleophiles are potential bases), it acts that way very sluggishly, and can be used in alcohol solvent (EtOH commonly!) and even  $H_2O$  (as long as it's basic).



**$LiAlH_4$**  is far stronger, and not very selective. It attacks all carbonyl compounds pretty rapidly.

$LiAlH_4$  does not act sluggishly as a base, so adding EtOH or  $H_2O$  is a good way to get purple smoke and an explosion. The common solvent for use of  $LiAlH_4$  are aprotic ones like  $Et_2O$  or THF. Any free OH in your substrate will be deprotonated, although this is not always a critical problem (if you have enough  $LiAlH_4$ ).



Some examples of reduction of carbonyl type compounds with  $NaBH_4$  or  $LiAlH_4$  follow. Note that the reduction of amides (either 1° or 2°) with  $LiAlH_4$  gives amines, not alcohols.

