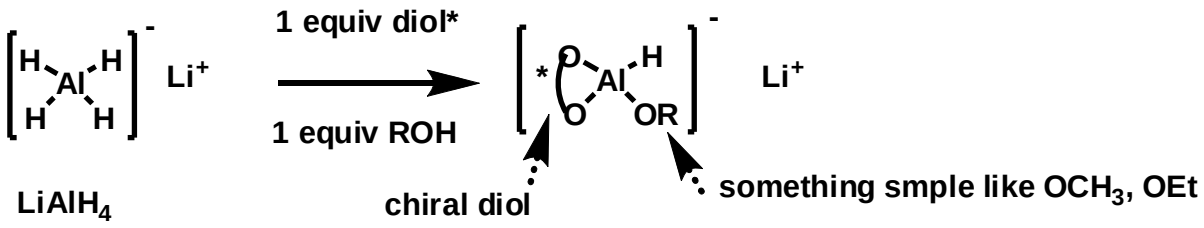
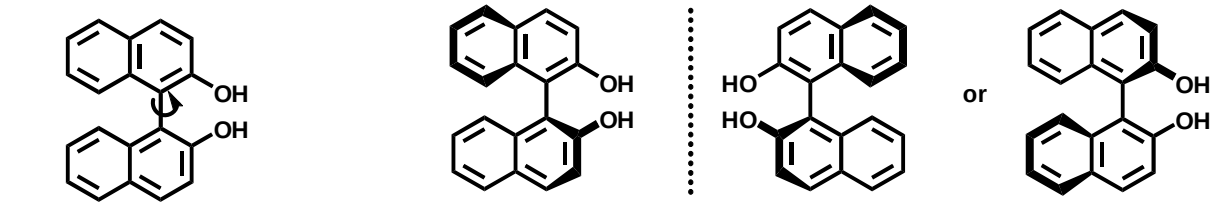
Enantioselective Reduction of Ketones

One of the simplest methods of creating a new stereogenic (chiral) centre. There are many different approaches; we will look at two.

Conceptually simplest is to take a very common carbonyl reductant, $LiAlH_4$, and modify it with a simple chiral organic molecule. For example



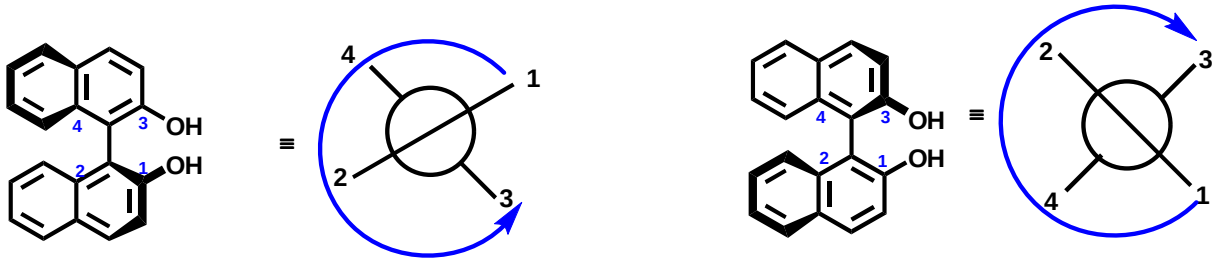
The most popular chiral diol is 1,1'-binaphthol, which does not have a chiral *centre*, but rather has *axial* chirality.



rotation about central bond is so hindered that the rotational isomers don't interconvert, so.....

non-superimposable mirror images

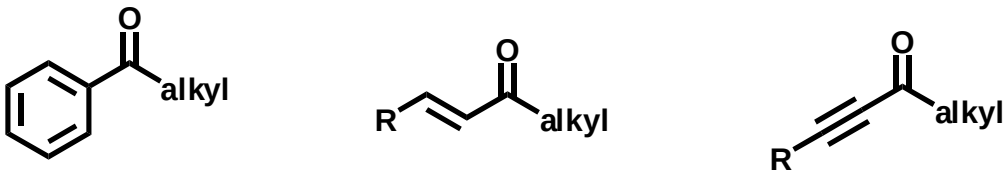
(R)-and (S)- are assigned by ranking by priority 1- and 2- at the near end, and 3- and 4- at the remote end, and then tracing out 1→2→3→4 as with chiral centres. So…



counterclockwise - therefore (S)-
-the less expensive one

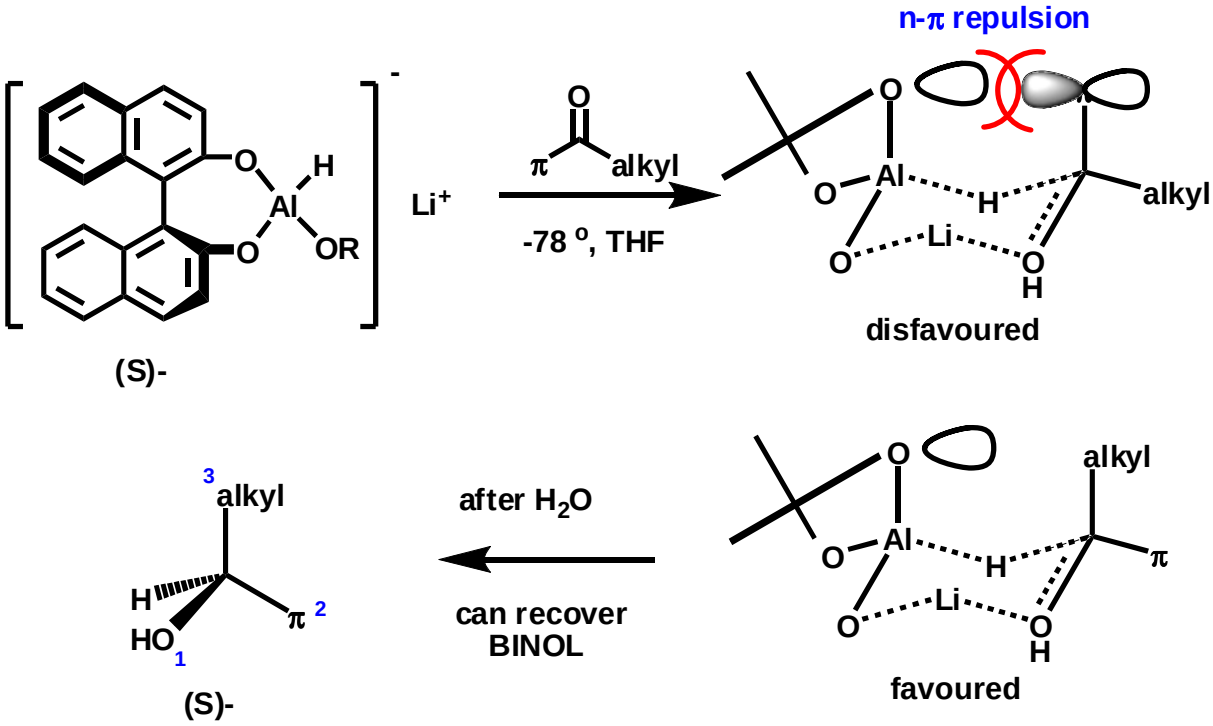
clockwise - therefore (R)-
-the more expensive one

These reagents, often called BINAL-H, give pretty high enantioselectivity for reduction of ketones that have a π- system directly attached on one side; this means ketones such as ….



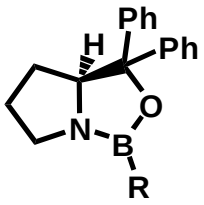
The size of the group has some effect, but it is *much less* than the role of the π system.

For these systems, and assuming that the group that is comprised of the π system has a higher CIP priority than the alkyl group, there is a very simple mnemonic for the reactivity trend**: the (S)- BINAL-H gives the (S)- enantiomer of alcohol, while the (R)- BINAL-H gives the (R)- alcohol**. The reason can be seen from the accepted transition state for these reactions; they are chair-like transition states, and the π system of the transforming ketone avoids the axial position (and prefers the equatorial one), because tin the former there is a repulsive interaction between the π system of the ketone and the lone pair of an oxygen atom of the BINAL-H. This is called n-π repulsion.

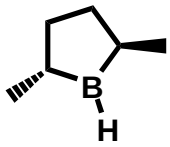


A caution, however – this is not a good reagent for dialkyl ketones

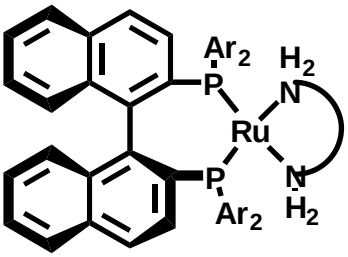
We'll look at one other in some detail, but we'll list some of the other popular reagents here. It can be seen that there's been success with modified hydroboration reagents, and chiral hydrogenation catalysts.



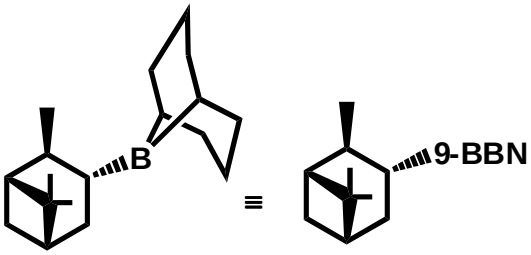
oxaborolidinones
CBS- reagents
(Corey)



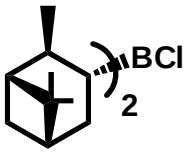
boralane
(Masamune)



Ru-BINAP-diamine
(hydrogenation catalysts)
(Noyori)



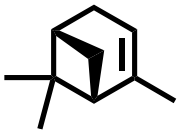
Alpine-Borane
(Midland)



Ipc_2BCl or
DIP-Chloride
(Brown)

Since it's quite popular, we'll look at DIP-Chloride in more detail. The reagent is commercially available in both enantiomers, but is made from α- pinene, which is relatively cheap for each enantiomer.

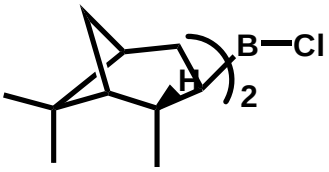
2 equiv



α-pinene
(+)- or (1R, 5R)-

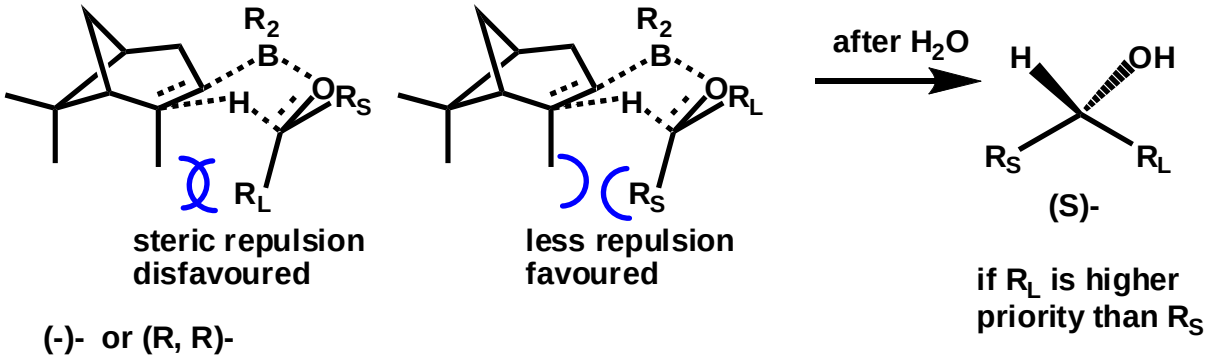
1 equiv Cl-BH_2
or

1) BH_3-SMe_2, THF
2) HCl, 0 °

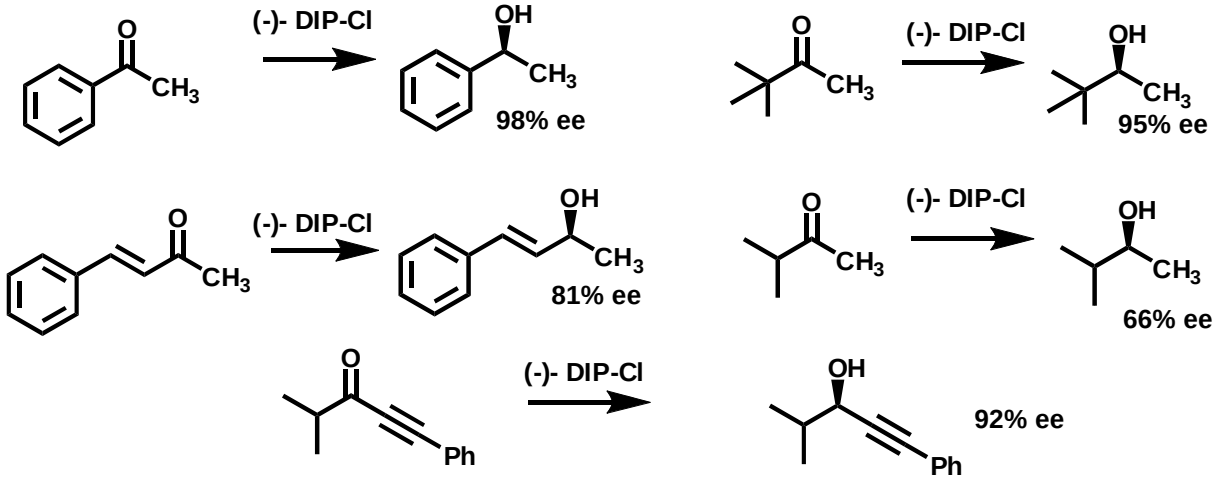


(-)-DIP-Chloride

In reagents like these, boron has no H, so rather than a conventional hydroboration, the formal H^- transfers from the carbon next to the boron. This is less unusual than you might think (see Meerwein-Pondorf-Verley reduction), and is often called a *transfer hydrogenation*. The accepted model again involves a six- membered transition state, but the fact the the H and B are cis-, and since the bridged bicyclic does not have a lot of conformational flexibility, the transition state has to be a boat. The discrimination *is* based on sterics of the R groups of the ketone, so…..



In this case, the reagent from (R, R)- pinene or (-) DIP-Cl reagent, usually gives the (S)- alcohol. The analogous considerations govern Alpine-Borane, too. Again, R group preferences are based on size (one should use the conformational A values for size measurements), not the presence of a π system. Nevertheless, these are most often used on aryl alkyl ketones. Some examples follow.



Here's a simple use in the synthesis of Prozac…