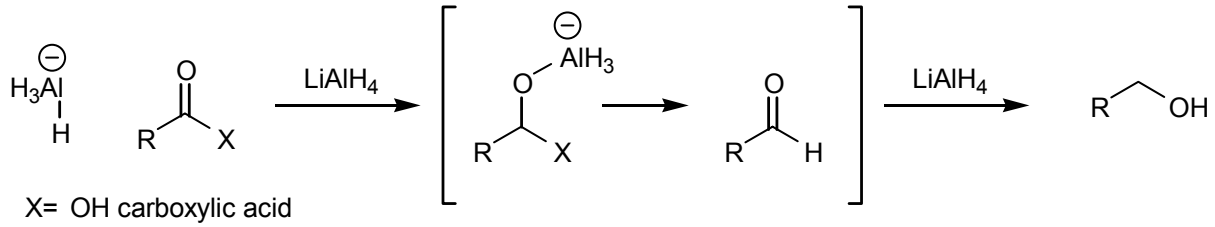
Functional Group Interconversions - Lecture 3

Section 2: Reduction of Carboxyl and related functions

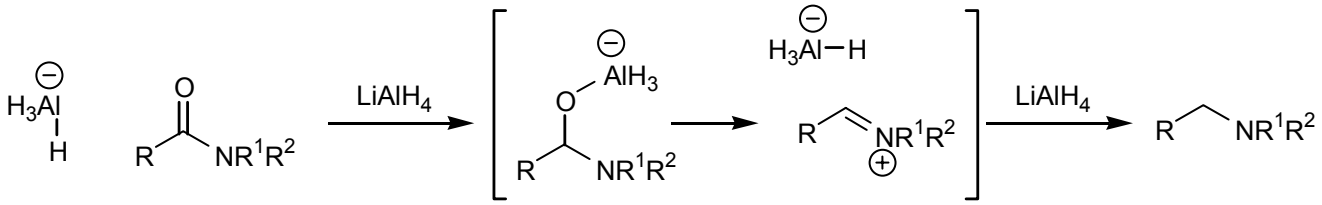
(a) Using $LiAlH_4$

Remember from 1st year that reduction of carboxylic acids, acid halides or esters using $LiAlH_4$ leads to the formation of primary alcohols *via* cleavage of the C-X bond:



X= OH carboxylic acid
Cl acid chloride
OR' ester

However, you should also remember that amides behave differently – due to the lower electronegativity of N relative to O or Cl, it is the C-O bond that is cleaved in the tetrahedral intermediate **A**, leading to formation of the amine.



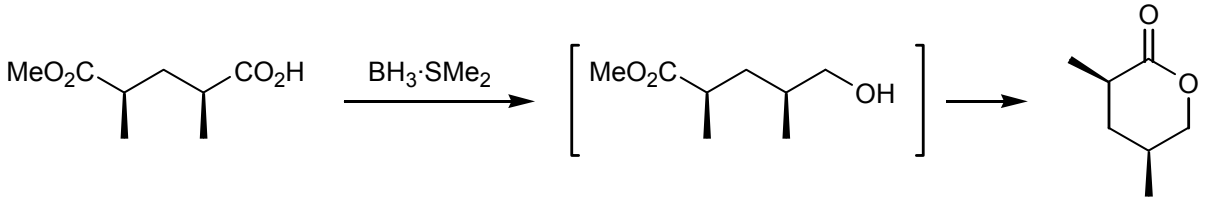
amide

A

(b) Functional group selectivity

We have already met two important aspects of functional group selectivity:

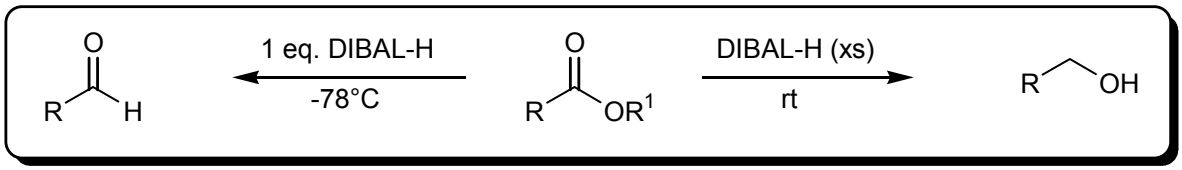
- $NaBH_4$ will usually reduce aldehydes or ketones without reducing esters
- Borane will allow selective reduction of carboxylic acids in the presence of *e.g.* esters – see lecture 2 for a mechanistic explanation.

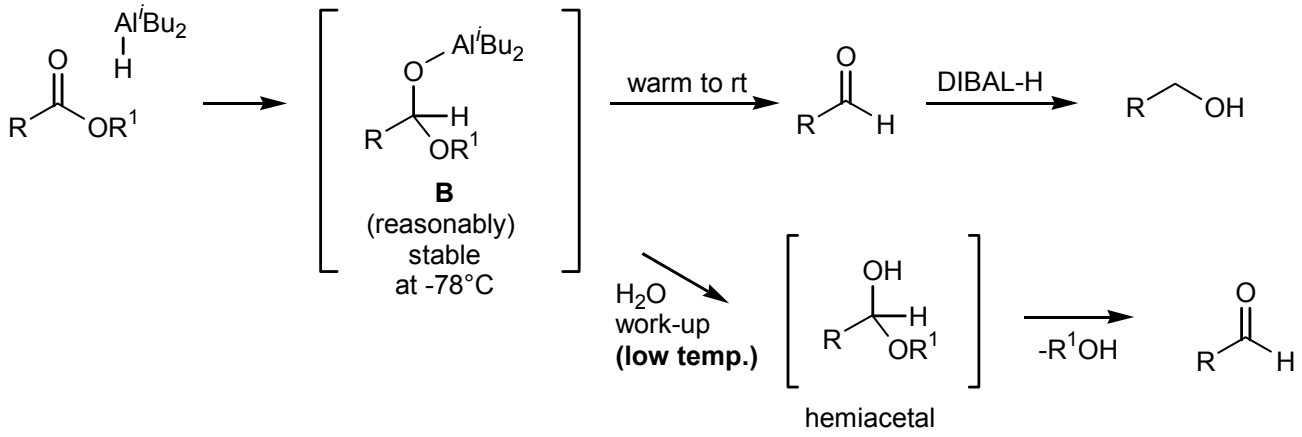


(c) Partial reduction of esters

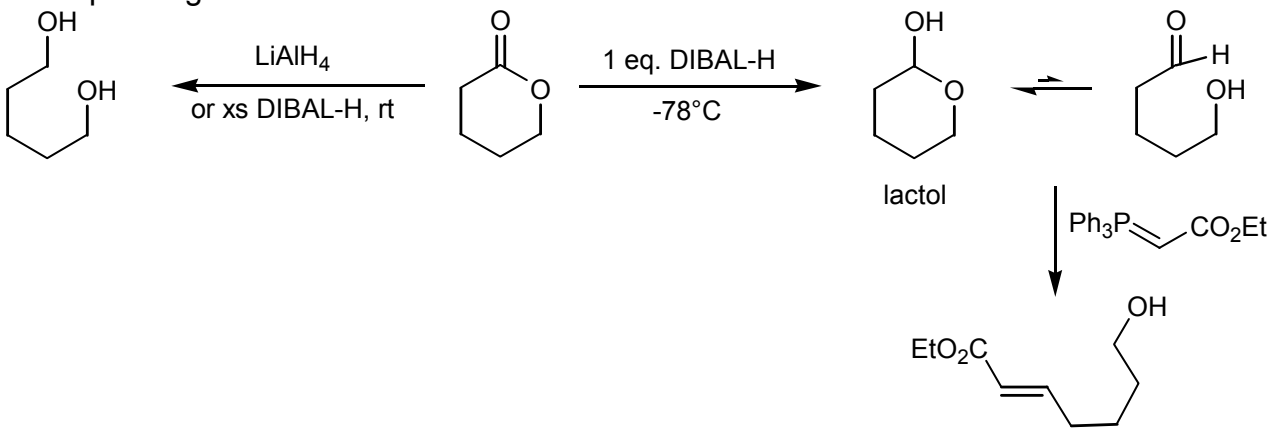
As we saw above, reduction of esters with $LiAlH_4$ gives us the primary alcohol product, since the intermediate aldehyde is very rapidly reduced. But what if we want to make the aldehyde from the ester? We could use $LiAlH_4$ to reduce the ester to the alcohol, and then oxidize the alcohol to the aldehyde…..in practice, this is often the best way, but there is an alternative trick that sometimes works. It involves the use of 1 eq. DIBAL-H at low temperature (usually at -78ºC, a temperature that is easily obtained using a dry ice/acetone mixture). The key to this is that at low temperature, the tetrahedral intermediate **B** is stable, and so does not break down to liberate the aldehyde. Work-up by addition of H_2O/acid (still at low temperature) quenches any unreacted DIBAL-H and converts **B** into the hemiacetal, which breaks down to give the aldehyde product.

If the DIBAL-H reaction is carried out at room temperature, the intermediate **B** is not stable and breaks down to the aldehyde, which is then further reduced by DIBAL-H to the alcohol.



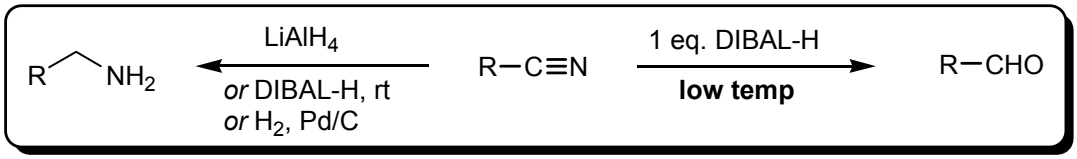


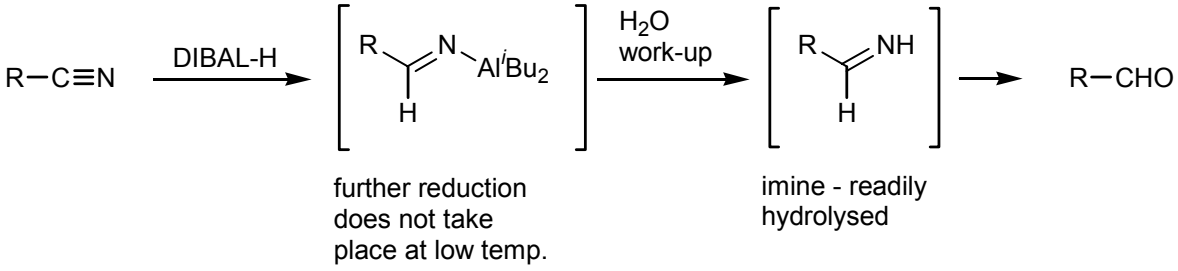
The partial reduction reaction often works best with cyclic esters (lactones). The resulting hydroxyaldehydes may (depending *e.g.* on ring size) exist in equilibrium with the corresponding lactols.



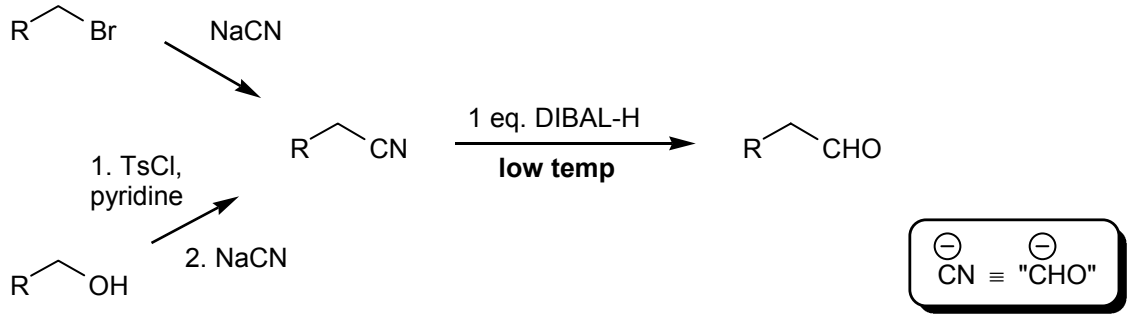
(d) *Reduction of nitriles*

We'll consider reduction of nitriles alongside carboxylic acid derivatives, since the nitrile C is at the same oxidation level. Reduction of nitriles with $LiAlH_4$, an excess of DIBAL-H at room temp., or by catalytic hydrogenation (H_2/Pd-C) gives the primary amine. However, the use of DIBAL-H at low temp. can again allow partial reduction, leading to the aldehyde,





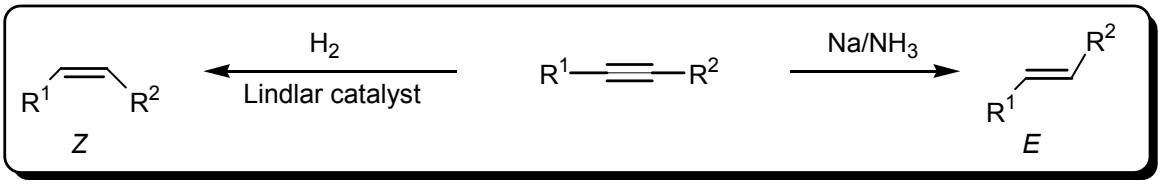
This is useful since the nitrile group can be introduced *via* S_N2-displacement of a leaving group with cyanide anion. The overall process allows elongation of the carbon chain.

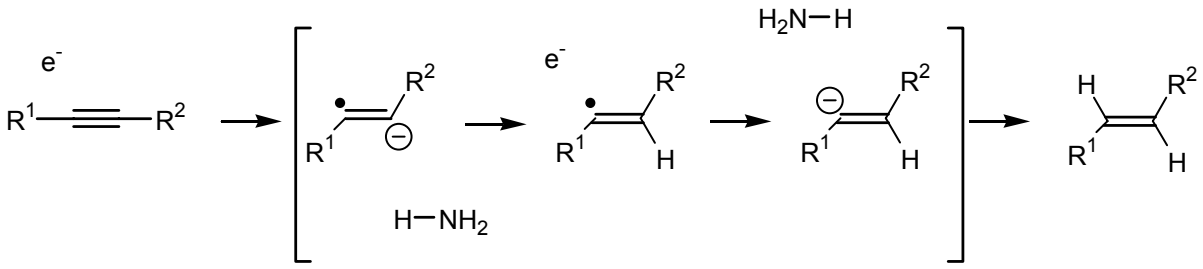


Section 3: Reduction of C-C multiple bonds

3.1 Alkynes

Alkynes can be reduced to alkanes if so desired (H_2 and Pt, Pd or Raney Ni catalysts), but this isn't so useful. Much more useful is the fact that we can stereoselectively synthesise either (*E*) or (*Z*)-olefins from alkynes, by either dissolving metal reduction or catalytic hydrogenation over partially poisoned catalysts respectively. The catalyst usually used for partial hydrogenation is Lindlar's catalyst ($Pd/CaCO_3$ deliberately poisoned with Pb).

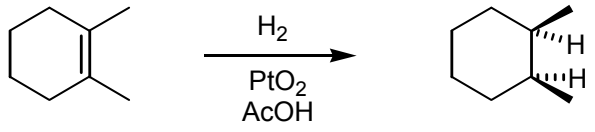


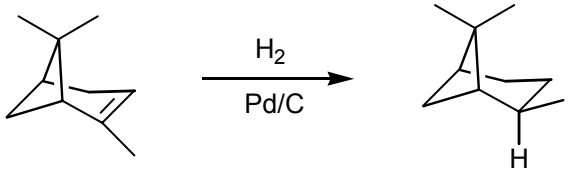


intermediates are configurationally labile, and adopt most stable arrangement with R groups *trans*

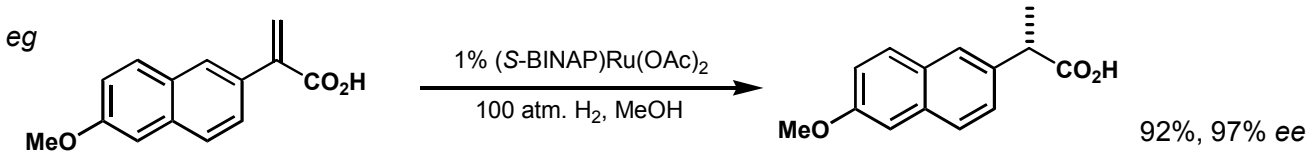
3.2 Isolated alkenes

(We'll look at the reduction of enones *etc* later.) Hydrogenation of olefins to alkanes is a common synthetic procedure. We talked about the catalysts in lecture 1: one can use *e.g.* Pt, Pd, Rh, or Raney Ni as heterogeneous catalysts, or use homogeneous catalysts such as $(Ph_3P)_3RhCl$ (Wilkinson's catalyst, after the Nobel-winning chemist of this Department). Useful facets of hydrogenation include: *cis*-stereoselectivity in addition of H_2; attack of H_2 from less hindered face of cyclic olefins, and application in asymmetric synthesis (BIG, BIG industrial process! – the importance of enantioselective hydrogenation was recognized by the award of a share of the 2001 Nobel Prize to Profs. Noyori and Knowles).

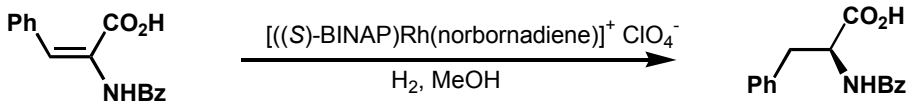




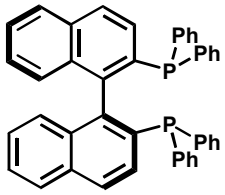
Ruthenium diphosphine catalysed reduction of acrylic acids



(*S*)-naproxen (anti-inflammatory)



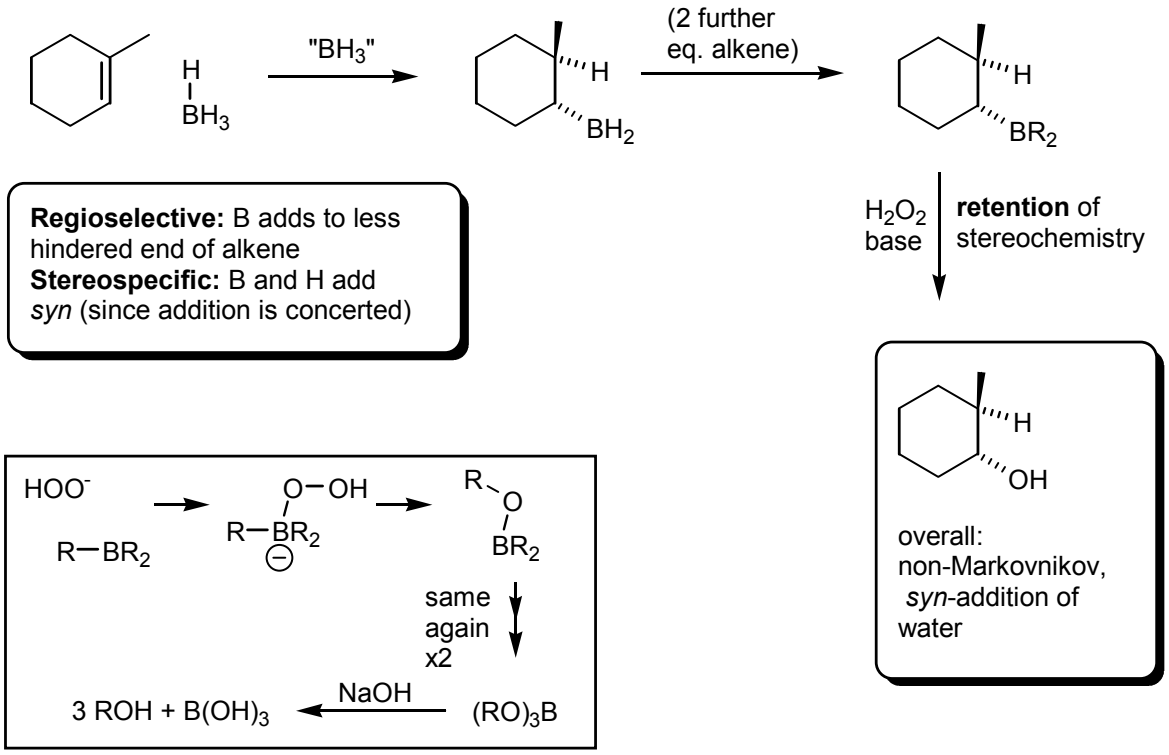
phenylalanine (constituent of aspartame)



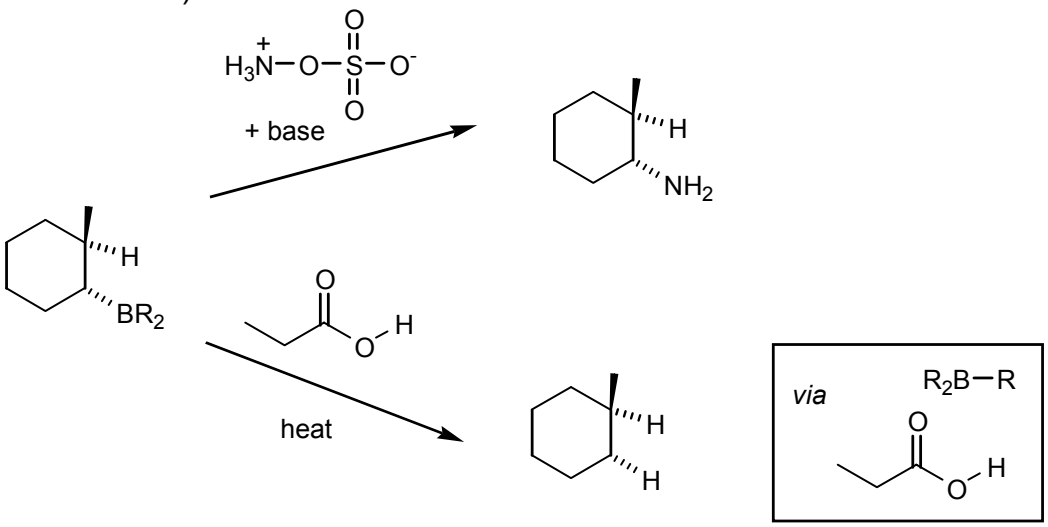
(*S*)-BINAP

3.3 Hydroboration

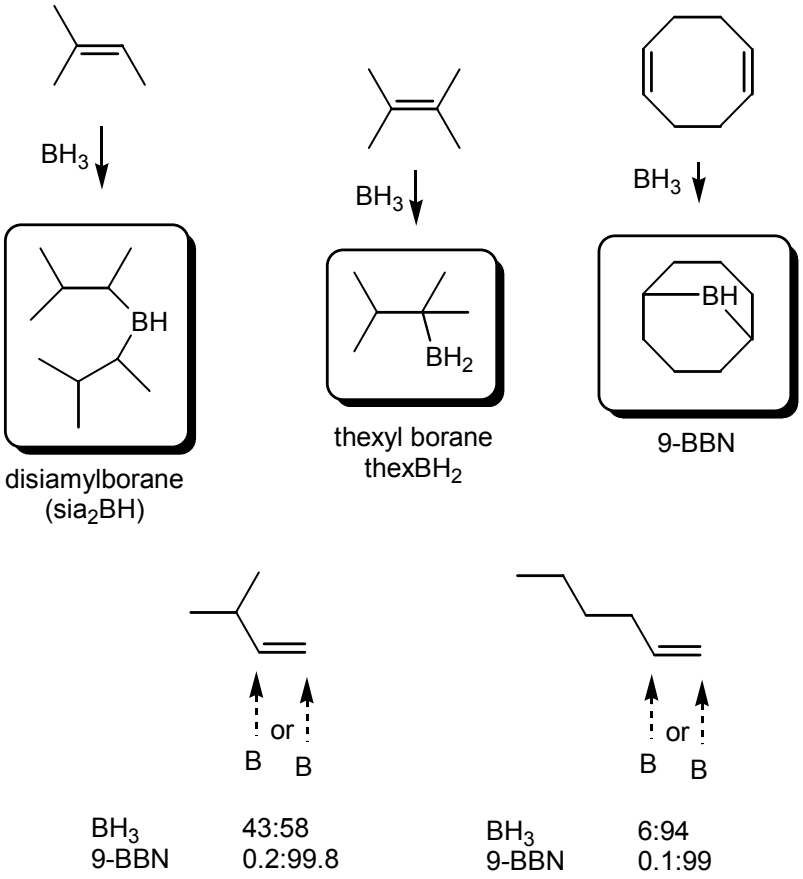
You've met this in first year. It's (surprise!) the addition of boron and hydrogen across a C-C double or triple bond, and takes place *via* a concerted four-membered transition state. This is a VERY useful reaction - Nobel Prize for Herbert C Brown (Purdue University) in 1979.
The utility springs from three observations about the reaction: it is **stereospecific** (*cis*-addition); **regioselective** (addition of B to less hindered end of the unsaturation); and the C-B bond is **synthetically useful** (can be used to make C-H, C-C, C-O and C-N bonds with retention of stereochemistry).



As alternative uses of the C-B bond, C-N bond formation is achieved by treatment with hydroxylamine-*O*-hydrogen sulfate; and C-B to C-H bond cleavage is achieved by heating with carboxylic acids. (As you will probably see next year, the C-B bond can also be used for C-C bond formation….)

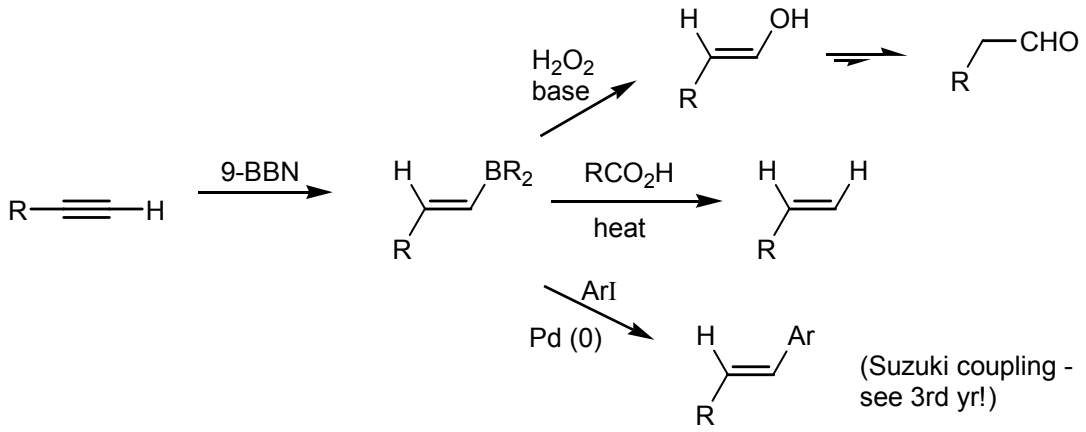


Remember that boron attacks the less hindered end of an alkene, and that less hindered alkenes react quicker. We can use this to make di and monoorganoboranes, which can be used as more selective borane equivalents. For example, 9-BBN gives better regioselectivity in the hydroboration of monosubstituted alkenes than does BH_3 itself.
Although we won't go into this, it's also possible to make chiral boranes which can be used for enantioselective hydroboration of alkenes.



3.2.1 Hydroboration of alkynes

Hydroboration of alkynes gives vinyl boranes, which will undergo exactly the same kind of reactions as alkyl boranes.



Next time (Thurs 11th Dec at 9am): reduction of aromatics, enones, C-X.

AA 4.12.03