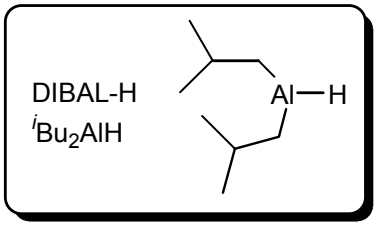
Functional Group Interconversions - Lecture 2

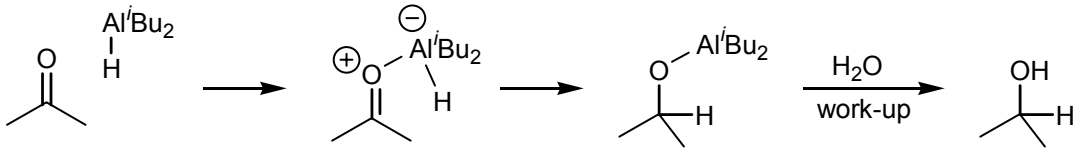
2. Hydride transfer reagents (cont.)

ii) 'electrophilic' hydride reagents

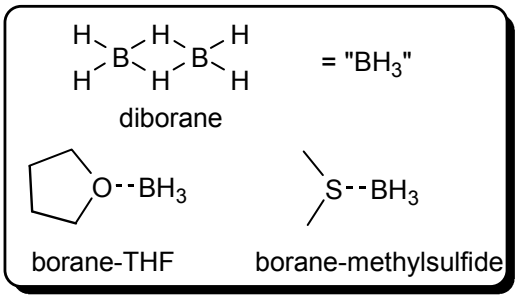
a) diisobutylaluminium hydride



Available as solutions from Aldrich. The tricoordinate aluminium is, of course, a strong Lewis acid. It won't give up H^- to become an Bu_2Al^+ cation; rather it waits until it is complexed by a Lewis base (*eg* a carbonyl group!) then donates its hydride. The fact that only one hydride per molecule of DIBAL-H is delivered, coupled with its electrophilic character, makes it a useful reagent - often it can perform selective reductions not available with $LiAlH_4$, *eg* selective reduction of esters to aldehydes (see later).



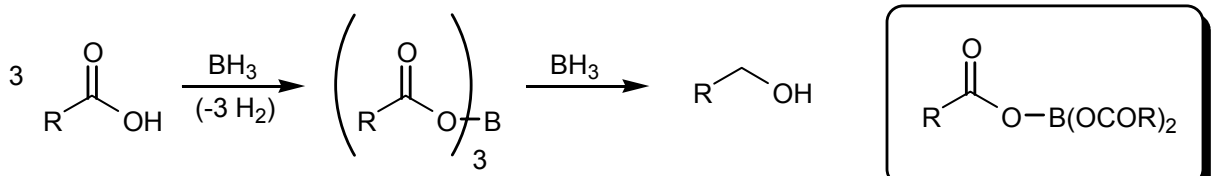
b) boranes



The parent compound is diborane (B_2H_6), but it is commonly used as a solution in THF (where the active species is a BH_3·THF complex) or as its complex with dimethyl sulfide (BH_3·Me_2S). Note also that we can replace up to two of the hydrides by alkyl groups (mono and dialkylboranes) which still perform the same reactions, but being bulkier can often offer greater selectivity compared to 'BH_3'.
Since boron is in the same period as aluminium, there are similarities in the mode of action to DIBAL-H (though not in terms of absolute reactivity).

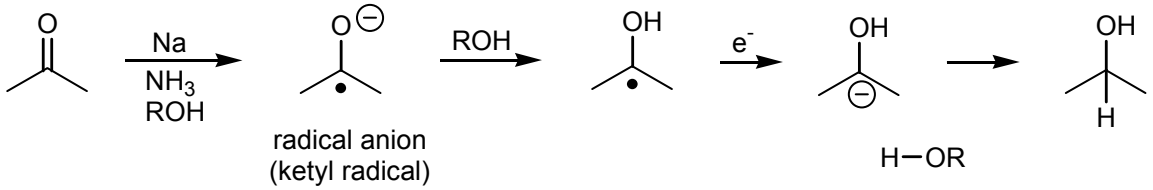
Reaction of BH_3 with aldehydes and ketones is slow unless a catalyst is added….see later for a useful application of this! Reaction with alkenes and alkynes (hydroboration) is of course facile - we'll also discuss this later.

Note the speed of reaction with carboxylic acids, since they rapidly form triacyloxyboranes. These intermediates are readily reduced (possibly because the overlap of the O lone pair with B reduces their "ester type" resonance stability). ***Thus, borane can be used to selectively reduce RCO_2H in the presence of ketones and esters.***



3. Dissolving metal reductions

Usually metals such as Li, Na, K, Ca, Mg, Zn, Sn, Fe (often as amalgams - to improve reactivity).
Reactions are often carried out in liquid ammonia, and can be viewed as being caused by 'solvated electrons'. The intermediates are often radical anions, and a range of useful transformations of C=O, C=C and other multiple bonds and C-X bonds can be accomplished.



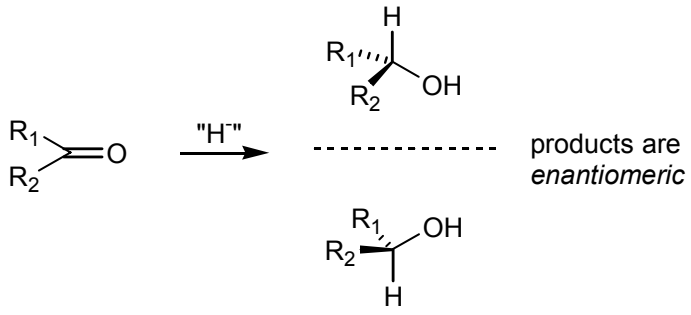
Now we've seen the main classes of reducing agent, we'll look at the issues surrounding the (selective) reduction of various FG, including the "best" reagent for each case.

Section 1: C=X reductions

1.1 *Reductions of aldehydes and ketones to alcohols*

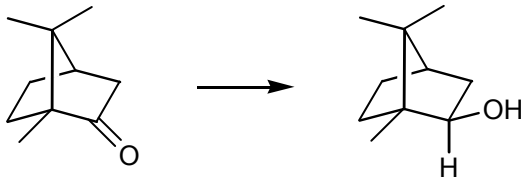
Many reagents will effect this transformation. **$NaBH_4$** is often the reagent of choice.

Stereochemistry in the reduction of ketones to alcohols
As we've already seen, addition of hydride to unsymmetrical ketones gives rise to an asymmetric centre. Reaction of achiral reagents with ketones containing no existing asymmetric centres gives rise to a racemic mixture. This can be altered by the use of chiral reagents (or catalysts) - see later.

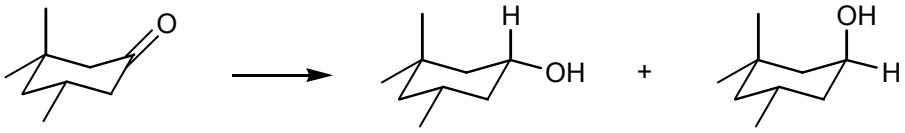


If the ketone already contains some asymmetric centres, the reaction with even achiral reagents gives rise to *diastereomeric* products. We can predict the stereochemical outcome using certain models. They usually revolve around making sure the hydride approaches from the less hindered 'diastereotopic' face of the ketone.

For cyclic ketones, it is often easy to predict which face is less hindered. For example:



Reduction of cyclohexanones has been particularly widely studied. In the absence of steric hindrance in the ketone substrate, unhindered reducing agents (e.g. $LiAlH_4$, $NaBH_4$) often prefer to attack from an axial trajectory (see Dr. Spivey's course for an explanation). More hindered reagents are likely to provide more of the product arising from attack on the less hindered face (often from an equatorial trajectory). In contrast to these kinetically controlled (irreversible) hydride reductions, dissolving metal reduction of carbonyls will often lead to the thermodynamically more stable alcohol.

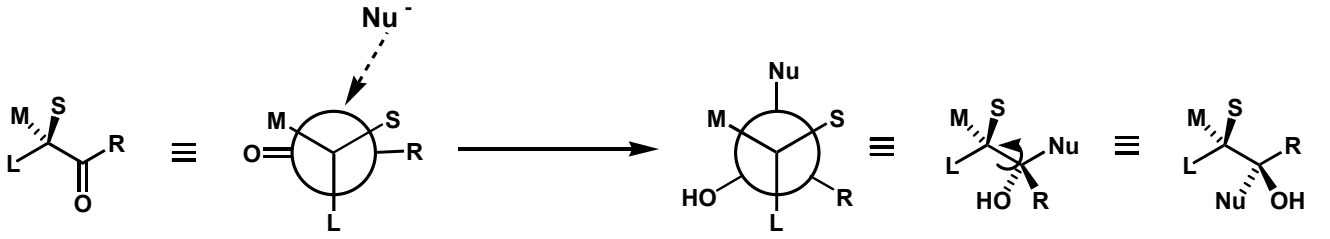


$LiAlH_4$	1 : 1
$LiAl(O^tBu)_3H$	1 : 10
Na / ROH	99:1

For acyclic ketones, it is often much less obvious which face is the less hindered. However, there are some very useful predictive models. Historically, the first was *Cram's rule* (Professor D J Cram, UCLA, Nobel Prize, 1987), so you will often hear people talking about the "Cram product" or "Cram selectivity"). However, a much more widely accepted model nowadays is the ***Felkin-Anh model*** as it agrees with theoretical studies on the transition state for addition to carbonyl groups. It also allows us to predict facial attack on α-alkoxy ketones when a non-chelating reducing agent is used.

The key feature in the Felkin-Anh model is the need to prevent eclipsing interactions (torsional strain) – in other words, a staggered arrangement in the transition state is preferred. The substituents on the stereocentre α-to the carbonyl group are assigned as **L**arge, **M**edium and **S**mall (based primarily on their steric size). The ketone is drawn in a Newman projection with the **L**arge group perpendicular to the carbonyl. The nucleophile would then be expected to attack opposite to the **L**arge group. However, there are two possible conformations which would lead to attack on "opposite" (diastereotopic) faces of the carbonyl group. Remembering the preferred attack angle on the carbonyl group of ca. 109º– the Burgi-Dunitz angle (see Dr Spivey's course) we predict that reaction via conformation A, where the nucleophile's closest contact is with the **S**mall group, will be favoured over conformation B, where the nucleophile approaches over the **M**edium group.

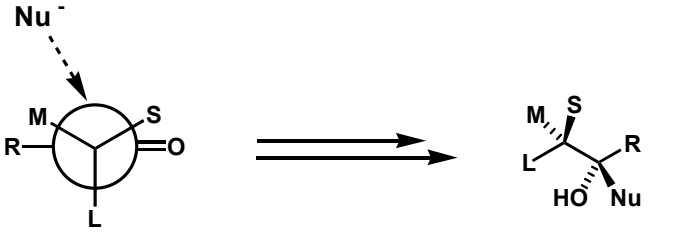
Felkin-Anh model



major product

(*conformation **A***)
Nucleophile approaches anti to L
from Burgi-Dunitz angle

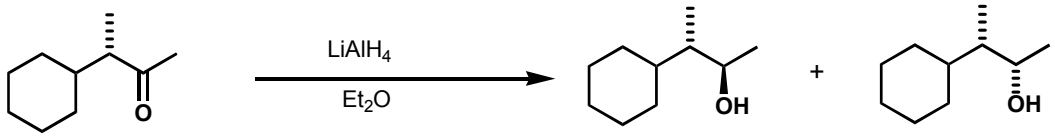
favoured over:



minor product

(*conformation **B***)

The Felkin-Anh model allows us to predict what will be the major diastereomer formed, but the exact ratio of diastereomers will depend on a range of factors (substituents, reducing agent, solvent, temperature, etc….). In the example below, the major isomer obtained is that predicted by the Felkin-Anh model - check this!



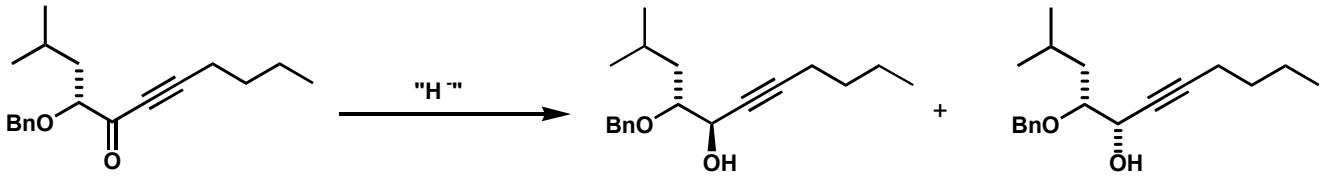
72 : 28

α-heterosubstituted ketones

An α-heteroatom (often an α-alkoxy substituent) often occupies the position of the "**L**arge" substituent, which may not be obvious based on simple steric considerations. This is due to electronic effects as indicated below, or to electrostatic repulsion between the nucleophile and OR.

When we have an α-alkoxy substituent and chelating metal salts are used as or with reducing agents, we need to use a different model – the *chelate model* (or "chelation control"). The chelating metal holds the carbonyl group and the α-alkoxy substituent in the same plane, and the nucleophile then attacks from the less hindered face.

Note that Felkin-Anh and chelate modes of attack on α-alkoxy ketones give opposite diastereomers from the same starting compound – we can use this to our advantage!

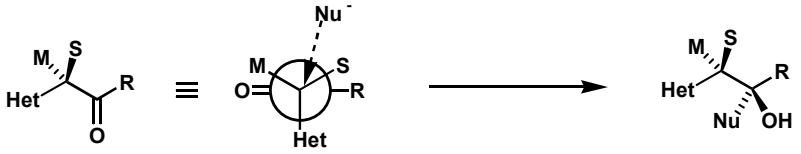


K-selectride (K^sBu_3BH): 90 : 10

$Zn(BH_4)_2$: 5 : 95

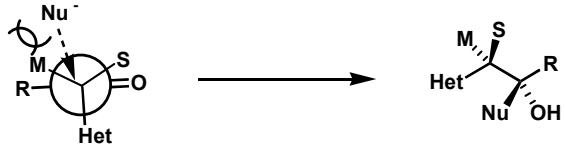
With K-selectride: non-chelate control. Felkin-Anh model with the α-heteroatom adopting the "**L**arge" position.

heteroatoms sit perpendicular to the C-O bond (ie in plane with the π-cloud) in the Felkin-Anh model:

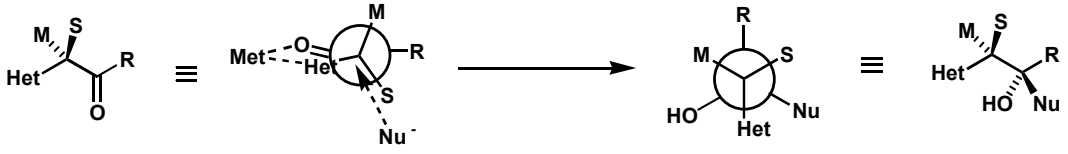


(reason is extra stabilisation of nucleophilic attack by C-Het anti-bonding orbital)

cf:



With $Zn(BH_4)_2$: chelate control:

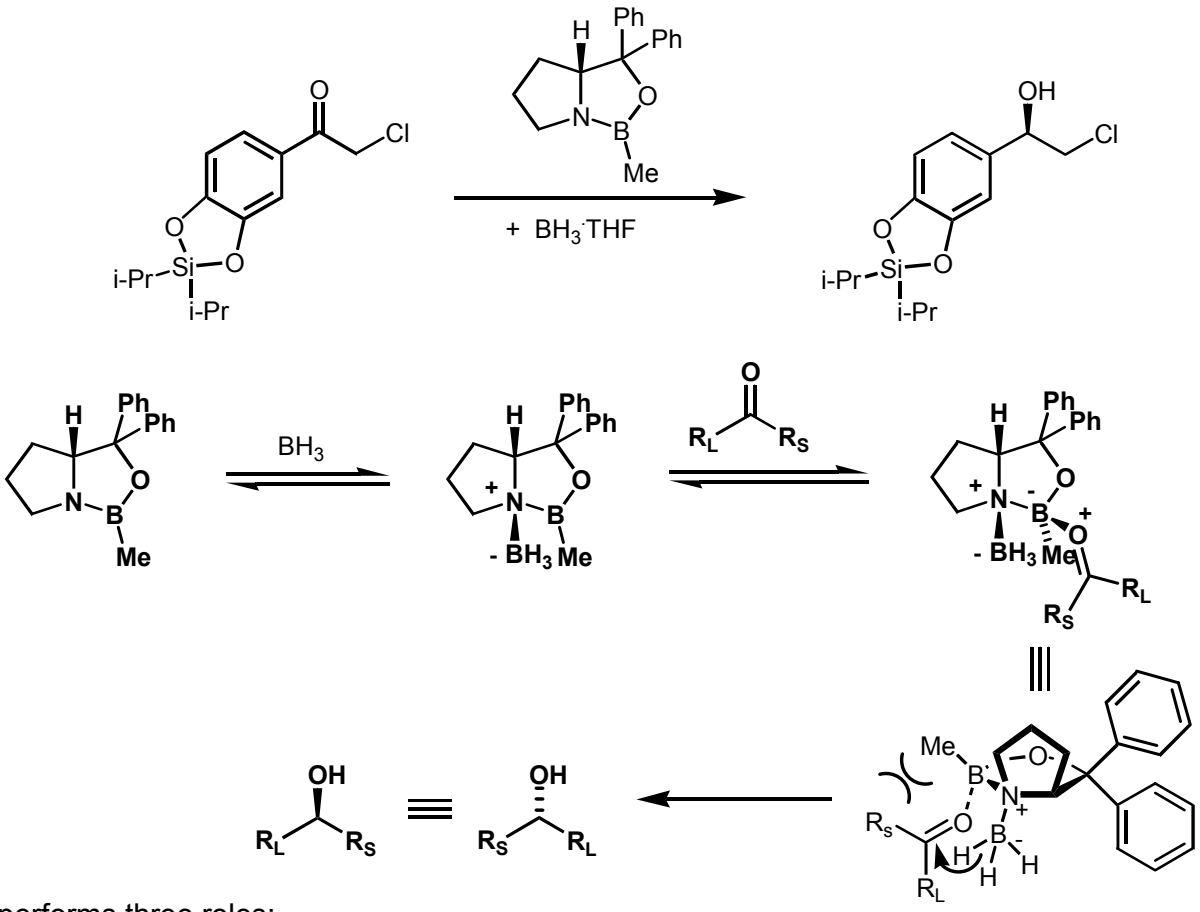


path depends upon nature of the heteroatom (O best), nature of the metal (divalent cations good for chelation), protecting group on the heteroatom (bulky groups prevent chelates), solvent (chelate favoured in non-polar solvents)

Asymmetric reduction

Can make use of chiral reagents or, better, chiral catalysts. The chiral oxazaborolidine catalysts perfected by Professor E J Corey (Harvard University, Nobel Prize 1990 - you'll hear more of him!) are a beautiful example of design in synthesis.

Catalytic asymmetric reduction with oxazaborolidines



Catalyst performs three roles:

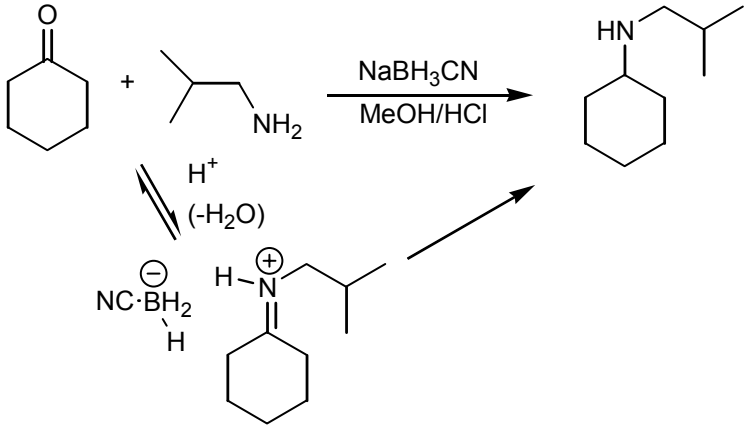
a) activates borane as reducing agent through coordination of Lewis basic nitrogen

b) activates carbonyl towards reduction through coordination to Lewis acidic boron

c) pre-organises substrates for intramolecular hydride delivery in asymmetric environment

1.2 *Reduction of imines to amines*

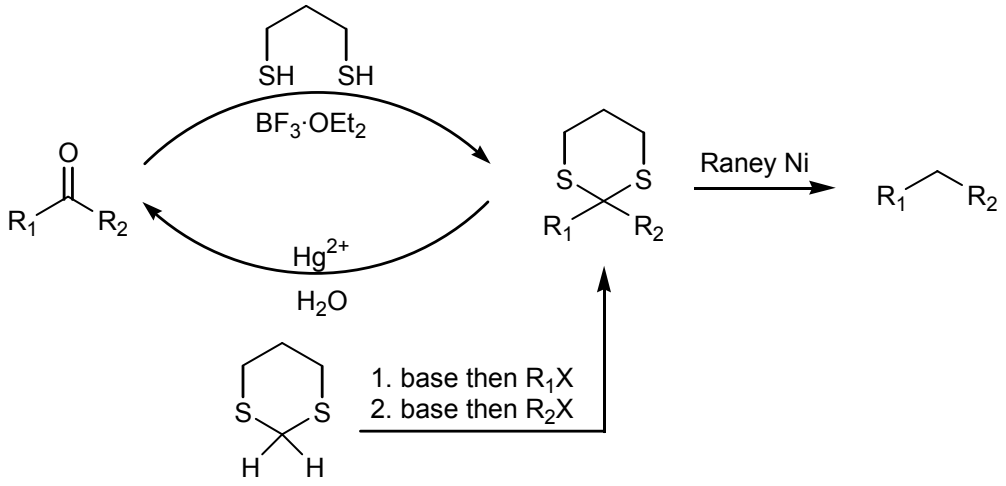
Imines are less electrophilic than ketones, so although $LiAlH_4$ and H_2/Pd will reduce them, $NaBH_4$ is often slow. If you protonate them, this produces the much more electrophilic iminium species. The acidic reaction conditions require the use of $NaBH_3CN$ as a more acid-stable version of $NaBH_4$. The iminium formation can be performed in the same reaction pot as the reduction – this is called *reductive amination*, and is an important method for amine synthesis:



1.3 *Reduction of ketones to alkanes*

Ketones can be reduced to alkanes by several methods; you met some of these last year (Dr Law's Carbonyls course): the Clemmensen reduction (Zn/Hg, HCl), and the wonderfully named "Huang-Minlon modification of the Wolff-Kischner reaction" (heating with hydrazine (NH_2NH_2) and KOH in ethylene glycol ($HOCH_2CH_2OH$). Another method is formation of a 1,3-dithiane derivative followed by treatment with Raney Ni. (Raney Ni is a finely divided form of Ni with H_2 adsorbed on it).

Remember from Prof Craig's course earlier this term that the 1,3-dithiane group can be deprotonated and reacted with carbon electrophiles, thus serving as an acyl anion equivalent. If we reduce it to the alkane instead, it acts overall as a methylene anion equivalent.



Next time (Thurs 4th Dec at 9am): carboxyl reduction and C=C reduction.

AA 27.11.03