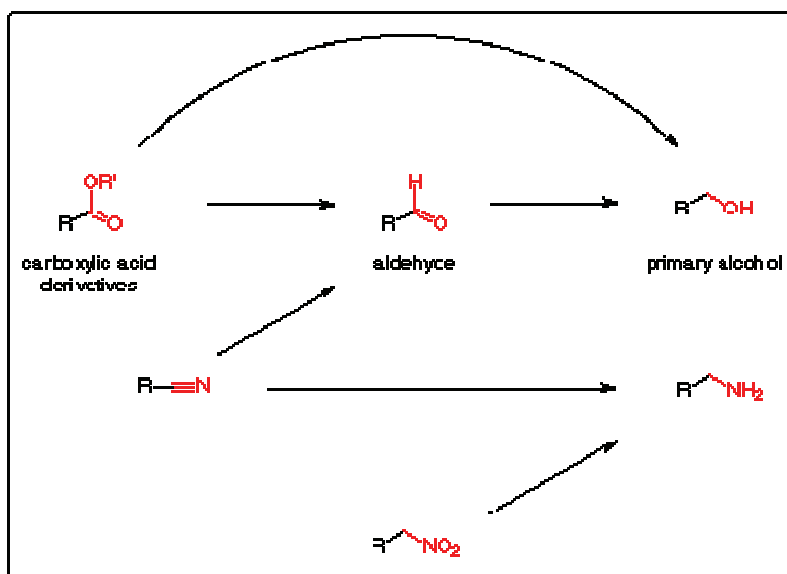


Reduction Reactions

Reduction of Carboxylic Acid Derivatives and Related Functionality



- **Chemoselectivity.** Many different functional groups can be reduced in a variety of ways. We often need to selectively reduce one functional group whilst leaving others intact.
- In the case of carboxylic acid derivatives there are two possible reduction products: aldehyde and alcohol. Ideally we need methods for selectively accessing either product.
- **Stereoselectivity.** Asymmetrically substituted ketones (prochiral ketones) provide secondary alcohols on reduction and introduce a new stereogenic centre into the molecule. We need methods for controlling the stereochemical outcome (relative and absolute) of this reduction using substrate or reagent (or both) control. Substrate-controlled diastereoselective reductions are considered in the following. Enantioselective reductions are covered in the organic classes of the master level.

1. Hydride Reducing Agents

Some of the most important reducing agents are hydrides derived from aluminium and boron. There are numerous varieties differing principally in their reactivity. They all act as sources of nucleophilic hydride and therefore are most reactive towards electrophilic species.

1.1 Lithium Aluminium Hydride (LiAlH₄)


One of the most powerful reductants

Highly flammable reagent and therefore must be used with care.

Reactions are normally carried out in ethereal solvents (*e.g.* THF, Et₂O); LiAlH₄ reacts violently with protic solvents (*c.f.* NaBH₄).

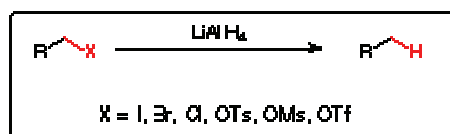
The extremely high reactivity of LiAlH₄ imparts relatively low levels of chemoselectivity for this reagent. However it is most reactive towards strong electrophiles.

Ease of Reduction of some Functional Groups with LiAlH₄

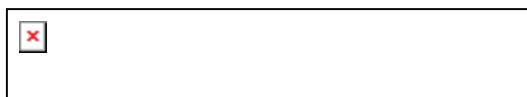
substrate	product	ease of reduction
aldehyde RCHO	RCH ₂ OH	most readily reduced most
ketone RC(O)R'	RCH(OH)R'	
acid chloride RC(O)Cl	RCH ₂ OH	
lactone	diol	
epoxide 	RCH ₂ CH(OH)R	
ester RC(O)OR'	RCH ₂ OH + R'OH	
carboxylic acid RCO ₂ H	RCH ₂ OH	
carboxylate salt	RCH ₂ OH	
amide RC(O)NR' ₂	RCH ₂ NR' ₂	
nitrile RCN	RCH ₂ NH ₂	
nitro RNO ₂	RN=NR	difficult to reduce
isolated alkene RCH=CHR		

In addition to being capable of reducing virtually every carboxylic acid derivative, the high reactivity of LiAlH₄ makes it useful for reducing other functional groups:

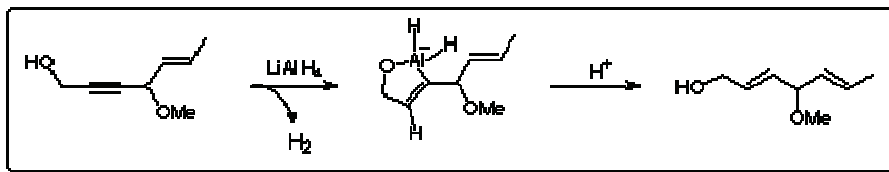
Reduction of halides and sulfonates:



Reduction of propargylic alcohols to (*E*)-allylic alcohols:



In this case the proximal alcohol is essential. The reaction proceeds through *trans*-selective hydrometallation of the triple bond releasing the alkene on protolytic work-up:

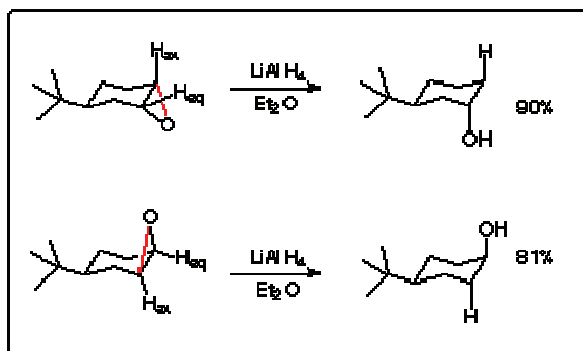


Epoxide Ring-Opening

In the case of unsymmetrically substituted epoxides issues of **regioselectivity** arise. In acyclic systems the nucleophile (hydride) tends to react in an S_N2 fashion at the less hindered end of the epoxide.



In cyclic systems there is a strong preference for axial attack (*trans* diaxial ring opening)



1.2 Sodium Borohydride (NaBH_4)

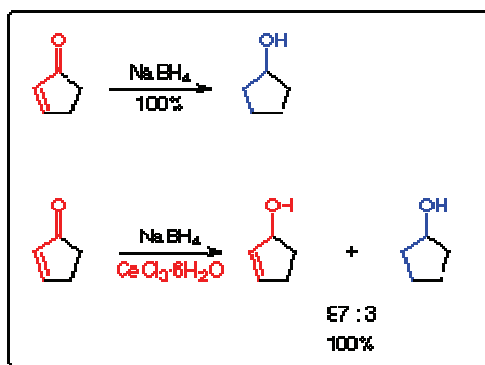
- Much milder than LiAlH_4
- Frequently used to chemoselectively reduce aldehydes and ketones in the presence of esters (esters are reduced with NaBH_4 but usually at a much lower rate; they are less electrophilic)
- reactions are carried out in protic solvents including H_2O . NaBH_4 is insoluble in most common aprotic solvents

Related Reagents: Lithium and Calcium Borohydride

Although the reactive component of sodium borohydride is the hydridic anion, the counterion can also be used to modulate the reactivity of the reagent system. A number of other borohydride reagents are available including LiBH_4 and $\text{Ca}(\text{BH}_4)_2$. Both these reagents are more reactive and readily reduce esters in addition to aldehydes and ketones. The increased reactivity of these reagents can be attributed to the increased Lewis acidity of the cations which confers increased electrophilicity on the carbonyl group (by Lewis acid-Lewis base formation).

1.3 Sodium Borohydride-Cerium (III) Chloride**Regioselective reduction of unsaturated carbonyl groups***1,2-Reduction using a 1:1 ratio of NaBH_4 and CeCl_3*

- good route to allylic alcohols



A. L. Gemal, J.-L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454-5459.

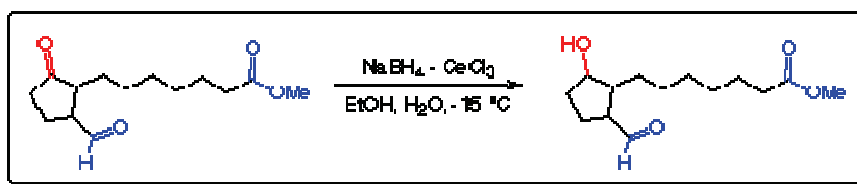
Methods to obtain selective 1,4-reduction:

- catalytic hydrogenation
- 'copper hydride' $[\text{PPh}_3\text{CuH}]_6$ (Stryker's reagent)

Chemoselective reduction of a ketone in the presence of a more electrophilic aldehyde

- Aldehydes are more electrophilic than ketones and therefore much more prone to hydration/acetalisation.
- Acetals are not reduced by borohydride reagents.
- Ce(III) is a good Lewis acid and strongly oxophilic - it promotes hydration of carbonyl groups especially aldehydes. Therefore it should be possible to temporarily mask an aldehyde as its acetal/hydrate to allow selective reduction of the ketone. Unmask the aldehyde in the work-up.

Solution: use 1:1 NaBH₄-CeCl₃ in wet EtOH:



A. L. Gemal, J.-L. Luche, *J. Org. Chem.*, 1979, **44**, 4187-4189.

1.4 Sodium Cyanoborohydride (NaCNBH₃)

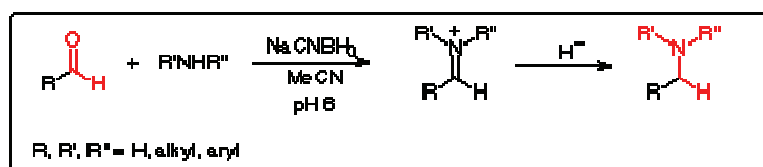
C. F. Lane, *Synthesis*, 1975, 135-146.

- a very useful borohydride reagent
- milder than NaBH₄ at pH 7
- reactivity is strongly pH dependent - it is one of the few borohydrides which tolerates acidic conditions (down to ~pH 3)

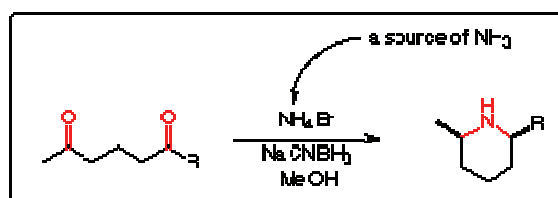
at pH 3-4: NaCNBH₃ readily reduces aldehydes and ketones

at pH 6-7: NaCNBH₃ readily reduces iminium ions but NOT C=O groups - this property is responsible for its most important use - **REDUCTIVE AMINATION**:

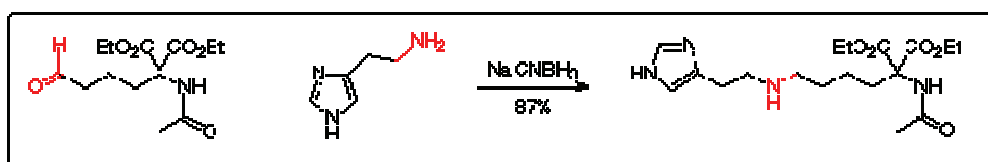
- a very useful method for synthesising secondary and tertiary amines by coupling a secondary or primary amine with an aldehyde or ketone.



Example 1

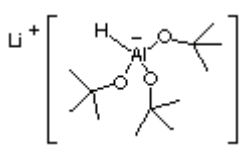
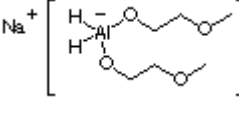
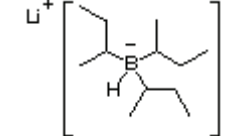


Example 2

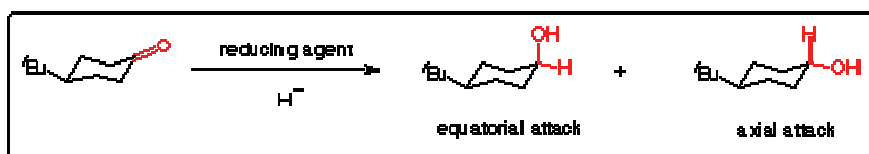


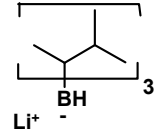
1.5 Other Hydridic Reducing Agents

There are many other hydride reducing agents. The following have been developed as bulky reducing agents for use in stereoselective reduction:

Reducing Agent	Comment
$\text{LiAl}(\text{O}i\text{-Bu})_3$ 	good for converting carboxylic acid derivatives to aldehydes
Red-Al $\text{Na}[\text{H}_2\text{Al}(\text{OCH}_2\text{CH}_2\text{OMe})_2]$ 	similar reactivity to LiAlH_4
L-Selectride $\text{LiHB}(\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3)_3$ 	similar reactivity to LiBH_4

Stereoselective Reduction of 4-tert-Butylcyclohexanone



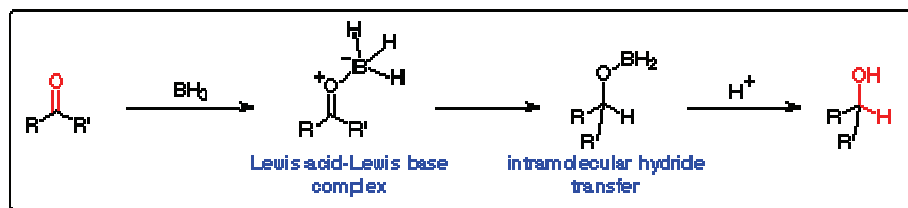
Reducing agent	equatorial attack	axial attack
LiAlH_4 (unhindered)	10	90
$\text{LiAlH}(\text{O}t\text{Bu})_3$ (more hindered)	10	90
$\text{LiBH}(s\text{Bu})_3$ (very hindered)	93 (RT)	7 (RT)
	96.5 (-78 C)	3.5 (-78 C)
Lithiumtris(tert-butyl)borohydride  (very very hindered)	100	0

2. Neutral Reducing Agents

The reagents discussed above are all hydridic and behave as nucleophiles - they react most readily with good electrophiles.

Another class of reducing agents are those which are neutral. They react through a different mechanism and as a result have quite different selectivities which are often complementary to the hydride reagents discussed earlier.

Basic mechanism



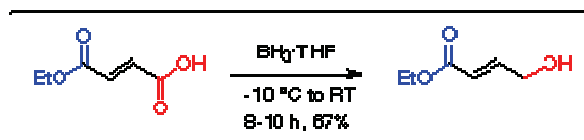
Comparison between Borohydride and Borane

Borohydride	Borane
Negatively charged	Neutral
Nucleophilic	Electrophilic
Valence shell of the central boron is a complete octet	6 electrons in the valence shell of the central boron - vacant pAO confers Lewis acidity
hydride transfer proceeds intermolecularly	hydride transfer is often intramolecular <i>via</i> a Lewis acid-Lewis base complex

2.1 Borane (BH₃)

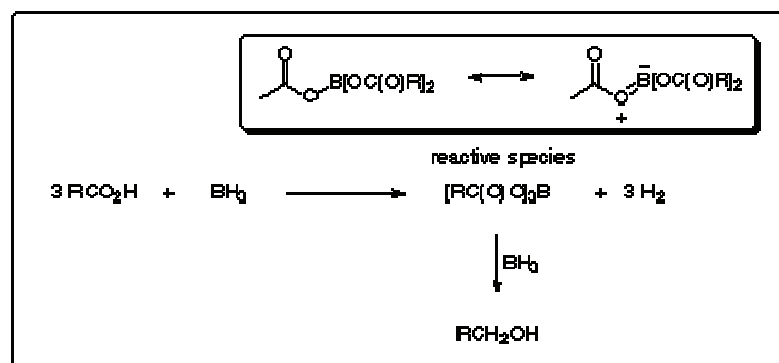
Borane is too unstable to be isolated (exists either as the dimer B₂H₆ or a Lewis acid-Lewis base complex *e.g.* BH₃ x THF or BH₃ x Me₂S).

- very useful reagent for selectively reducing carboxylic acids to alcohols in the presence of esters
- amides are also readily reduced to the corresponding alcohols



The more electron rich carboxylic acid derivatives appear to be reduced most readily - complete opposite reactivity to hydridic reducing agents.


Borane reacts with the carboxylic acid to generate a triacyloxyborane (protonolysis). This is essentially a mixed anhydride and therefore very reactive. Esters cannot react in this way and are therefore reduced at a slower rate.



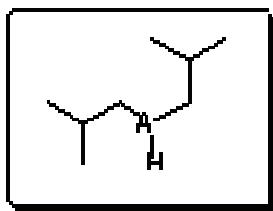
Caution!

Borane is a good reducing agent but it is also very useful for hydroborating unsaturated systems (triple and double bonds) - **chemoselectivity** may be a problem.

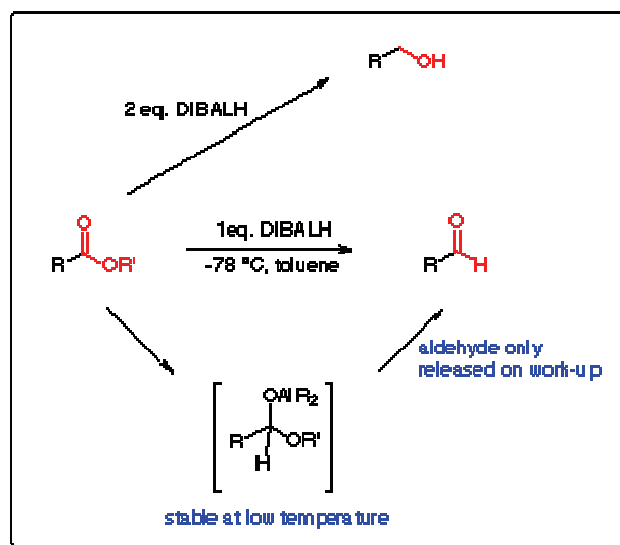
Ease of Reduction of some Functional Groups with Borane

Substrate	product	ease of reduction
Carboxylic acid RCO_2H	RCH_2OH	most readily reduced most
isolated alkene $\text{RCH}=\text{CHR}$	$(\text{RCH}_2\text{CHR})_3\text{B}$	
Ketone $\text{RC}(\text{O})\text{R}'$	$\text{RCH}(\text{OH})\text{R}'$	
Nitrile RCN	RCH_2NH_2	
Epoxide 	$\text{RCH}_2\text{CH}(\text{OH})\text{R}$	
Ester $\text{RC}(\text{O})\text{OR}'$	$\text{RCH}_2\text{OH} + \text{R}'\text{OH}$	difficult to reduce
Acid chloride $\text{RC}(\text{O})\text{Cl}$		

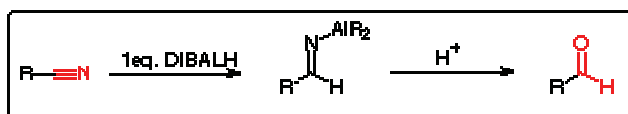
2.2 Diisobutylaluminium Hydride (DIBALH)



- very widely used reducing agent especially for reducing esters
- esters can be reduced to either the aldehyde **or** the alcohol depending on the stoichiometry and reaction conditions:



Nitriles are also reduced to aldehydes. In this case reaction proceeds *via* the imine which hydrolyses on acidic work-up to afford the aldehyde product:

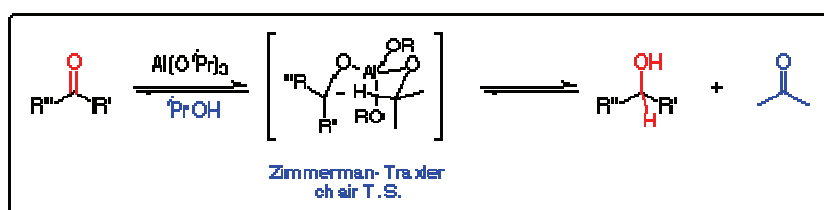


Lactones provide a useful method for preventing over-reduction of the aldehyde product. In these cases the lactone is reduced to a lactol, the hemiacetal functionality essentially masking the aldehyde and preventing over-reduction:



2.3 Meerwein-Ponndorf-Verley Reduction with $\text{Al}(\text{O}i\text{Pr})_3$

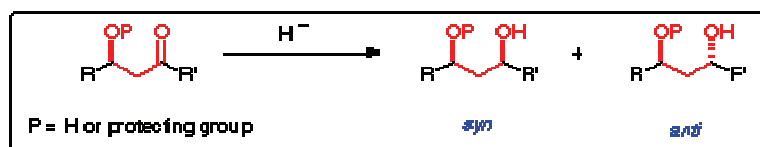
- a relatively old method of reducing carbonyl groups (principally aldehydes and ketones)
- isopropanol behaves as the hydride donor
- the by-product is acetone
- the reaction is reversible - the reverse oxidation is known as the **Oppenauer Oxidation**.
- the mechanism is typical of a range of reagents proceeding through a well-defined chair-like T.S. (Zimmerman-Traxler) in which the *beta*-hydride is transferred **intramolecularly** to the carbonyl group.



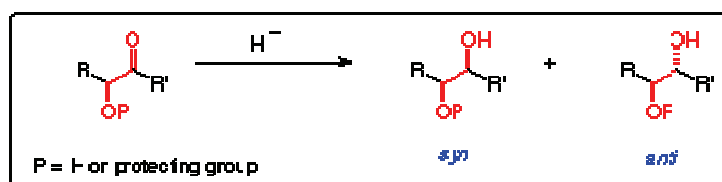
3. Stereoselective Reduction of Prochiral Ketones

The addition of hydride nucleophile to chiral ketones provides diastereoisomers - when the stereogenic centres are close to the carbonyl group then by careful choice of protecting group, reaction conditions and reducing agent a high degree of stereoselectivity can often be obtained in the reduction. 1,2- and 1,3-diols are widespread in natural products. Stereoselective reduction of hydroxyketones provides a reliable route to incorporating such functionality.

Diastereoselective 1,3-reduction:



Diastereoselective 1,2-reduction:



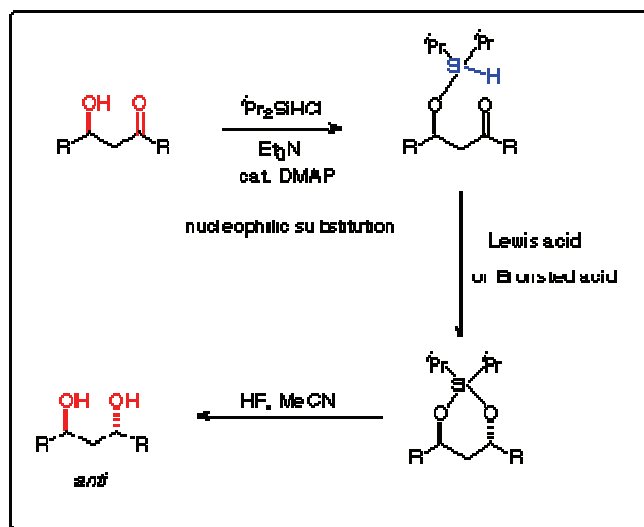
1. F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry: Volume B*, Plenum Press, New York, 1990 (3rd Edition), pp 241-244.
2. M. B. Smith, *Organic Synthesis*, McGraw-Hill, New York, 1994, pp 400-417.
3. E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, pp 858-938 for an indepth discussion of this area of Chemistry

3.1 Diastereoselective Formation of *Anti*-1,3-Diols

A number of methods have been developed for forming the *anti*-1,3-diol from the corresponding chiral 2-hydroxy-ketone. All rely on the so-called **DIRECTED REDUCTION** which takes advantage of the intramolecular hydride transfer through a well-defined 6-membered chair-like transition state (*compare*: Meerwein-Ponndorf-Verley reduction).

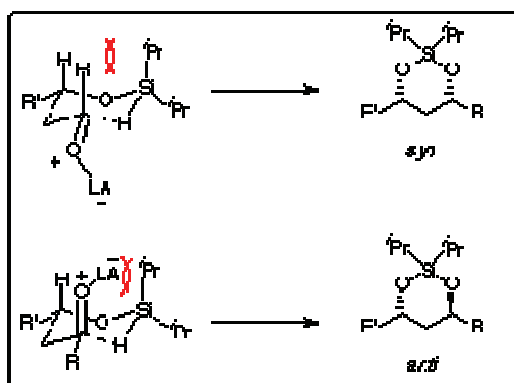
3.1.1 Intramolecular Hydrosilylation

S. Anwar, A. P. Davis, *Tetrahedron*, 1984, **40**, 2233-2238.



- Step 1: form silyl ether
- Step 2: Treat silane with Lewis or Brønsted acid to induce hydride transfer. Levels of diastereoselectivity are good to excellent *anti*:*syn* 320:1 to 120:1 (BF_3OEt_2 and SnCl_4 give particularly good results).
- The silyl acetal product is stable and the isopropyl groups make this functionality a suitable diol protecting group.
- Fluoride-induced deprotection of the silyl acetal provides the free diol.

Intramolecular hydride transfer through a chair-like T.S. accounts for the stereochemical outcome of the reaction.

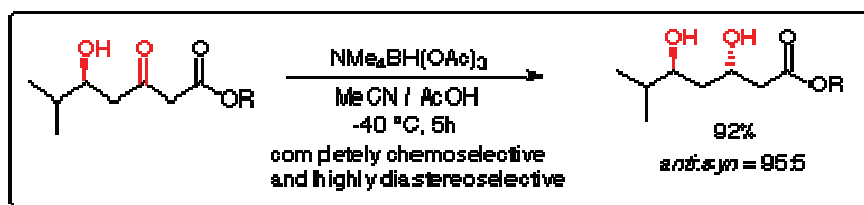


3.1.2 Tetramethylammonium Triacetoxyborohydride (Evans)

Evans has introduced an alternative approach using $\text{Me}_4\text{NBH}(\text{OAc})_3$.

D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560-3578.

Although the levels of selectivity are not as high as the Davis method the reaction is easier to perform and generally higher yielding (pay-off):



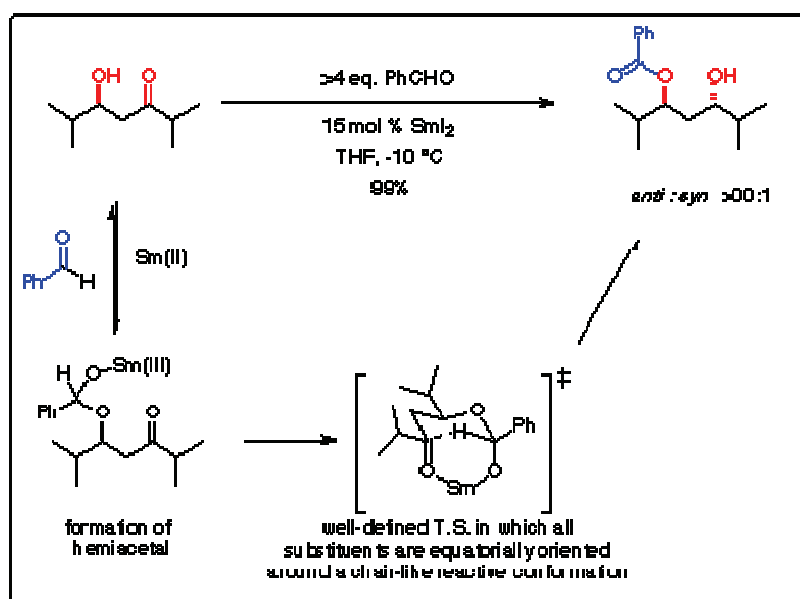
Note that only the ketone is reduced - the ester remains intact (**chemoselective**)

3.1.3 Evans-Tishchenko Reduction

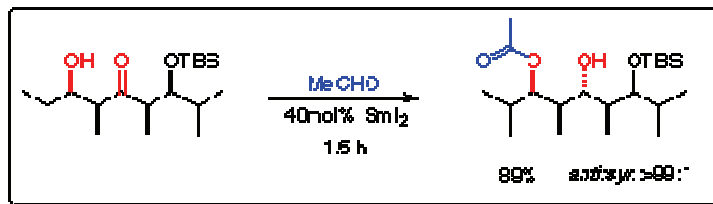
D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.*, 1990, **112**, 6447-6449.

- provides *anti*-1,3-diol with high levels of stereocontrol
- one potential advantage is that the directing hydroxyl group is protected as an ester (the choice of aldehyde determines the nature of the PG)
- this allows differentiation of two secondary alcohols which is sometimes difficult to achieve starting from the 1,3-diol.

The mechanism involves the reaction of a 2-hydroxy ketone with an aldehyde (source of acyl protecting group) and is mediated by samarium diiodide (SmI_2). The samarium ensures the formation of a well-defined transition state (by coordination - lanthanides are strongly oxophilic) and directs the transfer of hydride from the aldehyde to the ketone.



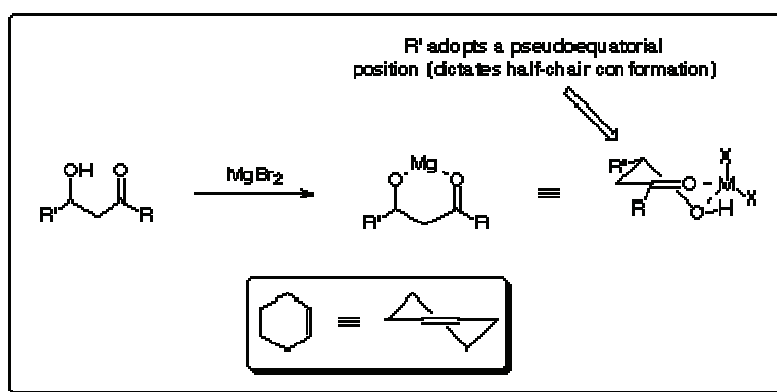
Another example:



3.2 Diastereoselective Formation of *Syn*-1,3-Diols

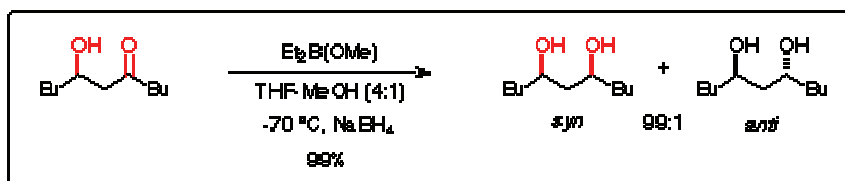
Chelate-Controlled Intermolecular Hydride Delivery

Metals capable of forming a chelate between the 2-hydroxyl group and ketone provide a molecular conformation which resembles that of cyclohexene:



- INTERmolecular hydride delivery on the chelate provides *syn*-1,3-diol products.
- The most reliable reaction conditions are Et₂B(OMe)-NaBH₄ at low temperature:

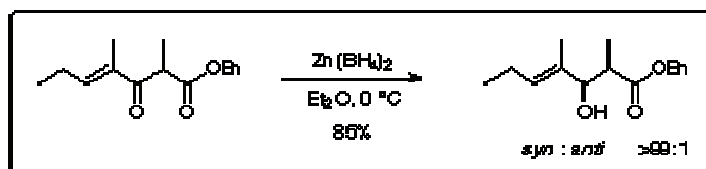
K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repic, M. J. Shapiro, *Tetrahedron Lett.*, 1987, **28**, 155-158.



- other reagents which also give good *syn* selectivity are Zn(BH₄)₂ and DIBALH

K. Narasaka, F.-C. Pai, *Tetrahedron*, 1984, **40**, 2233-2238.

There are numerous variants on this theme (internal chelation followed by intermolecular hydride delivery). For an example in which an ester is used to form the chelate:

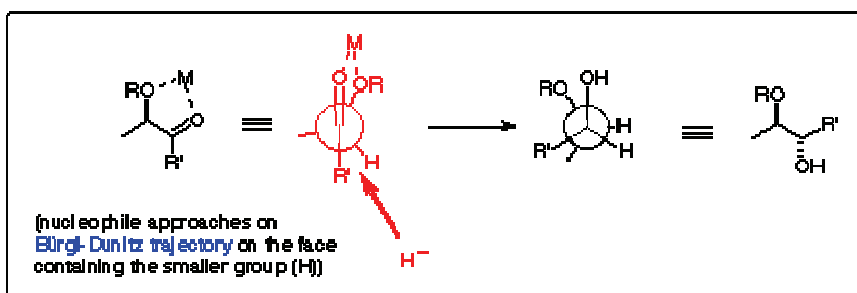


3.3 Diastereoselective Formation of *Anti*-1,2-Diols

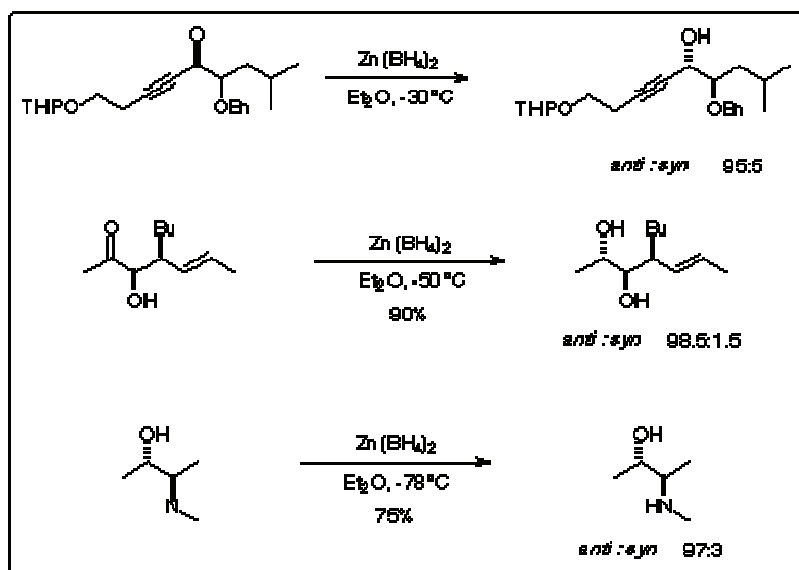
Chelation control requires:

- a free alcohol *or* a protected alcohol in which the protecting group can still form a chelate (alkyl ethers).
- a metal which can form a chelated intermediate (typical metals include Zn(II), Mg(II), Ti(IV) *etc.*)

The chelated intermediate is much more conformationally rigid and sterically differentiates the two diastereotopic faces of the carbonyl group. [This is Cram chelation]



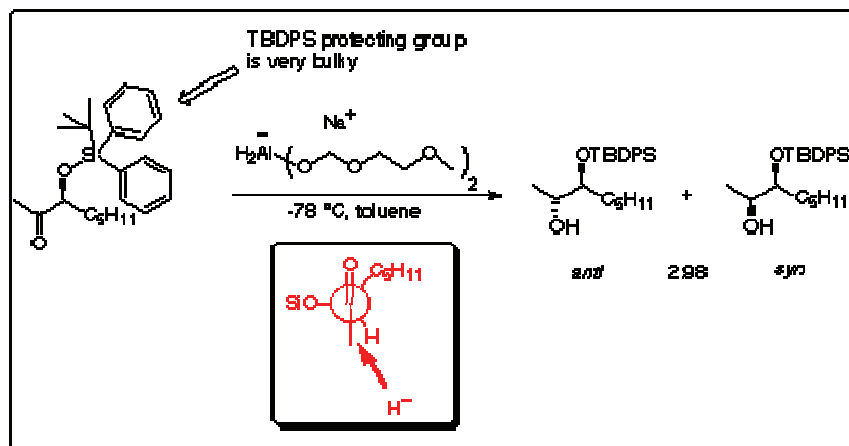
Examples:



3.4 Diastereoselective Formation of *Syn*-1,2-Diols

This requires:

- careful choice of protecting group; one which suppresses chelate formation and is very bulky (large silyl protecting groups are ideal).
- use Felkin-Anh T.S. analysis to account for the stereocontrol.



For other examples:

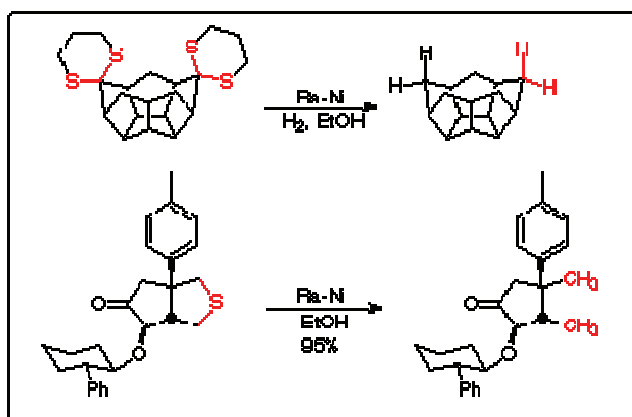
1. T. Takahashi, M. Miyazawa, J. Tsuji, *Tetrahedron Lett.*, 1985, **26**, 5139-5142.
2. L. E. Overman, R. J. McCready, *Tetrahedron Lett.*, 1982, **23**, 2355-2358.

4. Other Methods of Reduction

4.1 Raney-Nickel

most widely used in the *hydrogenolysis* of C-S bonds.

Examples:

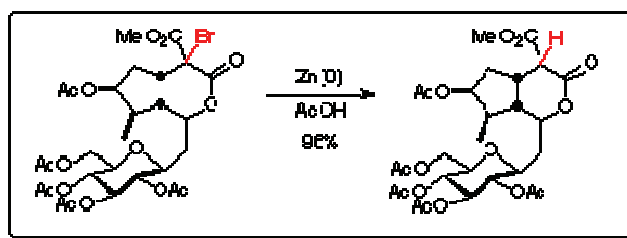


- also used in the hydrogenation of alkenes and alkynes.

4.2 Zinc in Acidic Media

Reduction of α -haloketones

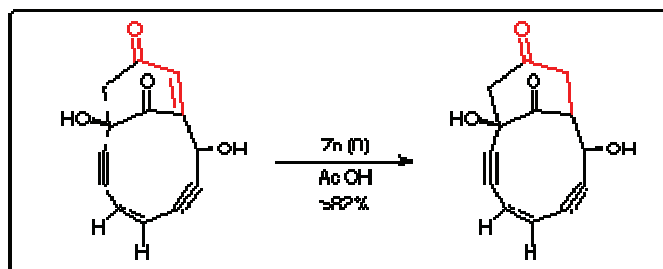
Example:



Note the lactone, acetate, glycosidic linkage and acetal all remain intact.

1,4-Reduction of Enones

Example:

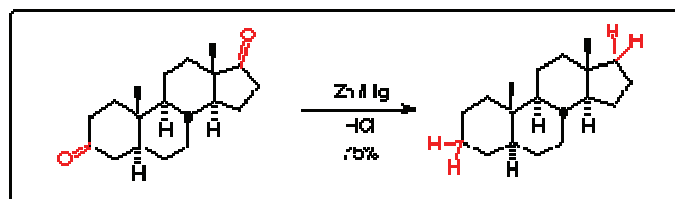


Note that there is a zinc enolate intermediate; this reaction can therefore be used for regioselective formation of enolates.

Clemmenson Reduction

- A classical method for complete reduction of a carbonyl group (in ketones and aldehydes).
- Reaction conditions are fairly vigorous.

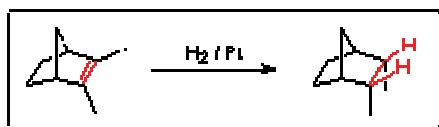
Example:



4.3 Hydrogenation with Hydrogen and a Transition Metal Catalyst

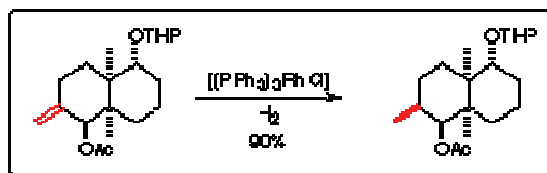
- Typical catalysts are Pt, Pd, Rh, Ru and Ni (late transition metals) - usually used as finely dispersed solids or adsorbed on an inert support such as charcoal or alumina.
- Reaction takes place on the surface of the metal - heterogeneous catalysis.
- Hydrogen is invariably transferred on to the less hindered face in a *syn* addition process.

Example:



- A variety of homogeneous catalysts are also effective *e.g.* Wilkinson's catalyst $[(PPh_3)_3RhCl]$
- Transition metal-catalysts in the presence of H_2 will reduce carbonyl groups although the rate is usually lower than the reduction of olefins (allows chemoselectivity).

Example:

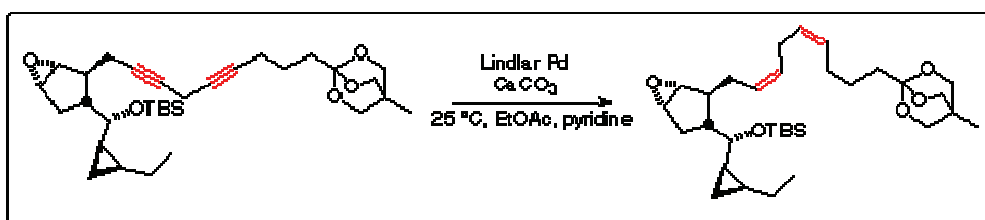


Enantioselective reduction is possible, but is not discussed here.

4.3.1 Partial Reduction of Alkynes

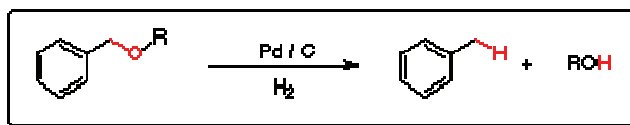
- a useful route to (*Z*)-alkenes
- need to modify the catalyst to minimise over-reduction
- Lindlar's catalyst (Pd-CaCO₃-PbO) is the most widely used. The PbO tempers the reactivity of the catalyst by acting as a catalyst poison.
- Other systems include Pd-BaSO₄ poisoned with quinoline.

Example:



4.3.2 Hydrogenolysis

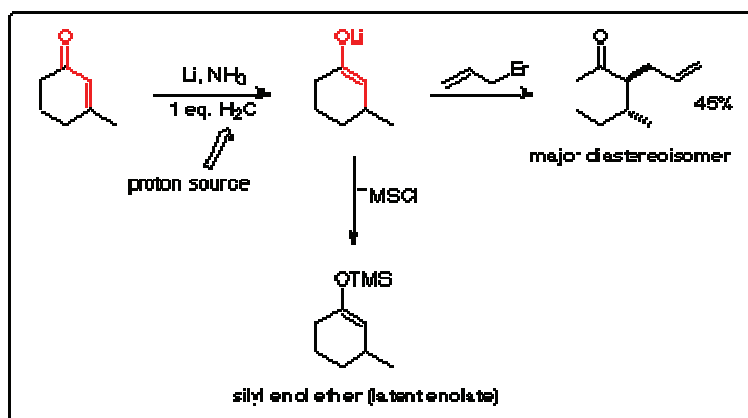
- Benzyl ethers are readily cleaved by Pd/C/H₂ to provide the free alcohol and toluene.
- Cleavage occurs under mild and neutral conditions.
- As a result, benzyl ethers are frequently used as alcohol protecting groups.



5. Dissolving Metal Reductions (Sodium/Ammonia or Lithium/Ammonia)

- Reactions proceed *via* single electron transfer processes.

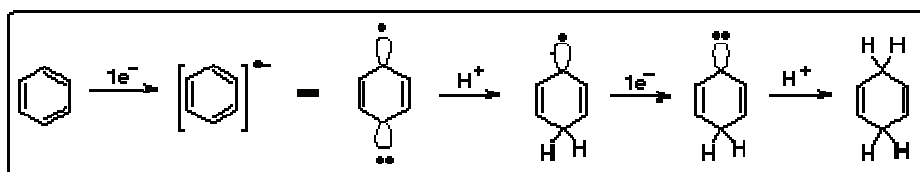
5.1 Regiospecific Enolate Formation



5.2 Birch Reduction

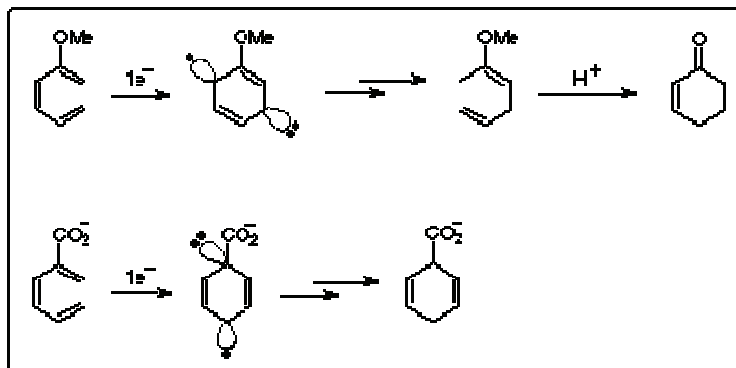
Partial reduction of aromatic rings

Mechanism:



- Under the (relatively controlled and mild) reaction conditions, reduction stops at the dihydro stage.

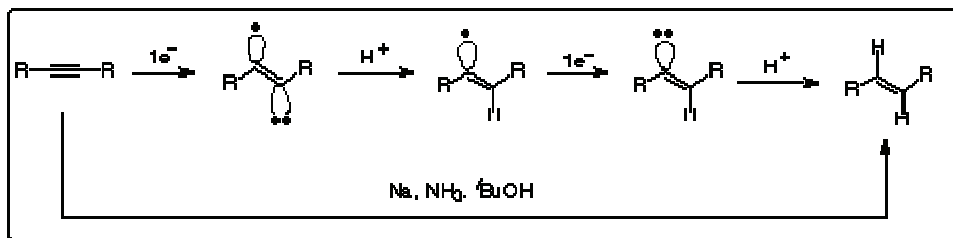
- The rate of reduction is influenced by the substituents on the ring - as the intermediates are negatively charged, the rate is, not surprisingly, increased by electron withdrawing substituents.
- Substituents also dictate the regiochemistry of protonation:



5.3 Reduction of Alkynes

- a useful route to (*E*)-alkenes
- equilibration of the radical or radical anionic intermediates ensures the thermodynamically more stable alkene is produced (usually the (*E*)-alkene).

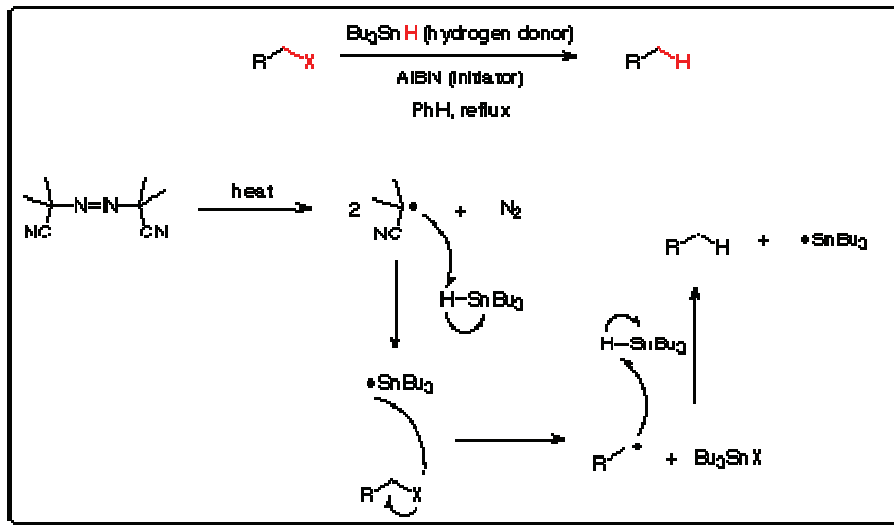
Mechanism:



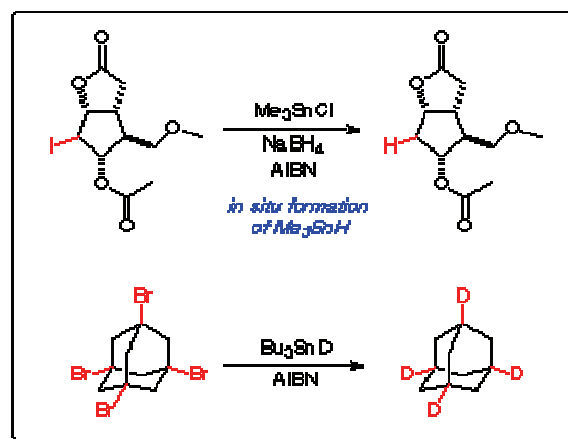
6. Free Radical Reductions

- used to reduce alkyl halides
- usual hydrogen atom donor is tributyltin hydride (Bu_3SnH)

Mechanism:



Some examples:



Deoxygenation of thioesters:

