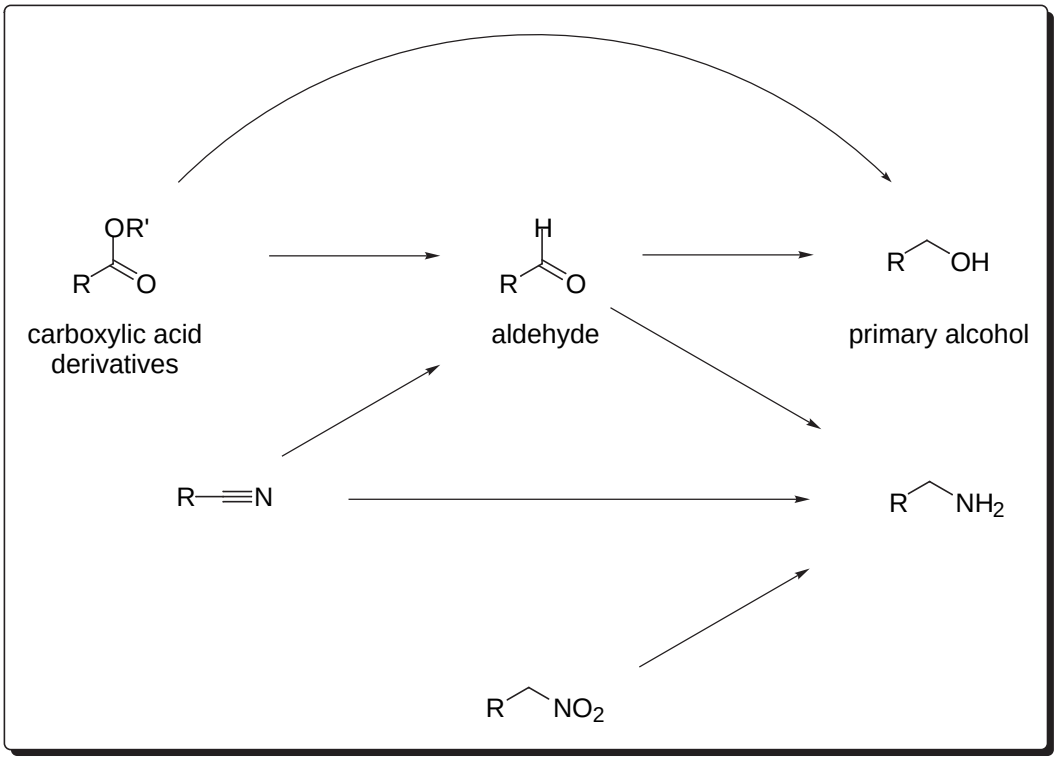
II Reduction Reactions

Objectives

By the end of this section you will:

1) be able to exploit the differences in reactivity of various reducing agents (hydride *vs* neutral reductants) in chemoselective reductions and be able to provide a mechanistic rationale to account for their differing reactivities;
2) be able to use the inherent chirality in a substrate to control the outcome of a reduction of proximal ketones to generate selectively *syn* and *anti* 1,3- and 1,2-diols;
3) be able to rationalise the outcome of these diastereoselective reactions using T.S. diagrams;
4) have gained an appreciation of the versatility of transition metals in reduction reactions;
5) have gained an appreciation of the synthetic utility of dissolving metal reductions;
6) be able to use radical chemistry for deoxygenation and reduction of halides.

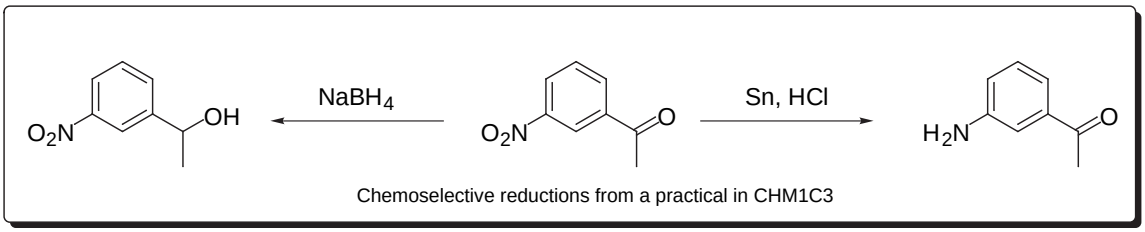
II.A Reduction of Carboxylic Acid Derivatives and Related Functionality



Issues of Reactivity and Selectivity

Similar issues of selectivity and reactivity to those we encountered in the case of oxidation reactions also arise in reduction reactions.

1. *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 (remember year 1 practical!).



Chemoselective reductions from a practical in CHM1C3

2. In the case of carboxylic acid derivatives there are two possible reduction products: an aldehyde and an alcohol. Ideally we need methods for selectively accessing either product.

Q? Why is it often difficult to stop the reduction of an ester at the aldehyde (consider the relative electrophilicities of the starting material and intermediate product.

3. *Stereoselectivity*. Asymmetrically substituted ketones provide secondary alcohols on reduction, which introduces 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. In this course we will only consider substrate-controlled diastereoselective reductions.

4. *Regioselectivity*. Ambident electrophiles such as α,β-unsaturated ketones can give a variety of reduction products. We need methods for obtaining only the one that we want.

II.A.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. Some of the most widely used hydride reagents are discussed below:

II.A.1.i Lithium Aluminium Hydride ($LiAlH_4$)

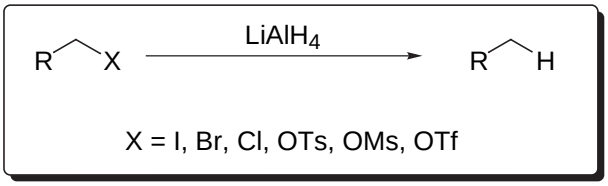
- one of the most powerful reductants
- highly flammable reagent and therefore must be used with care
- reactions are normally carried out in ethereal solvents (*e.g.* THF, Et_2O); $LiAlH_4$ reacts violently with protic solvents (*c.f.* $NaBH_4$)
- The extremely high reactivity of $LiAlH_4$ imparts relatively low levels of chemoselectivity on this reagent. However it is most reactive towards strong electrophiles.

Ease of Reduction of some Functional Groups with $LiAlH_4$

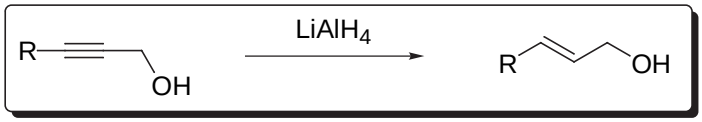
substrate	product	ease of reduction
aldehyde RCHO	RCH_2OH	most readily reduced
ketone RC(O)R'	RCH(OH)R'	
acid chloride RC(O)Cl	RCH_2OH	
lactone	diol	
epoxide 	$RCH_2CH(OH)R$	
ester RC(O)OR'	RCH_2OH + R'OH	
carboxylic acid RCO_2H	RCH_2OH	
carboxylate salt RCO_2^-	RCH_2OH	
amide $RC(O)NR'_2$	$RCH_2NR'_2$	
nitrile RCN	RCH_2NH_2	
nitro RNO_2	RN=NR	most difficult to reduce
isolated alkene RCH=CHR		unreactive

In addition to being capable of reducing virtually every carboxylic acid derivative, the high reactivity of $LiAlH_4$ makes it useful for reducing other functional groups:

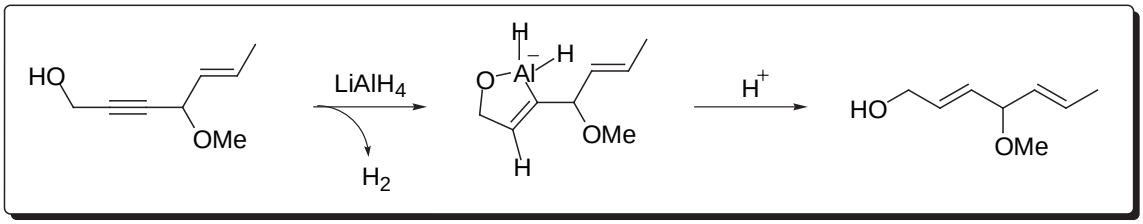
Reduction of halides and sulfonates:



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

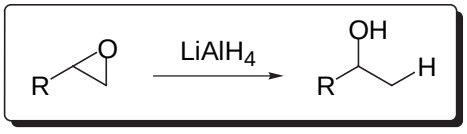


In this case the proximal alcohol is essential. The reaction proceeds through a *trans*-selective hydrometallation of the triple bond releasing the alkene on protolytic work-up:

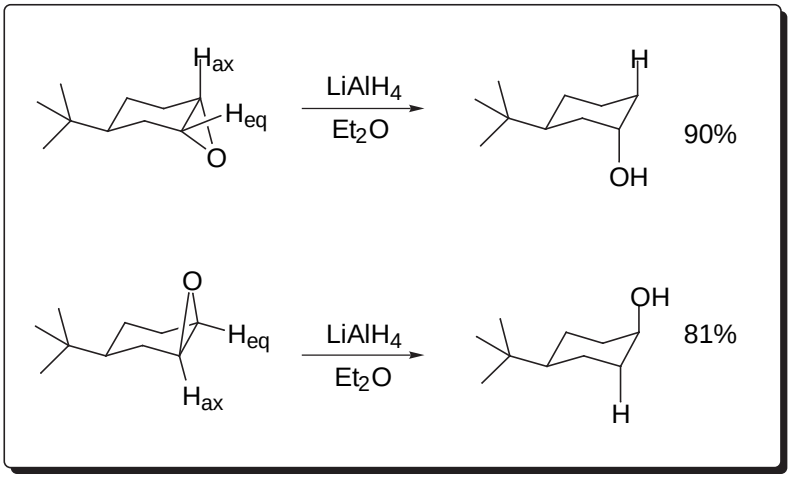


Epoxide Ring-Opening

In the case of unsymmetrically substituted epoxides, issues of regioselectivity arise. In acyclic systems the nucleophile (H^-) 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)



II.A.1.ii 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 (less electrophilic))
- reactions are carried out in protic solvents (including H_2O). $NaBH_4$ is insoluble in most common aprotic solvents

Related Borohydride Reagents

Lithium and Calcium borohydride

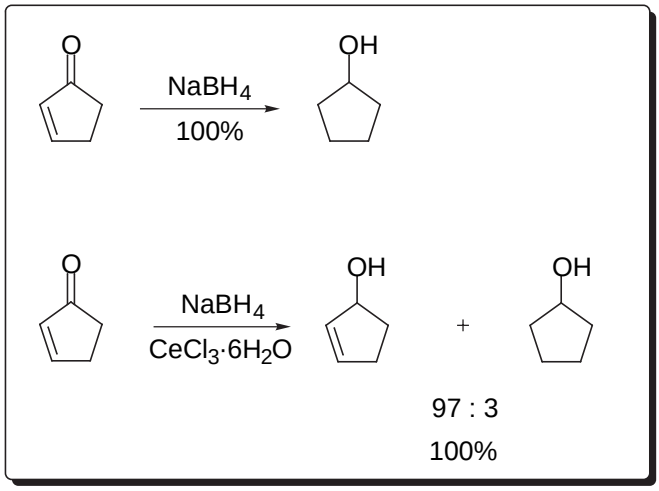
Although the reactive component of sodium borohydride is the hydride anion, the counterion can also be used to modulate the reactivity of the reagent system. A number of other borohydride reagents are available including $LiBH_4$ and $Ca(BH_4)_2$. Both these reagents are more reactive than $NaBH_4$ and 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).

II.A.1.iii Sodium Borohydride-Cerium(III) Chloride

Problem 1: Regioselective reduction of α,β-unsaturated carbonyl groups (ambident electrophiles).

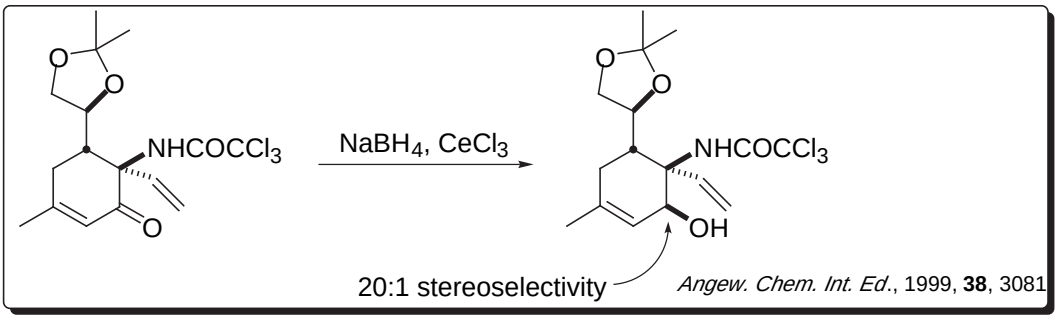
1,2-reduction

- good route to allylic alcohols (very important functional groups)
- use a 1:1 ratio of $NaBH_4$ and $CeCl_3$ - **Luche reduction**



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

Example from Isobe's synthesis of (–)-5,11-dideoxytetrodotoxin. This reaction is not only completely regioselective for the 1,2-reduction product but is also highly stereoselective.



To obtain selective 1,4-reduction a) catalytic hydrogenation

b) 'copper hydride' $[PPh_3CuH]_6$ Stryker's reagent

- Chemoselective reduction of aldehydes in the presence of ketones can usually be achieved by exploiting their increased reactivity towards nucleophilic hydride sources.

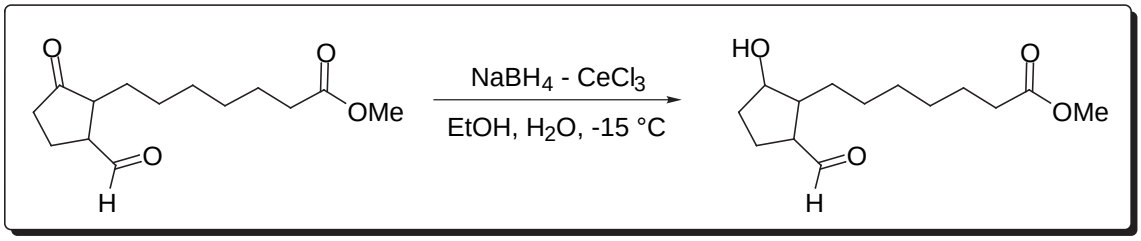
Q? Why are aldehydes more electrophilic than ketones?

Problem 2: How might we chemoselectively reduce a ketone in the presence of a more electrophilic aldehyde:

- The increased electrophilicity of aldehydes over ketones, however, renders them much more prone to hydration/acetal formation.
- 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 $NaBH_4$-$CeCl_3$ in wet EtOH:



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

II.A.1.iv Sodium Cyanoborohydride ($NaCNBH_3$)

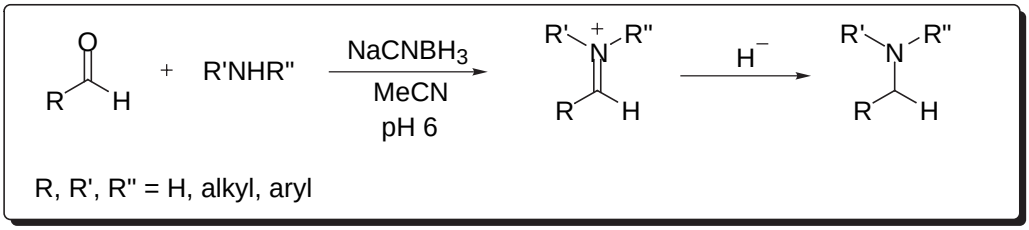
C. F. Lane, *Synthesis*, 1975, 135-146.

- a very useful borohydride reagent
- milder than $NaBH_4$ 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: $NaCNBH_3$ readily reduces aldehdyes and ketones

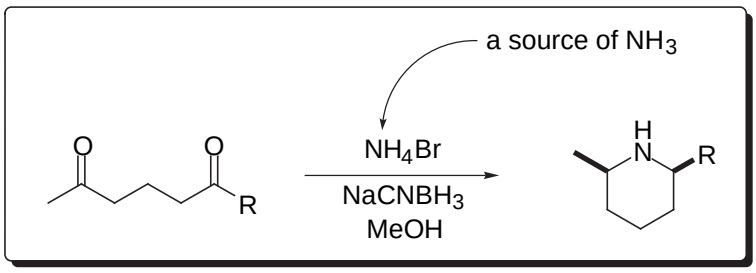
at pH 6-7: $NaCNBH_3$ readily reduces iminium ions but NOT C=O groups - this property is responsible for its most important use - **REDUCTIVE AMINATION**:

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



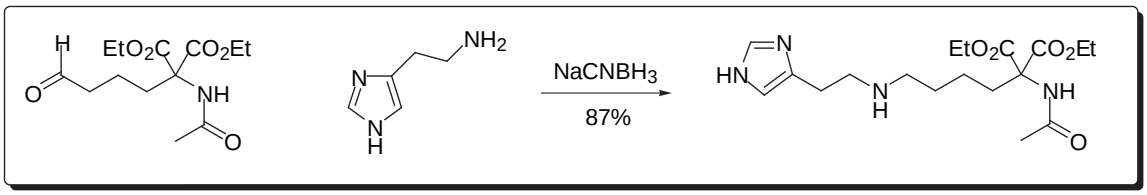
Q? An alternative method for amine formation is to alkylate a primary or secondary amine with an alkyl halide? What are the problems with this approach? Hint - is the product amine more or less nucleophilic than the starting material?

Example 1

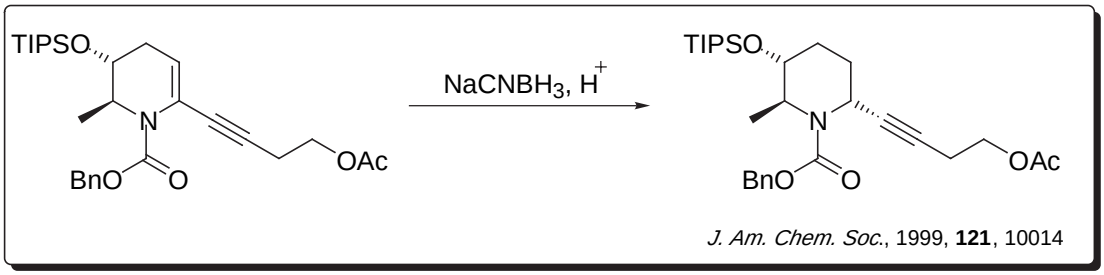


Q? Account for the stereoselectivity of this reaction.

Example 2



Example 3 from Cha's synthesis of clavepictine A:

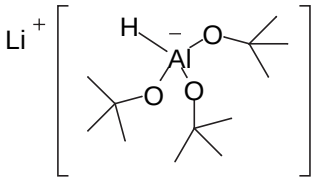
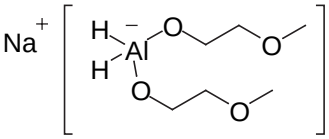
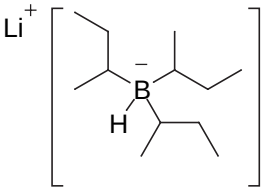


J. Am. Chem. Soc., 1999, **121**, 10014

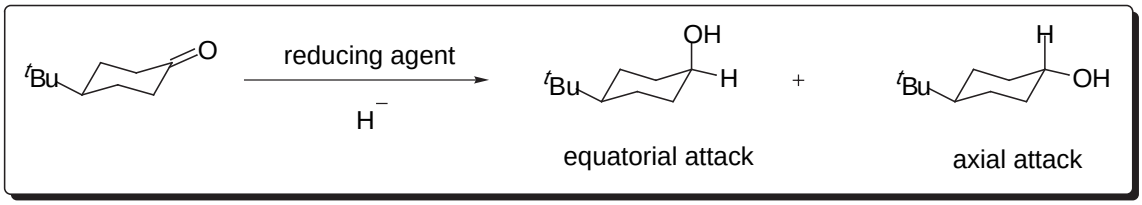
Q? What is the mechanism of this reaction? Account for the stereoselectivity.

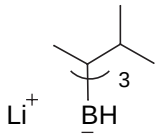
II.A.1.v Other Hydridic Reducing Agents

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

Reducing Agent		Comment
$LiHAl(O^tBu)_3$		good for converting carboxylic acid derivatives to aldehydes
Red-Al $Na[H_2Al(OCH_2CH_2OMe)_2]$		similar reactivity to $LiAlH_4$
L-selectride $LiHB(CH(CH_3)CH_2CH_3)_3$		similar reactivity to $LiBH_4$

Stereoselective Reduction of 4-tert-Butyl-Cyclohexanone



reducing agent	equatorial attack	axial attack
$LiAlH_4$ (unhindered)	10	90
$LiAlH(O^tBu)_3$ (more hindered)	10	90
$LiBH(^sBu)_3$ (very hindered)	93 (RT) 96.5 (-78 °C)	7 (RT) 3.5 (-78 °C)
Lithium trisamylborohydride  (very very hindered)	100	0

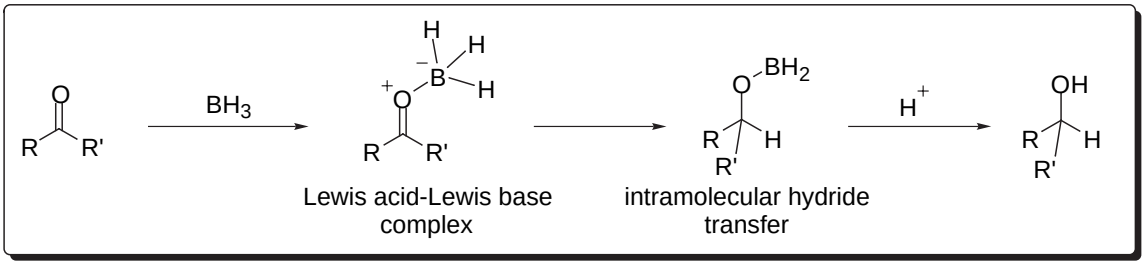
What factors might affect the stereochemical outcome of this reduction? Hint: consider such factors as the approach trajectory of the incoming nucleophile and the size of the nucleophile. Draw Newman projections of the starting ketone and the two products and consider how the molecule reorganises on proceeding from starting material to product; remember that eclipsing interactions are unfavourable.

II.A.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 involves those that 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



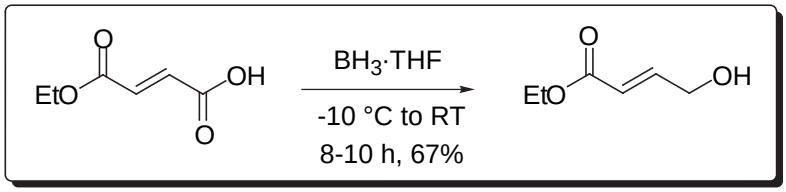
Comparison between BH_4^- and BH_3

BH_4^-	**BH_3**
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 *via* a Lewis acid-Lewis base complex

II.A.2.i Borane (BH_3)

Borane is too unstable to be isolated (exists either as the dimer B_2H_6 or a Lewis acid-Lewis base complex *e.g.* BH_3·THF or BH_3·Me_2S both of which are commercially available).

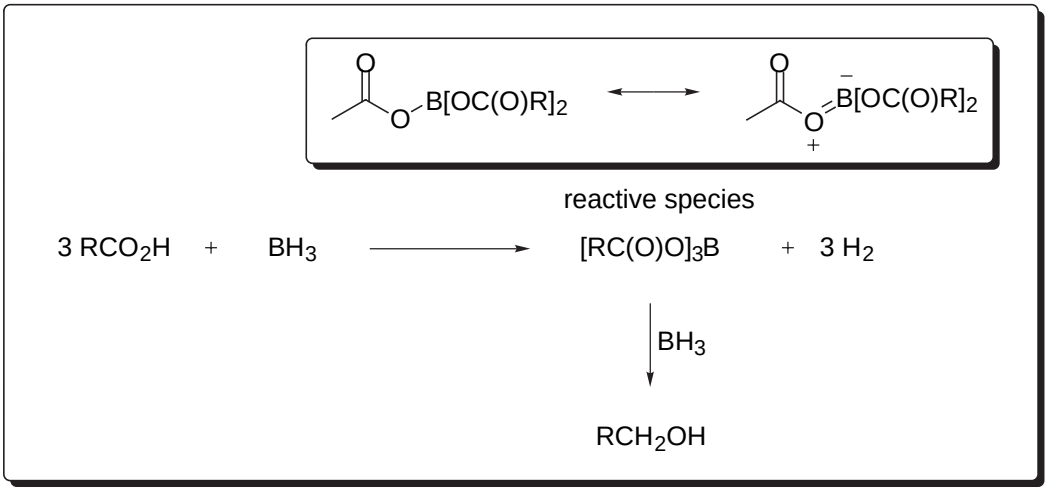
- very useful reagent for selectively reducing carboxylic acids to alcohols in the presence of esters
- amides are also readily reduced to the corresponding alcohols



Thus it seems that the more electron rich carboxylic acid derivatives appear to be reduced most readily - complete opposite reactivity to hydridic reducing agents.

Q? Why are carboxylic acids reduced so fast relative to esters?

Key: borane first *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.



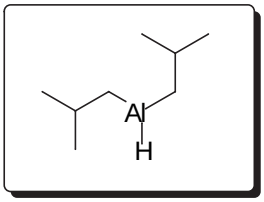
A note of caution!

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*.

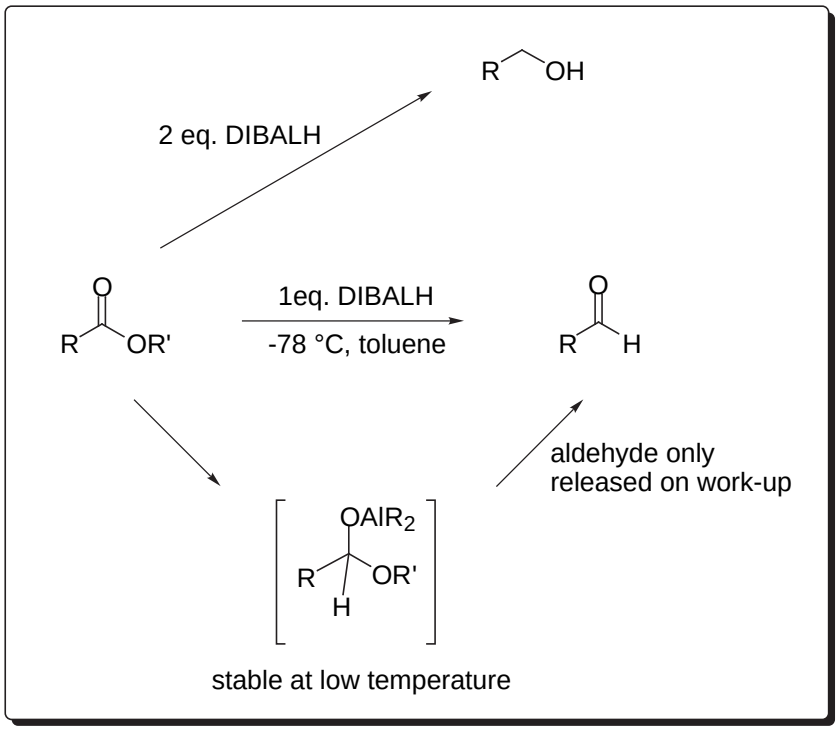
Ease of Reduction of some Functional Groups with Borane

substrate	**product**	**ease of reduction**
carboxylic acid RCO_2H	RCH_2OH	most readily reduced
isolated alkene RCH=CHR	$(RCH_2CHR)_3B$	
ketone RC(O)R'	RCH(OH)R'	
nitrile RCN	RCH_2NH_2	
epoxide 	$RCH_2CH(OH)R$	
ester RC(O)OR'	RCH_2OH + R'OH	most difficult to reduce
acid chloride RC(O)Cl		inert

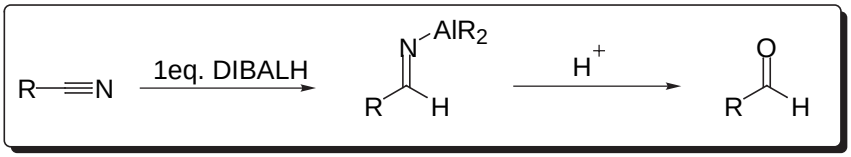
II.A.2.ii Diisobutylaluminium Hydride (DIBALH)



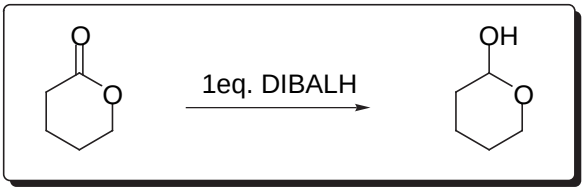
- very widely used reducing agent especially for reducing esters
- esters can be reduced to either the aldehyde **or** the alcohol depending on the stoichiometry and reaction conditions:



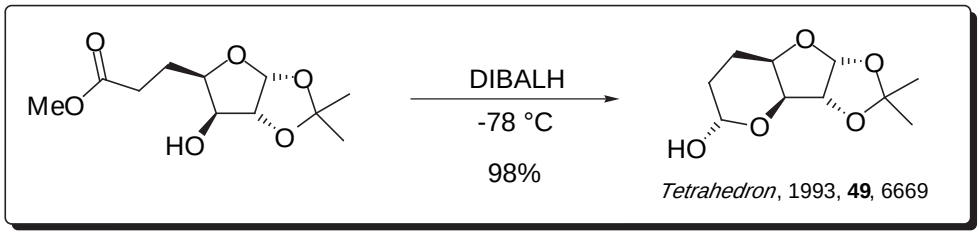
Nitriles are also reduced to aldehydes. In this case reaction proceeds *via* the imine which is hydrolysed on acidic work-up to afford the aldehyde product:



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:



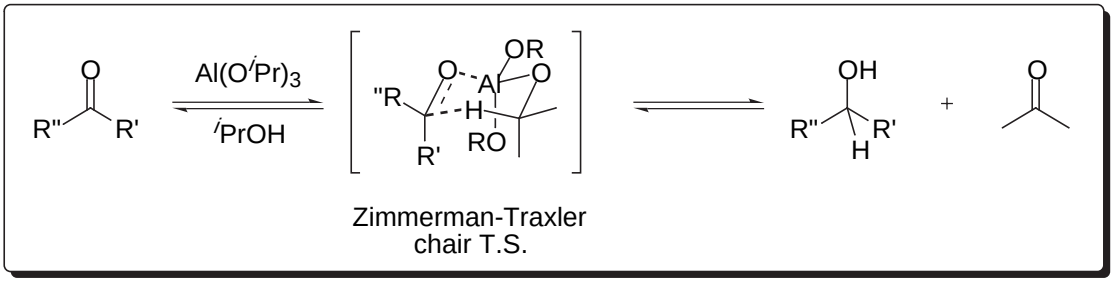
Esters with proximal alcohols can also be partially reduced by exploiting lactol formation.



Tetrahedron, 1993, **49**, 6669

II.A.2.iii Meerwein-Ponndorf-Verley Reduction with $Al(O^{i}Pr)_3$

- 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.



Zimmerman-Traxler chair T.S.

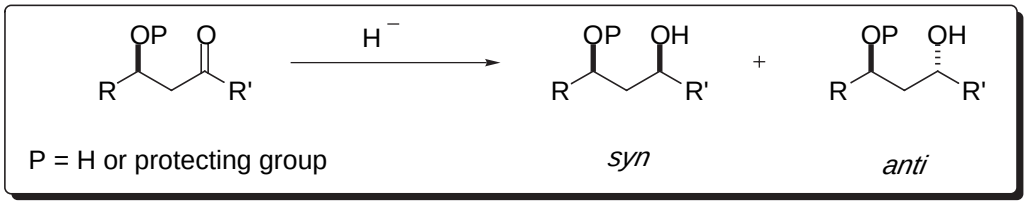
Compare this reaction mechanism with methods for directed reduction of β-hydroxy ketones ($Me_4NHB(OAc)_3$ and the Evans-Tischenko reduction) later - the mechanism is very similar - **CHAIR-LIKE ZIMMERMAN-TRAXLER transition states are very commonly used to rationalise the stereochemical outcome of reactions which can proceed through 6-membered transition states.**

II.B Stereoselective Reduction of Prochiral Ketones

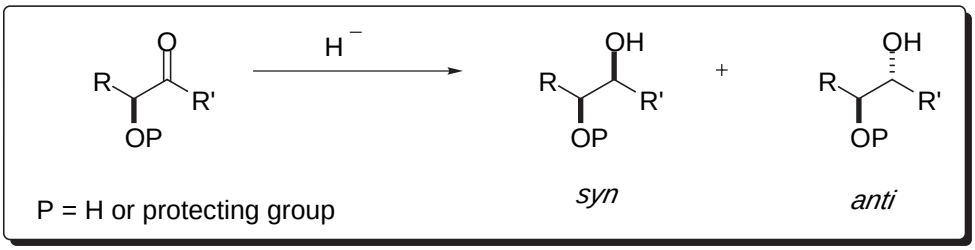
The addition of a hydride nucleophile to a chiral ketone provides diastereoisomers - when the stereogenic centres are close to the carbonyl group (1,2- or 1,3-disposed (*i.e.* α- or β-hydroxy ketones)) then by careful choice of protecting group, reaction conditions and reducing agent, a high degree of stereoselectivity can often be obtained in the reduction.

1,2-Diols and 1,3-diols are widespread in natural products (see erythromycin and related polyketide macrolides). Stereoselective reduction of hydroxyketones provides a reliable route for incorporating such functionality.

Diastereoselective 1,3-reduction:



Diastereoselective 1,2-reduction:



We will consider each reduction in turn. While some of the reagents may be new to you, you should already be aware of the underlying concepts and models; if you are not then REVISE this area of Chemistry - it will be cropping up time and time again in this lecture course.

for example see:

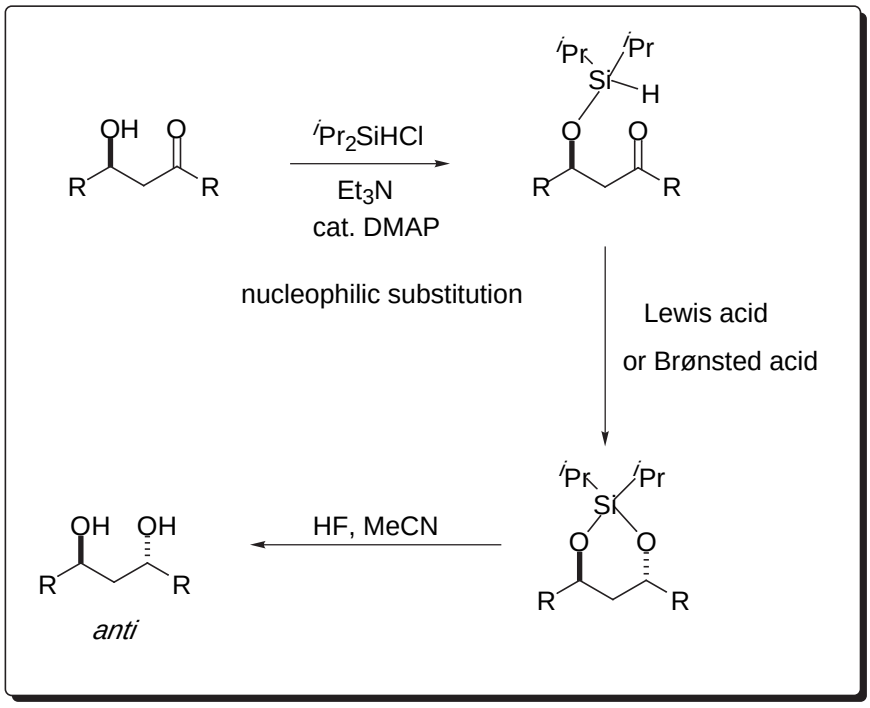
- F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry: Volume B*, Plenum Press, New York, 1990 (3rd Edition), pp 241-244.
- M. B. Smith, *Organic Synthesis*, McGraw-Hill, New York, 1994, pp 400-417.
- E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, pp 858-938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

II.B.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 β-hydroxy-ketone. All rely on a so-called **DIRECTED REDUCTION** which takes advantage of an *intra*molecular hydride transfer proceeding through a well-defined 6-membered chair-like transition state (*c.f.* Meerwein-Ponndorf-Verley reduction earlier).

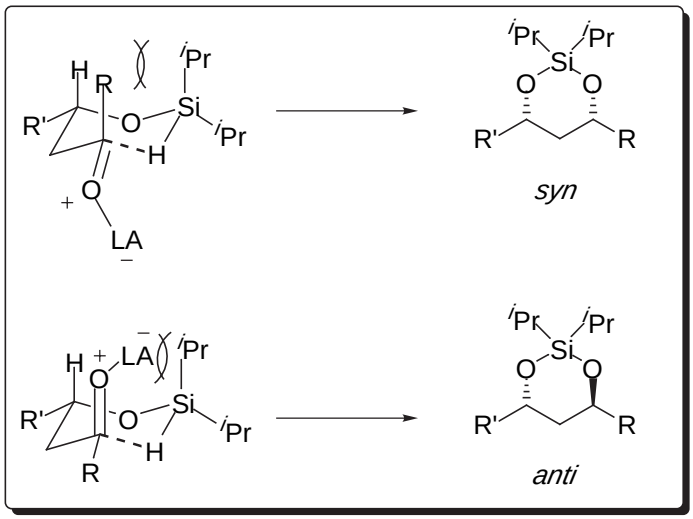
II.B.1.i Davis' Intramolecular Hydrosilylation

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 ($BF_3{\cdot}OEt_2$ 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.

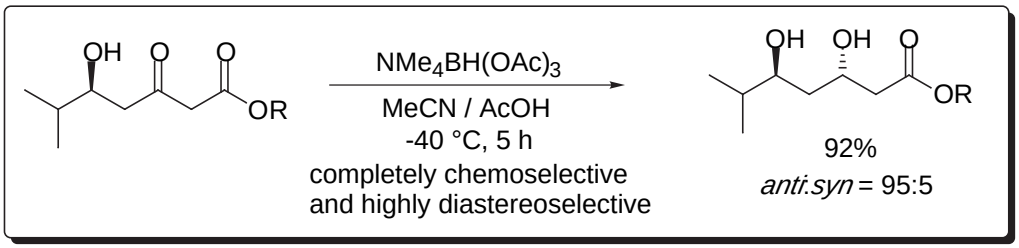


II.B.1.ii Tetramethylammonium Triacetoxyborohydride (Evans)

Evans has introduced an alternative reagent $Me_4NHB(OAc)_3$ for carrying out directed reductions.

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 Davis' method the reaction is easier to perform and generally higher yielding (a pay-off):



Note in this example that only the β-ketone is reduced; the ester remains intact (chemoselective)

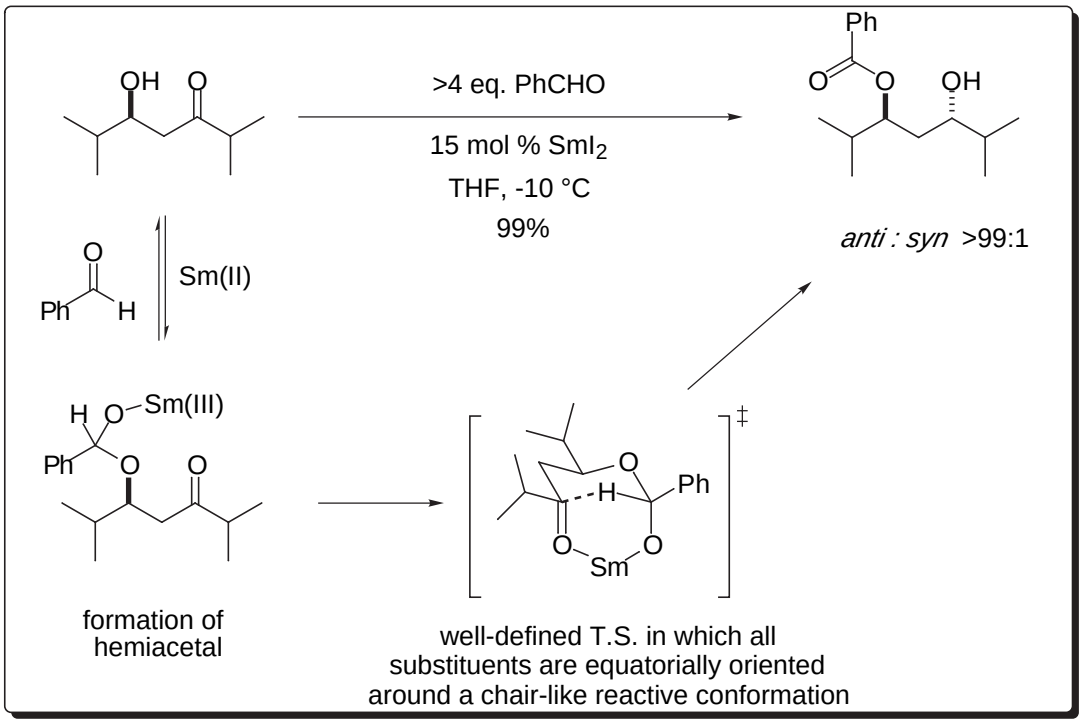
Draw a T.S. which satisfies the stereochemical outcome of the reaction (hint: the AcOH co-solvent acts as a Brønsted acid and activates the ketone electrophile).

II.B.1.iii Evans-Tischenko Reduction

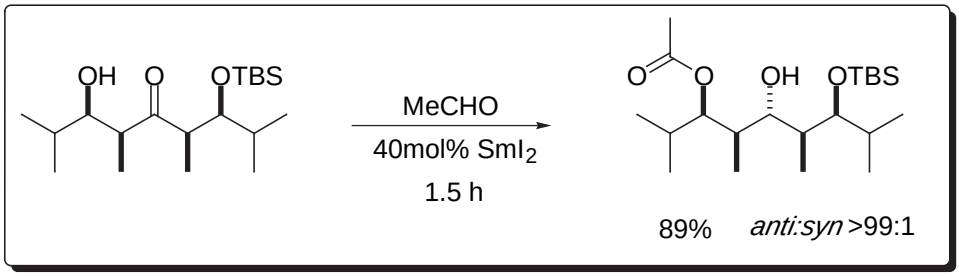
D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.*, 1990, **112**, 6447-6449.

- 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 type of ester PG)
- this ensures that the two secondary alcohols are differentiated (one is protected *in situ* as an ester). Selective monofunctionalisation of a 1,3-diol can be difficult to achieve.

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



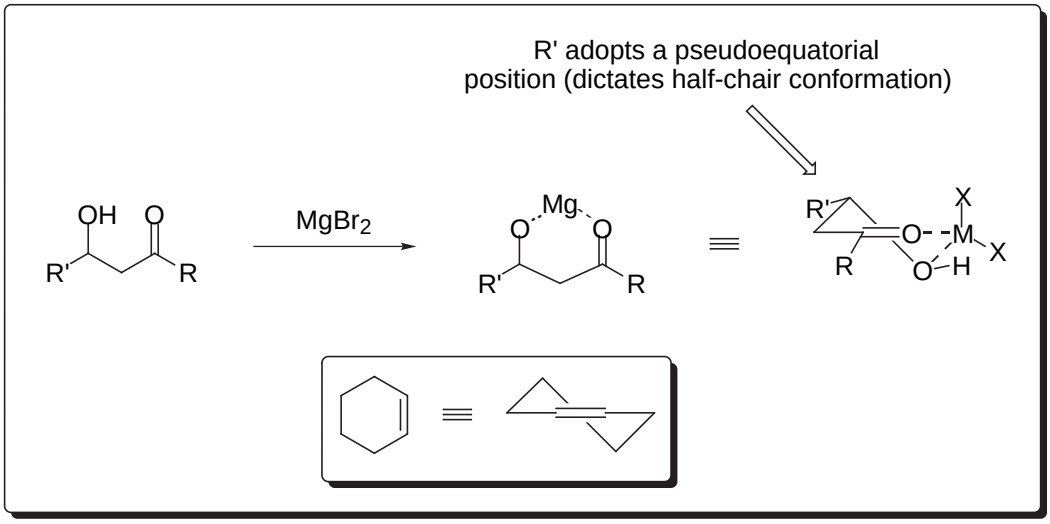
Another example:



II.B.2 Diastereoselective Formation of *Syn*-1,3-Diols

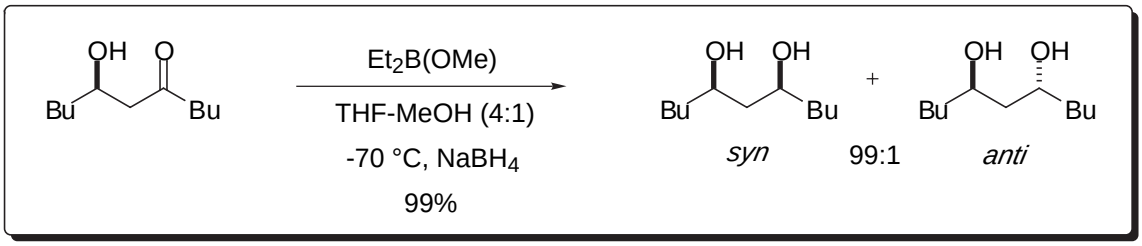
Chelation-Controlled Intermolecular Hydride Delivery

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



- INTERmolecular hydride delivery on the chelate would then be expected to provide the *syn*-1,3-diol products. This is indeed the case.
- The most reliable reaction conditions are $Et_2B(OMe)$-$NaBH_4$ at low temperature:

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

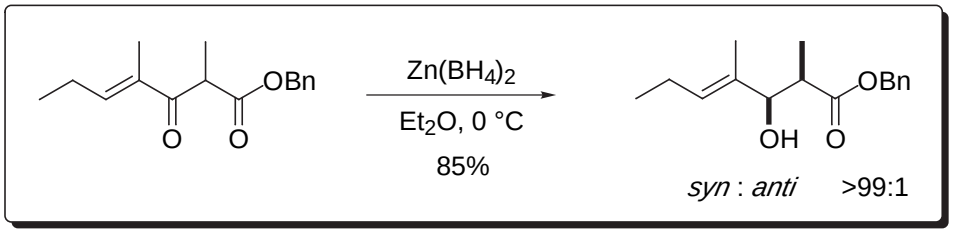


Make sure that you can rationalise the stereochemical outcome of this reaction using clear conformational diagrams.

- other reagents which also give good *syn* selectivity are $Zn(BH_4)_2$ and DIBALH

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

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



Draw a T.S. diagram which accounts for the observed stereochemical outcome of this reaction.

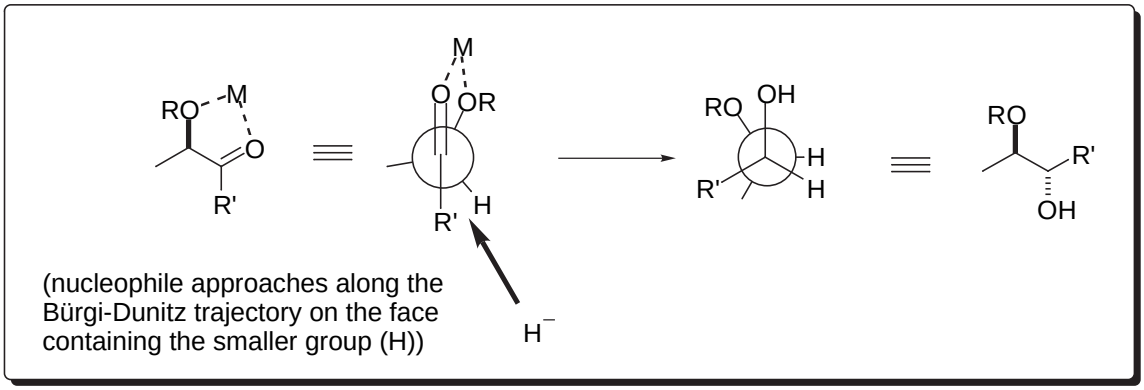
II.B.3 Diastereoselective Formation of *Anti*-1,2-Diols

Exploit chelation control; we therefore require:

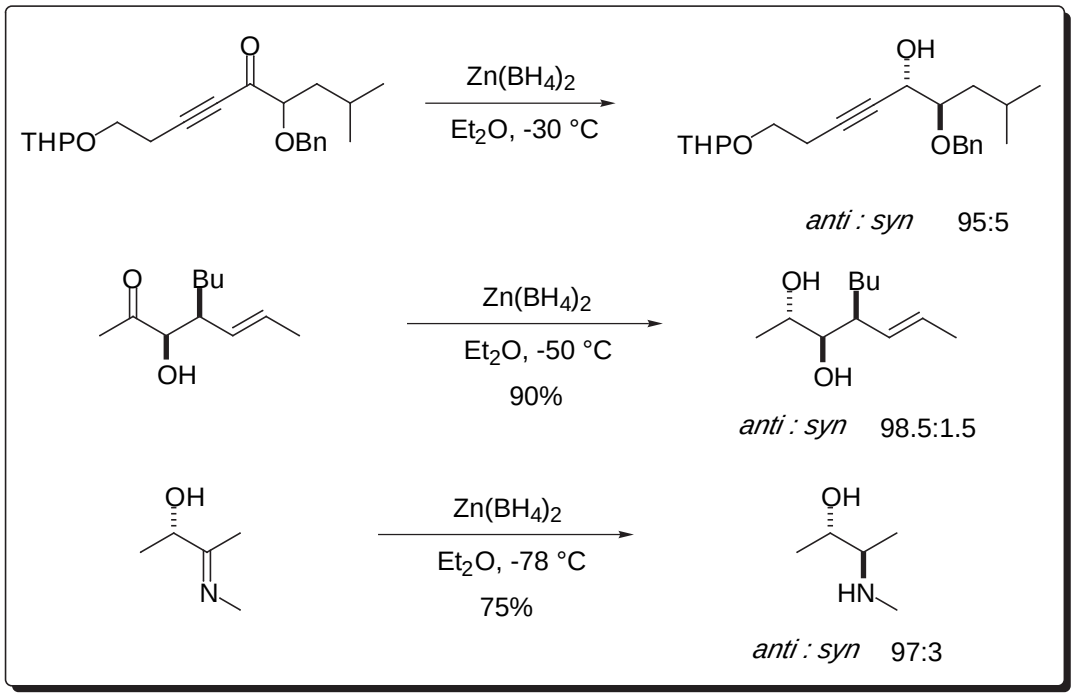
i) a free alcohol *or* a protected alcohol in which the protecting group can still form a chelate (alkyl ethers) *i.e.* the oxygen must still be able to behave as a Lewis base.

ii) a metal which can form a chelate (typical metals include Zn(II), Mg(II), Ti(IV) *etc*.)

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



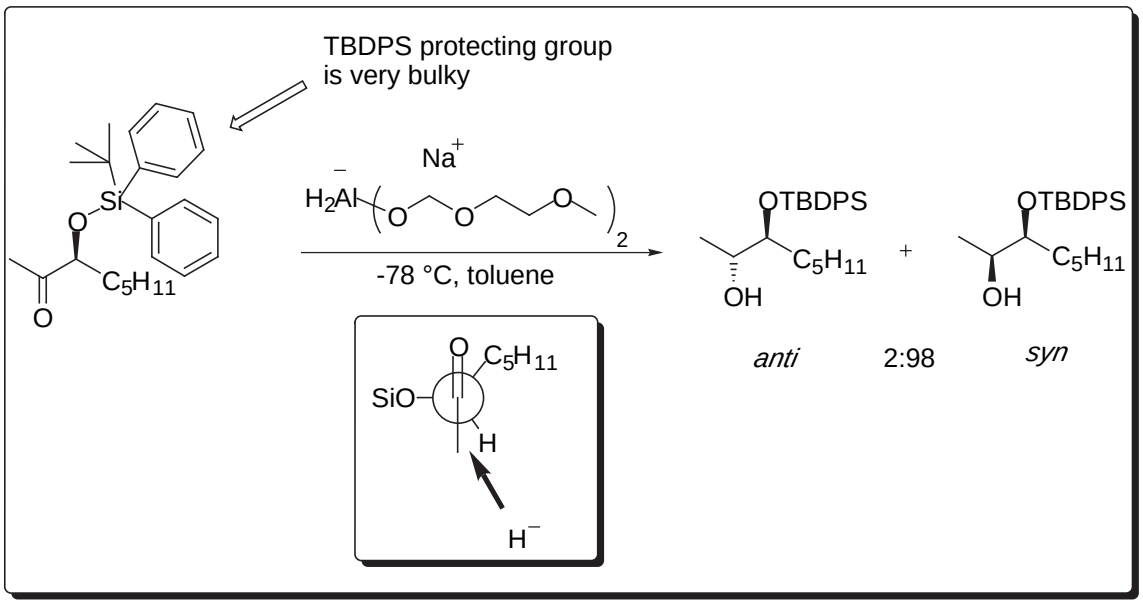
Examples:



II.B.4 Diastereoselective Formation of *Syn*-1,2-Diols

This requires i) careful choice of a protecting group which suppresses chelate formation and is very bulky (large silyl protecting groups are ideal).

ii) use Felkin-Anh T.S. analysis to account for the stereocontrol.



Make sure you understand the steric AND stereoelectronic arguments behind the Felkin-Anh T.S.

For other examples:

T. Takahashi, M. Miyazawa, J. Tsuji, *Tetrahedron Lett.*, 1985, **26**, 5139-5142.

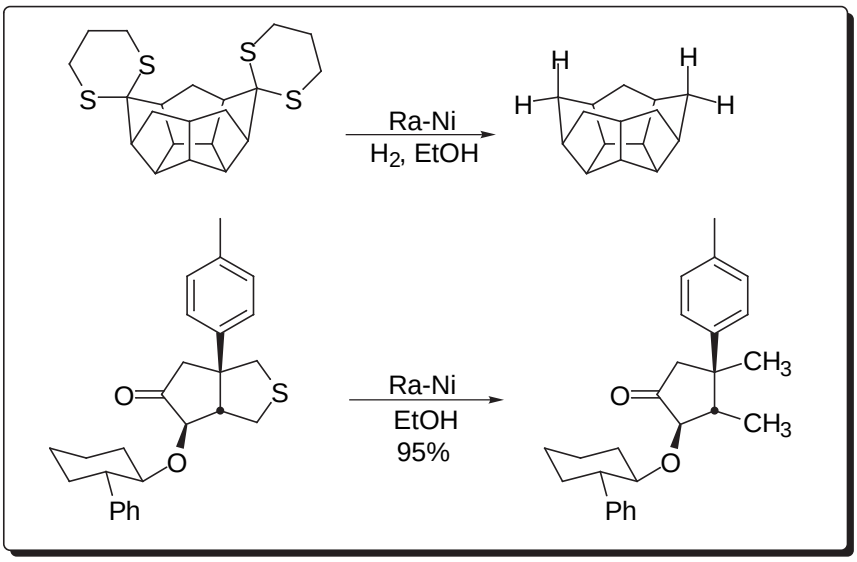
L. E. Overman, R. J. McCready, *Tetrahedron Lett.*, 1982, **23**, 2355-2358.

II.C Other Methods of Reduction

II.C.1 Raney-Nickel

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

Examples:



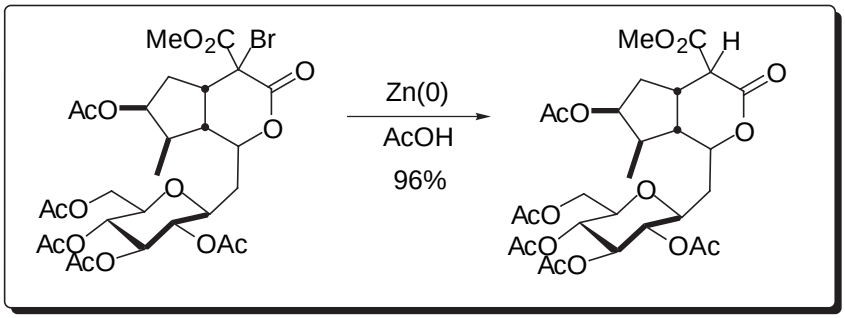
- also used in the hydrogenation of alkenes and alkynes.

II.C.2 Zinc in Acidic Media

Reduction of α-haloketones

- very mild
- highly chemoselective

Example:

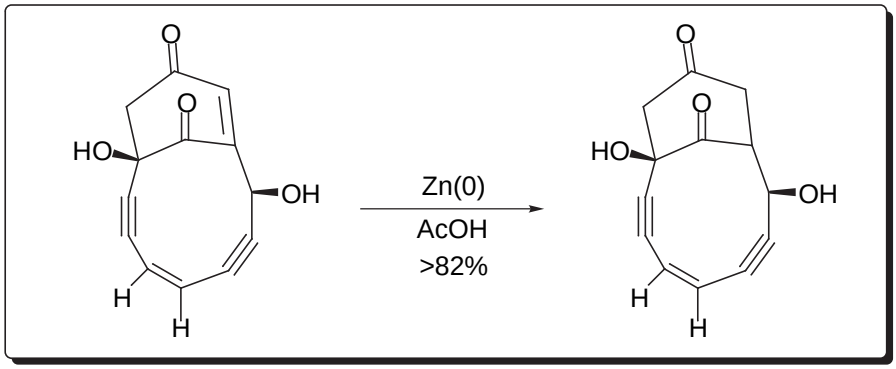


Note the lactone, acetate, glycosidic linkage and acetal *all* remain intact.

Q? What is the mechanism of reduction? Hint: the reaction involves single electron transfer.

1,4-Reduction of Enones

Example:

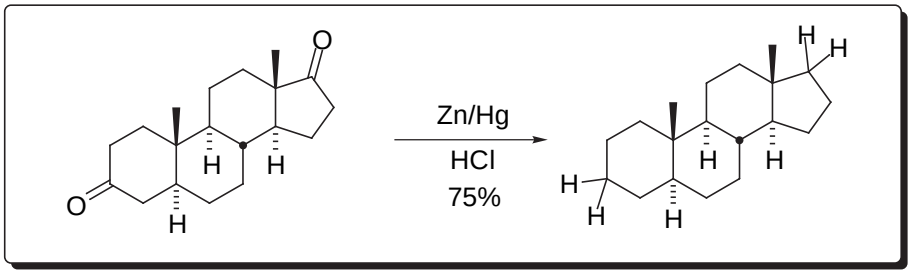


Note that there is a zinc enolate intermediate; this reaction can therefore be used for regioselective formation of enolates.

Clemmensen Reduction

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

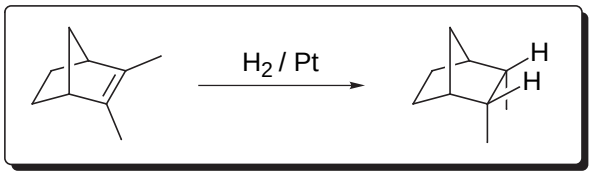
Example:



II.D Hydrogenation with Hydrogen and a Transition Metal Catalyst

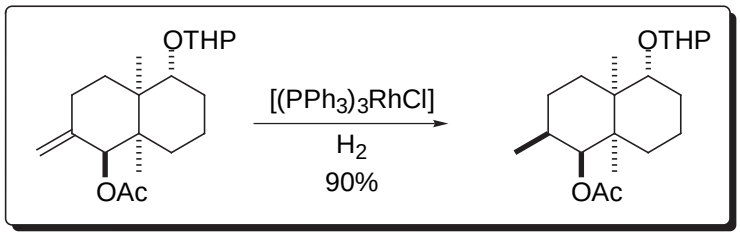
- Typical catalysts are Pt, Pd, Rh, Ru and Ni (late transition metals) - usually used as finely dispersed solids or adsorbed on to an inert support such as charcoal or alumina.
  - reaction takes place on the surface of the metal - heterogeneous catalysis
    - hydrogen is invariably transferred on to 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:



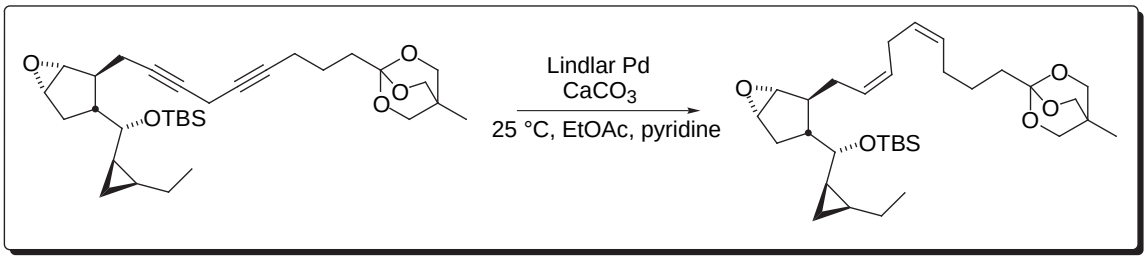
Q? How does the shape of the bicycle control the stereoselectivity of the hydrogenation?

Enantioselective reduction will NOT be discussed here.

II.D.1 Partial reduction of alkynes

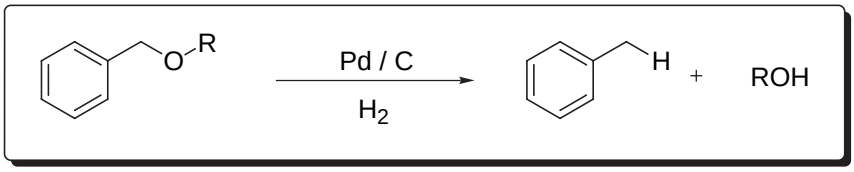
- a useful route to (*Z*)-alkenes
- need to modify the catalyst to minimise over-reduction
- Lindlar's catalyst (Pd-$CaCO_3$-PbO) is the most widely used. The PbO tempers the reactivity of the catalyst by acting as a catalyst poison.
- Other systems include Pd-$BaSO_4$ poisoned with quinoline.

Example:



II.D.2 Hydrogenolysis

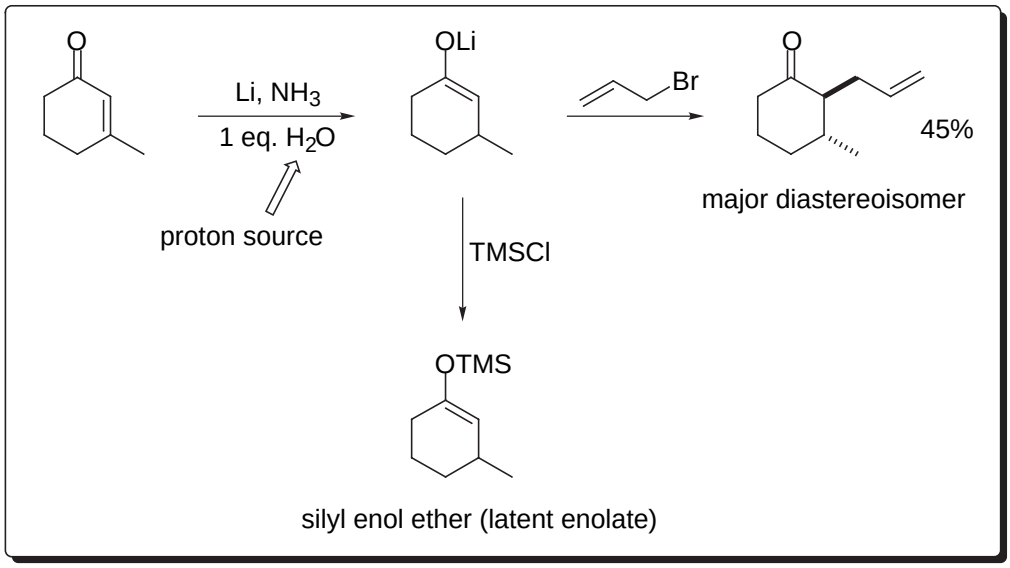
- Benzyl ethers are readily cleaved by Pd/C/H_2 to provide the free alcohol and toluene.
- Cleavage occurs under mild and neutral conditions
- as a result, benzyl ethers are frequently used as alcohol protecting groups.



II.E Dissolving Metal Reductions (Sodium/Ammonia or Lithium/Ammonia)

- a wide variety of uses, only three will be discussed here
- reactions proceed *via* single electron transfer processes

II.E.i Regiospecific Enolate Formation

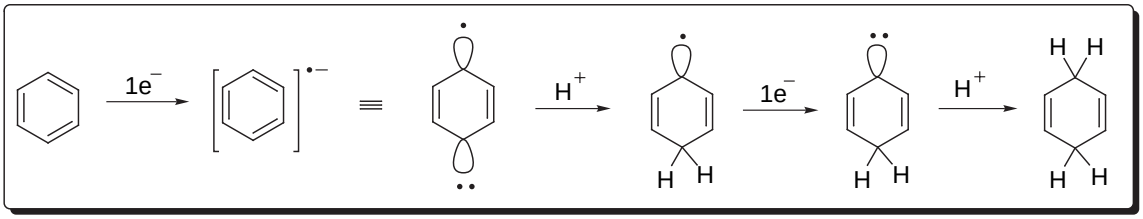


Enolates are ambident nucleophiles - you should be able to account for the differing regioselectivity of the reactions of the intermediate lithium enolate with the two different electrophiles.

II.E.2 Birch Reduction

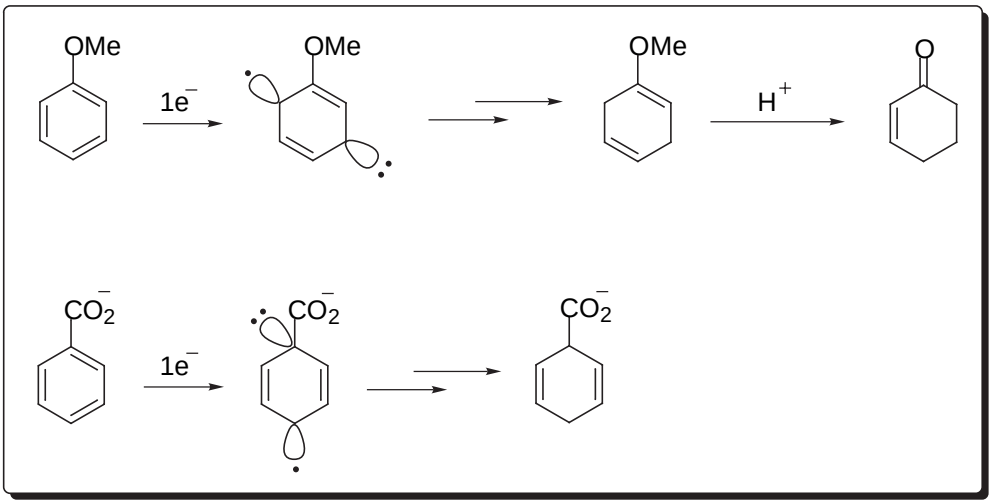
Partial reduction of aromatic rings

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:

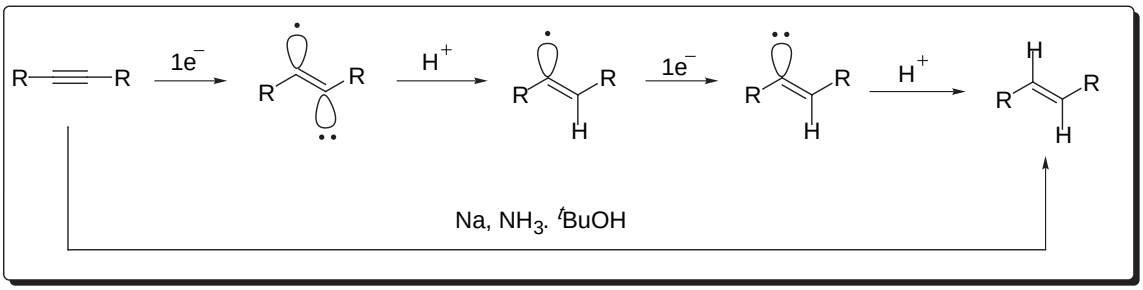


Make sure you can rationalise the regiochemistry of these reactions.

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).

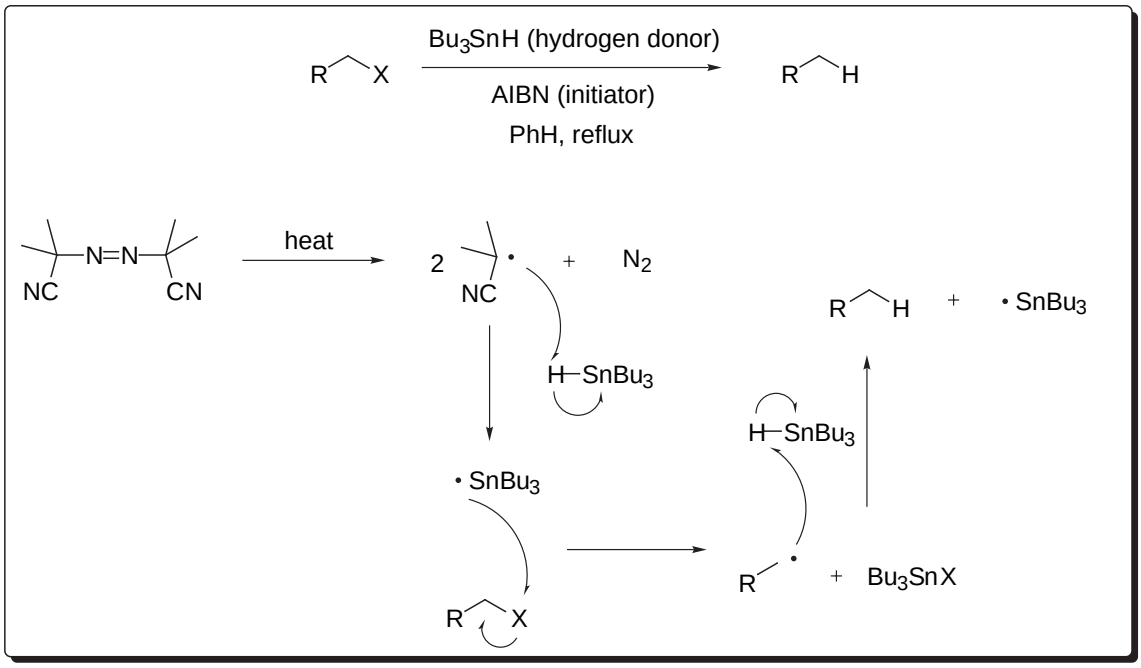
mechanism:



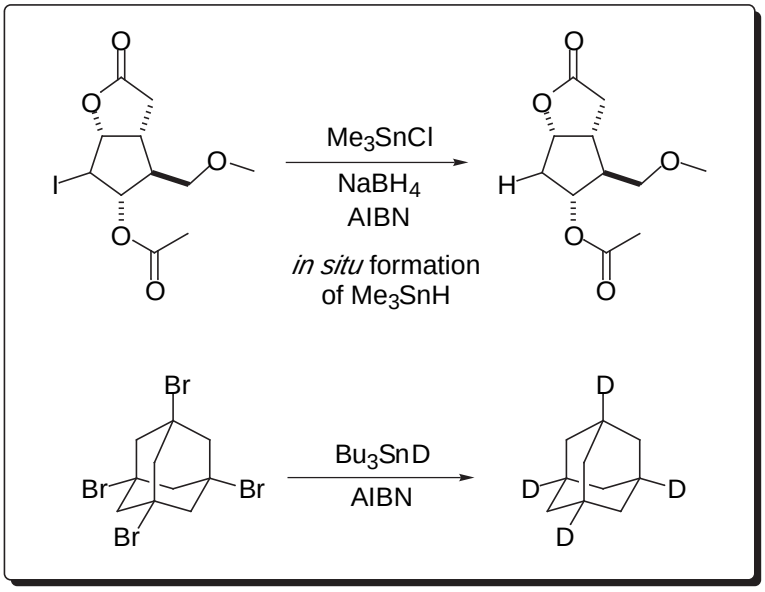
II.F Free Radical Reductions

- used to reduce alkyl halides
- usual hydrogen atom donor is tributyltin hydride (Bu_3SnH) (there are now less toxic alternatives to tributyltin hydride *e.g.* $(Me_3Si)_3SiH$)

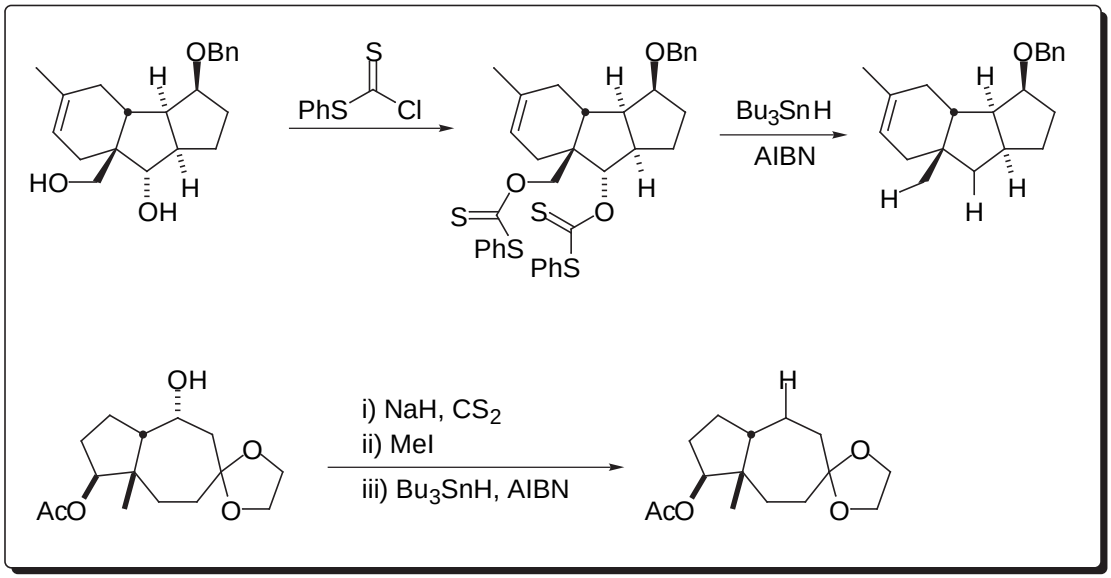
mechanism:



Some examples:



Deoxygenation of xanthate esters:



Q? What is the mechanism of this reaction? Hint: the driving force is formation of a C=O bond.

SUMMARY

In this section we have discussed a variety of methods for reducing carbonyl groups chemo-, regio- and stereoselectively and seen that this has necessitated the development of a wide variety of reducing agents. Furthermore, by understanding the mechanisms of various reducing agents we can rationalise their reactivity towards potentially reactive functional groups. We have also discussed various methods for reducing unsaturated compounds (olefins, alkynes and aromatic compounds) and seen the importance of late transition metals as catalysts for mediating such transformations. Reduction requires the gain of electrons; metals are a potential source of electrons. We have seen that Zn in acidic media and Li or Na in NH_3 are good reducing systems. Free radical reduction occupies a special niche; it is particularly useful for reducing halides and similar systems under mild, and neutral conditions.