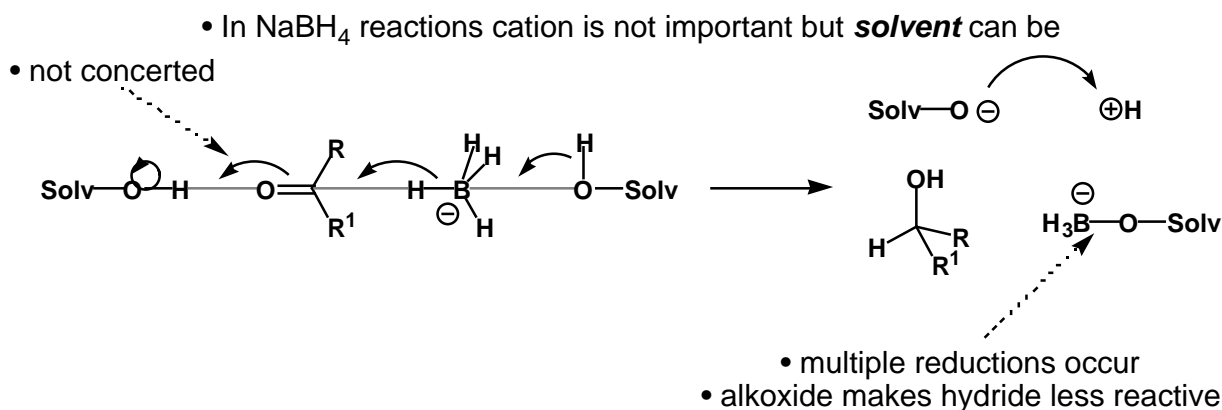
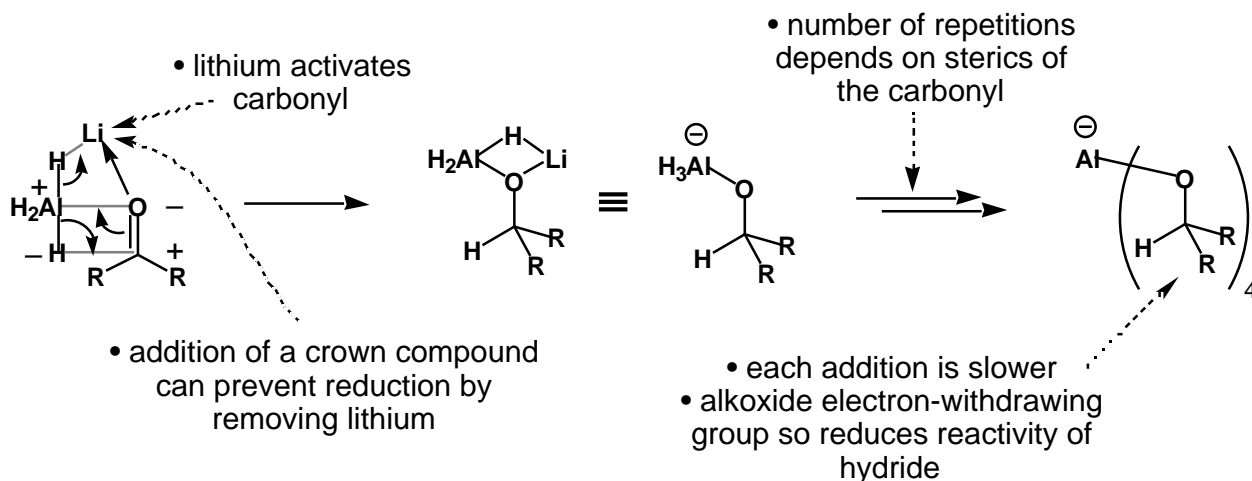


REDUCTIONS

- Invaluable process
- Can be used to remove functionality from a molecule
- A versatile method for introducing stereocentres
- Formally reduction is the **gain of electrons** but it is more easy to visualise it as the **gain of hydrogen** (although this far from mechanistically correct)

Metal Hydrides

- The most common metal hydrides are **lithium aluminium hydride (LiAlH₄)** and **sodium borohydride (NaBH₄)**
- There **are** differences mechanistically
- In many cases the lithium cation is **vital** for reaction



Chemoselectivity

- **LiAlH₄** – very reactive, will reduce most carbonyl functionality
- Care should be taken as it will react with **acidic protons** (RCO₂H, RCH₂OH, RCH₂NH₂)
- **NaBH₄** – much milder, can be used to **selectively** reduce aldehydes, ketones and acid chlorides in the presence of other functionality
- Properties of both reagents can be altered by the addition of substituents
- Some of these will be discussed below

Lithium Aluminium Hydride LiAlH_4

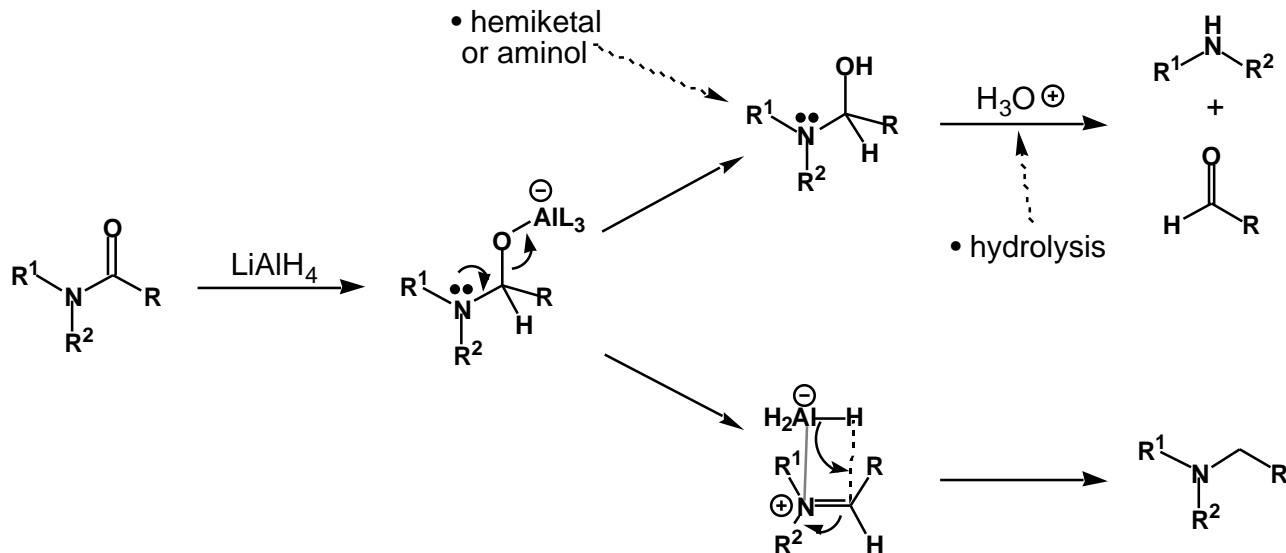
General

- All carbonyl groups are reduced
- Many other functional groups are reduced
- Reaction with acidic protons generates H_2 :



Amides

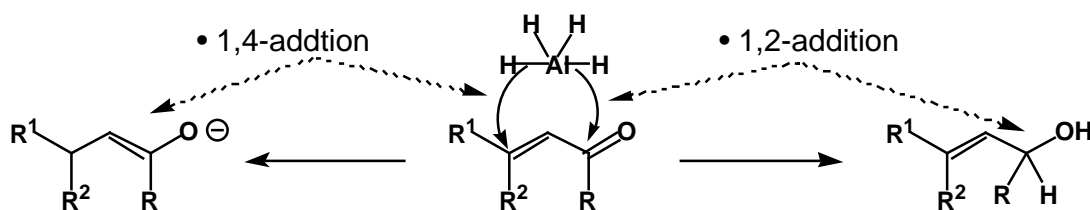
- Behave unpredictably (in my opinion)



- Which path is followed is a result of sterics and electronics around the amine
- Personally I have found it is also effected by solvent, temperature, day of the month

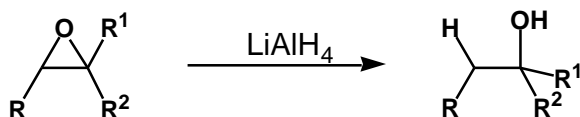
Enones

- Another problematic functional group

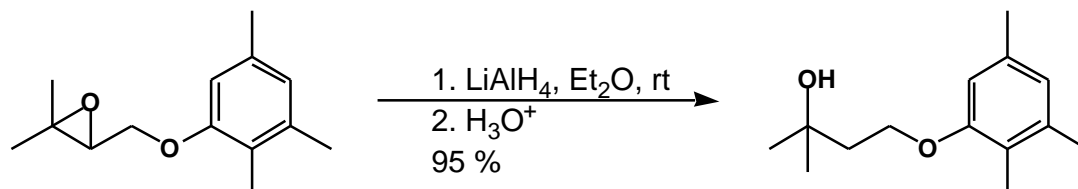


- Very dependant on the exact structure of the enone
- *Advisable to choose a different reagent*

Epoxides

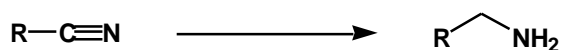


- Hydride normally delivered to the **least** hindered end
- Epoxides are **more** readily reduced than esters
- Epoxides are **less** readily reduced than aldehydes / ketones

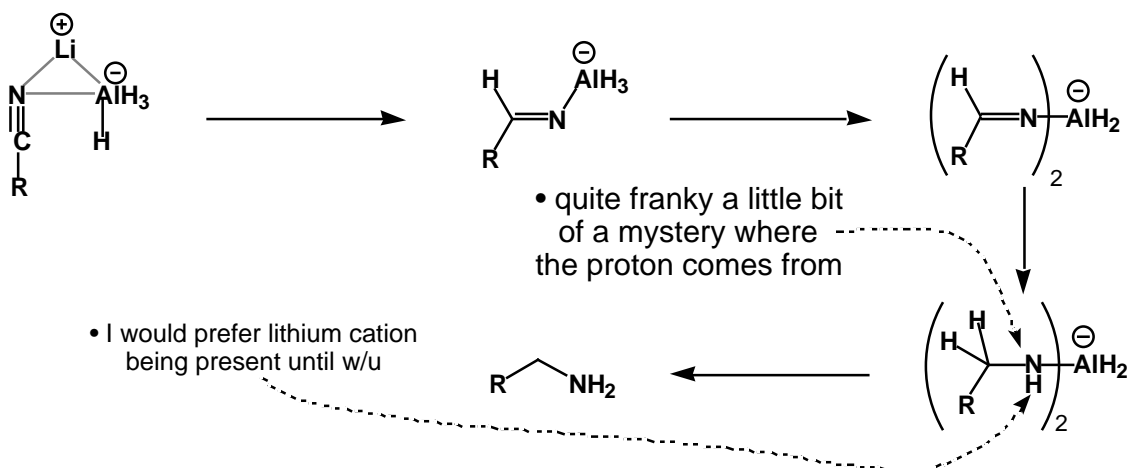


Nitriles

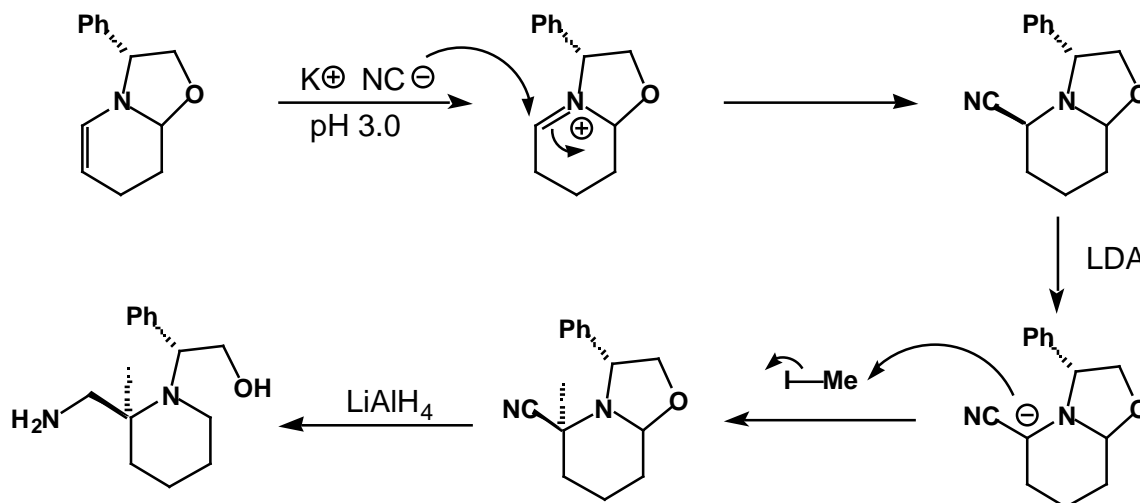
Transformation



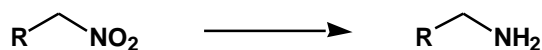
Postulated Mechanism



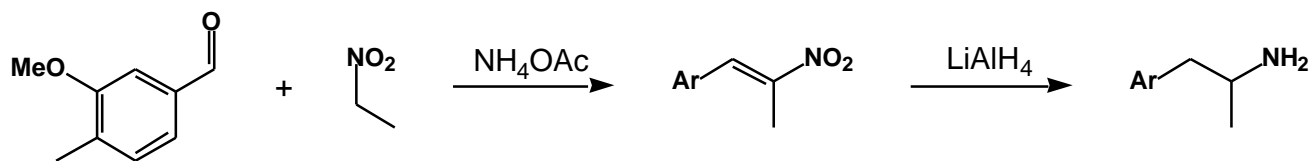
- Nitriles are easily introduced to a molecule
- Nitriles are useful in aiding C-C formation by stabilising anions



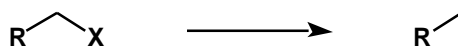
Nitro Group Transformation



Example

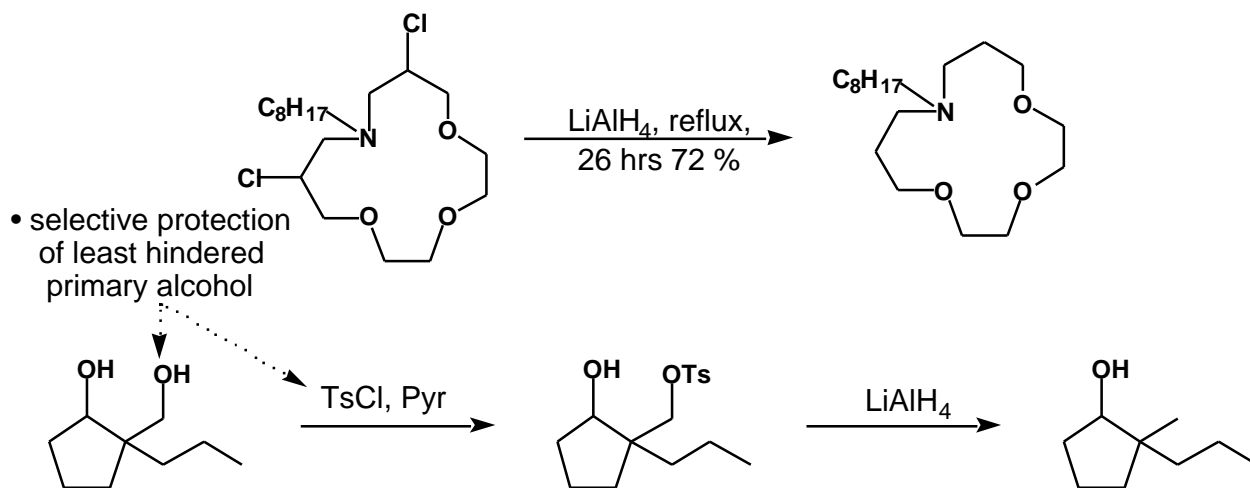


Hydrogenolysis Transformation

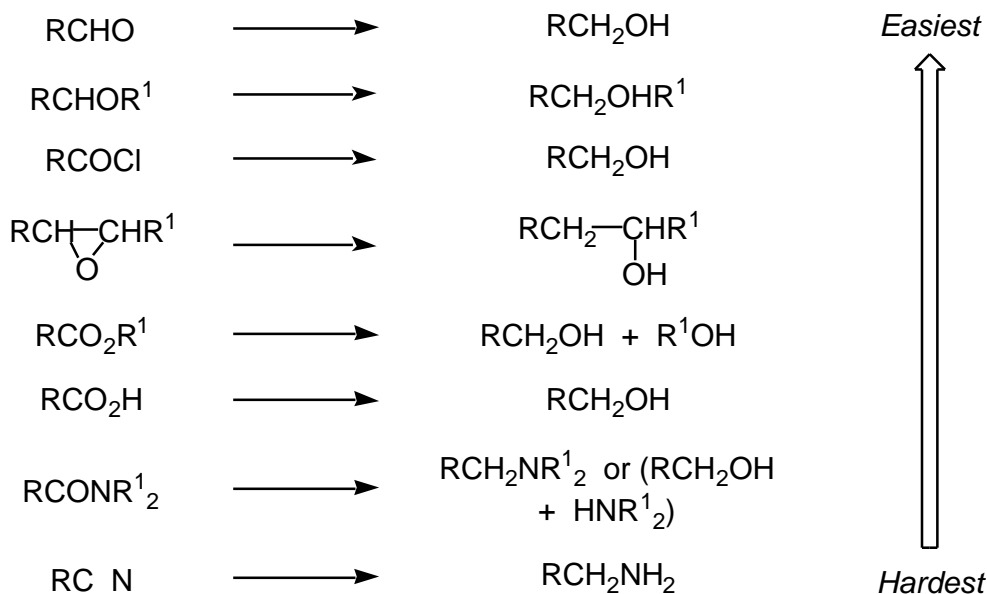


X = halide, sulfonate ester, good leaving group

Examples



Ease of Reduction of Functional Groups with LiAlH₄

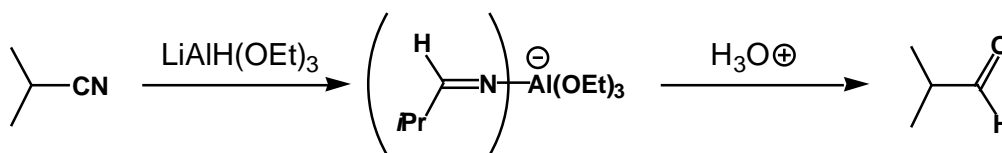


Alkoxyaluminate Reducing Systems

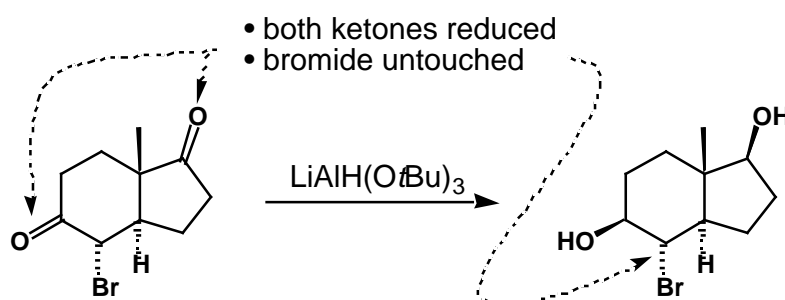
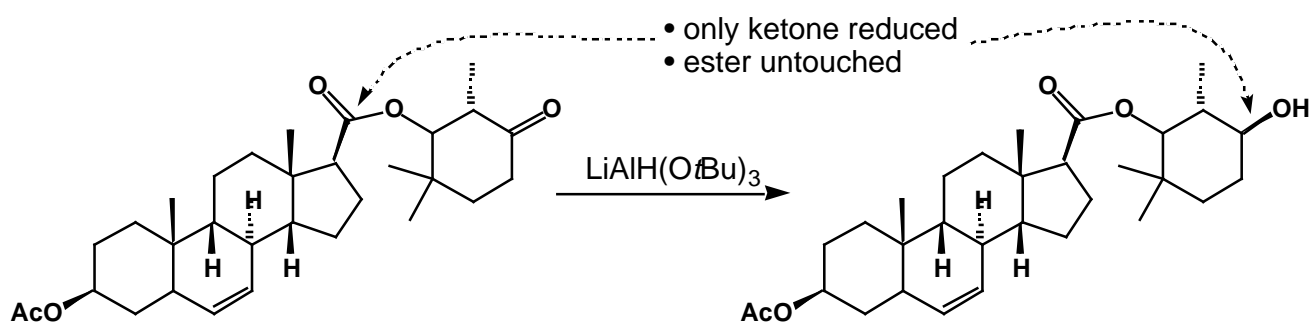
- By altering both the **sterics and electronics** of the substituents on LiAlH_4 it is possible to *tune* the reactivity of metal hydrides
- The addition of **alkoxides** reduces the reactivity of the hydride due to their electron-withdrawing properties
- This enables **chemoselective** reactions



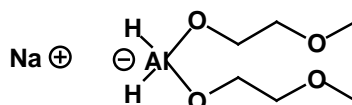
- Reduces nitriles to aldehydes



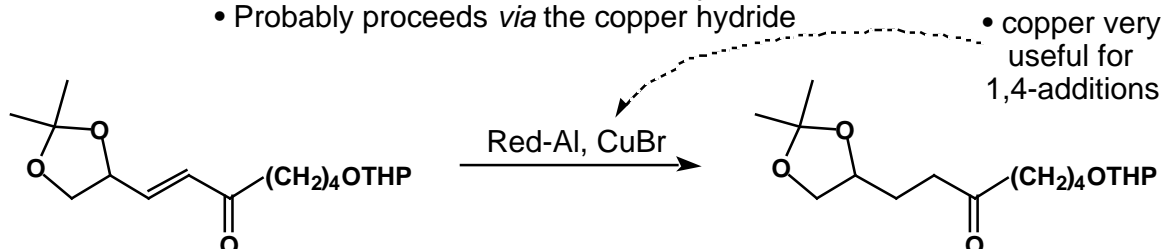
- Will reduce ketones, aldehydes and acid chlorides but little else
- Allows good selectivity



Sodium Bis(2-methoxyethoxy)aluminium Hydride (Red-Al)

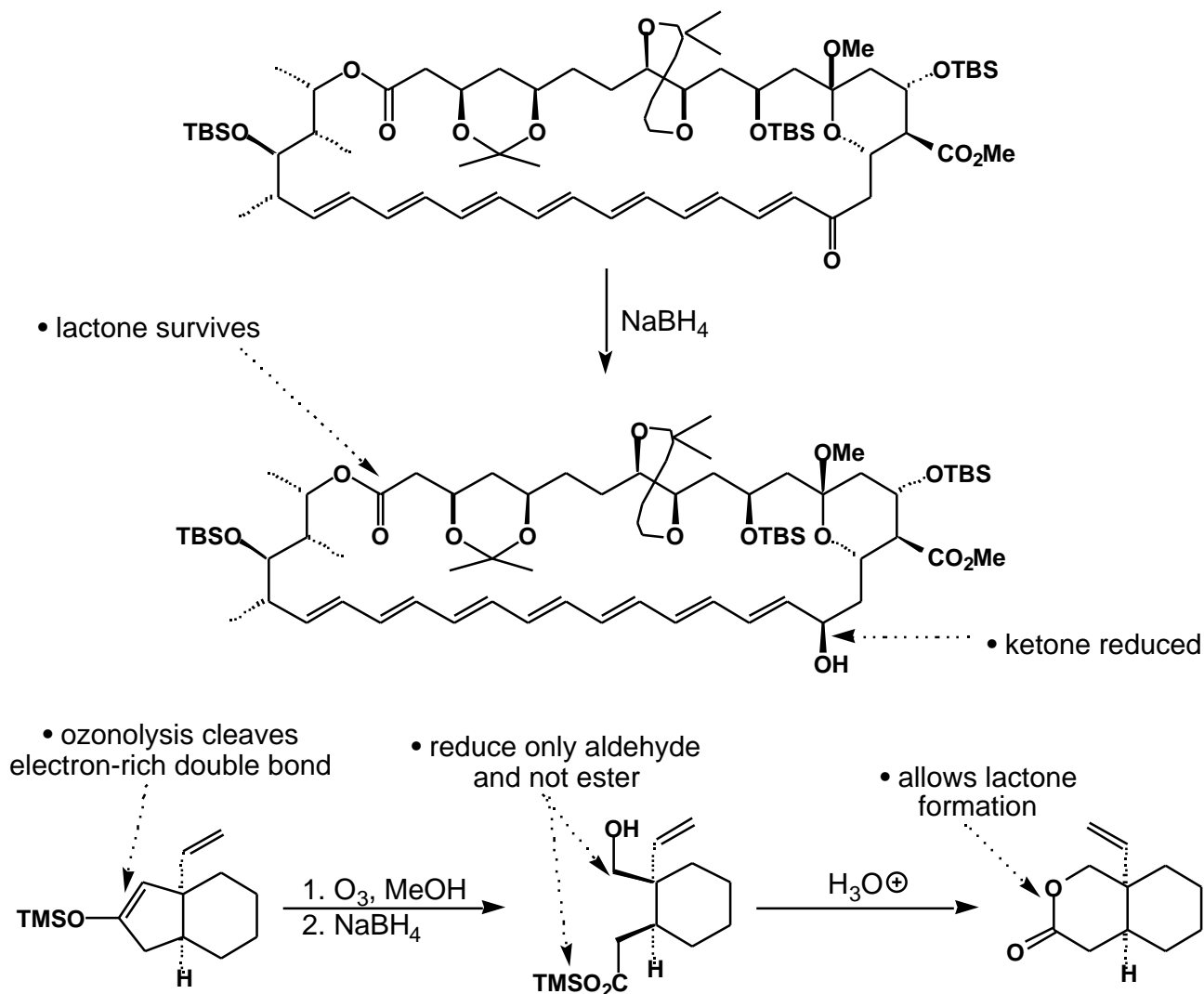


- Similar selectivity to LiAlH_4
- But more **stable** and **soluble** (so why it is sold as the most viscous gum known to mankind is anyone's guess)
- Can achieve 1,4-reductions in the presence of CuBr
- Probably proceeds *via* the copper hydride

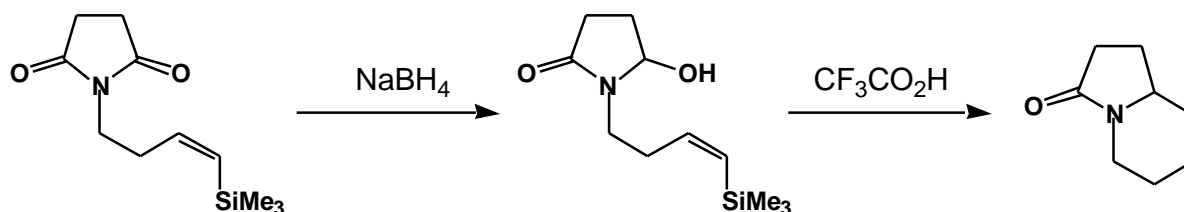


Sodium Borohydride NaBH_4

- Much less powerful reducing reagent
- Selective for aldehydes, ketones and acid chlorides
- Does not touch epoxides, esters, acids and nitriles



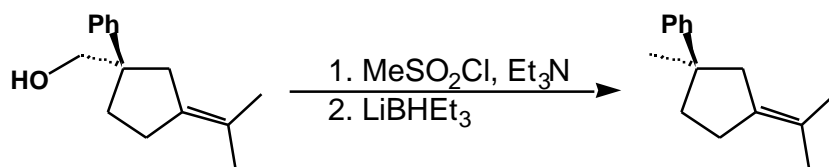
- NaBH_4 can reduce imides but only as far as the **aminol**
- Allows an elegant route to bicyclic alkaloids



Substituents on Boron

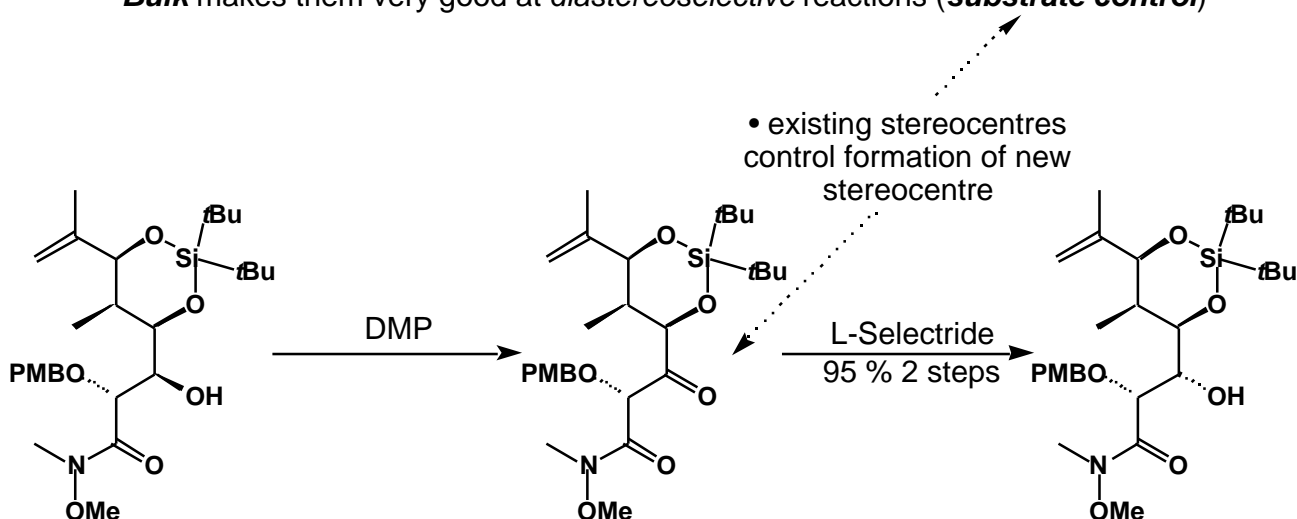
Super Hydride LiBHET_3

- Addition of electron-donating groups (*inductive effect*) **increases** reducing power
- One of the best reducing reagents
- Especially good at hydrogenolysis (superior to LiAlH_4)



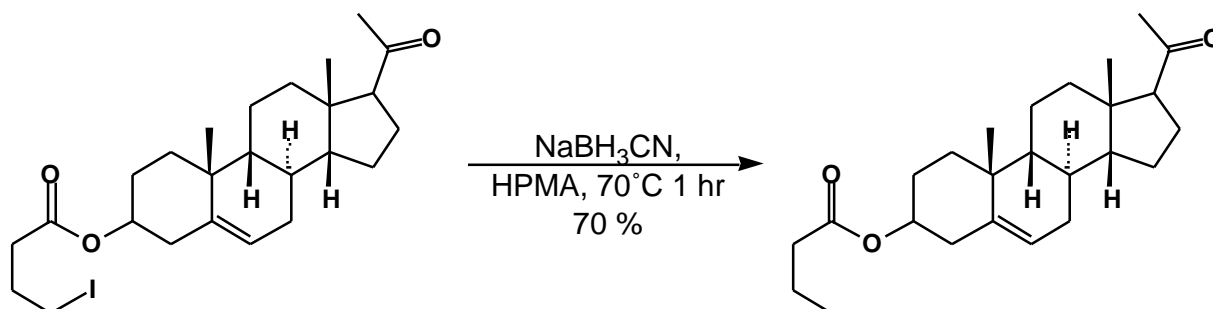
K & L-Selectride (K^\oplus or $\text{Li}^\oplus \text{BH}(\text{---})_3$)

- Very reactive hydride donors due to *inductive effect*
- **Bulk** makes them very good at *diastereoselective reactions (substrate control)*



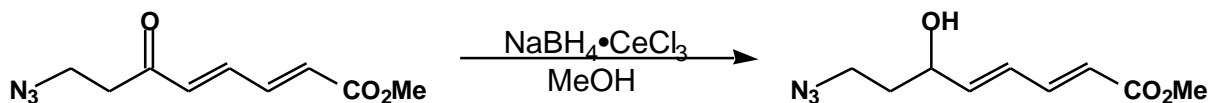
Sodium Cyanoborohydride NaBH_3CN

- Very unreactive therefore very selective
- Will reduce iodides, bromides and tosylates in HMPA *even* in the presence of carbonyls
- Ketones can be reduced BUT in **acid media** (ph 3-4)

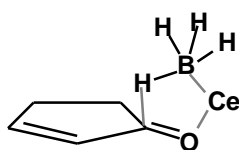


Effect of Counterions / Additives

- Changing the counter-cation can have a profound effect on the reactivity of NaBH_4
- Addition of LiBr , AlCl_3 or ZnCl_2 results in **more powerful** reducing agent (due to higher ionic potential)
- Addition of CeCl_3 (**Lucho Reduction**) gives very selective 1,2-reduction of conjugated aldehydes and ketones



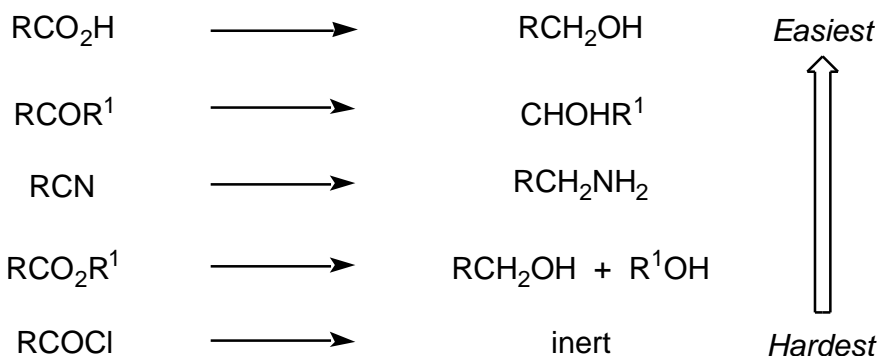
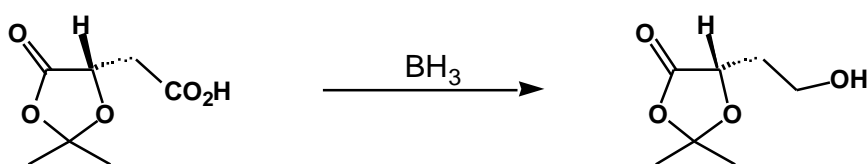
- Two reasons:
Co-ordination of the carbonyl and cerium result in increased hardness and more π character thus more reactive to "H⁻"
Tethering effect "intramolecularises reaction"
- Reaction is under **kinetic control** (irreversible)



- Use of Ni^{2+} or Co^{2+} results in a reversible complexation and a **thermodynamically controlled** reaction which results in *predominantly* 1,4-reduction

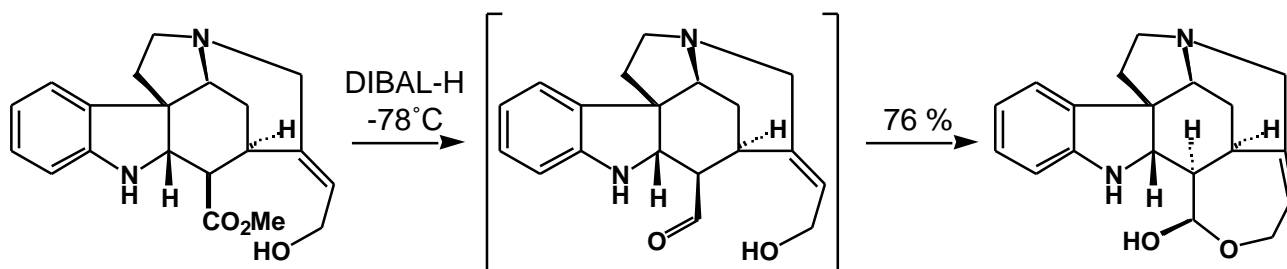
Borane / Diborane B_2H_6

- Very reactive
- But also **strong Lewis acid**
- Co-ordinates to electron-rich centres which alters its properties considerably
- **Complimentary** to LiAlH_4 (reverses much of its reactivity)

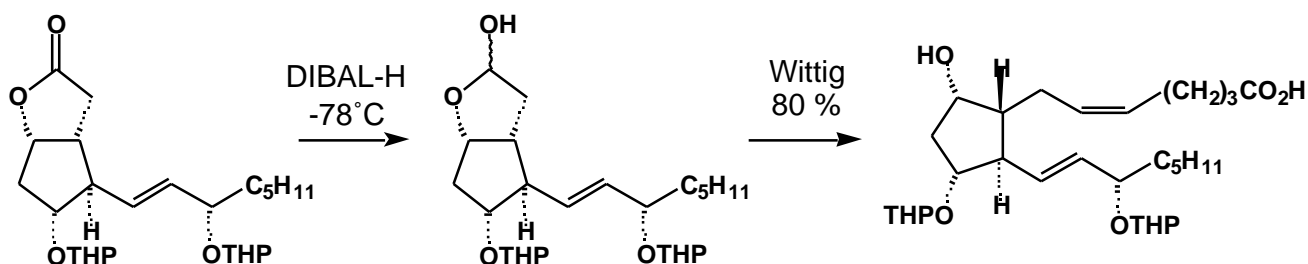


Diisobutylaluminium Hydride DIBAL-H ($i\text{Bu}_2\text{AlH}$)

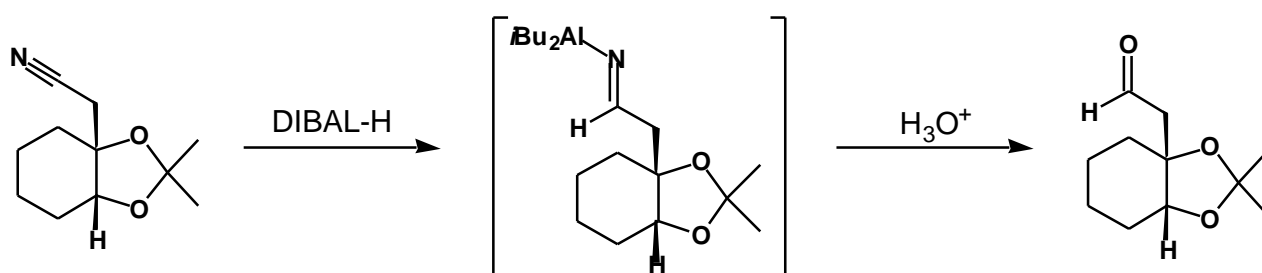
- Strong reducing agent
- But frequently possible to use it to reduce only one "oxidation state"
- Esters can be reduced to aldehydes



- Lactones reduced to lactols

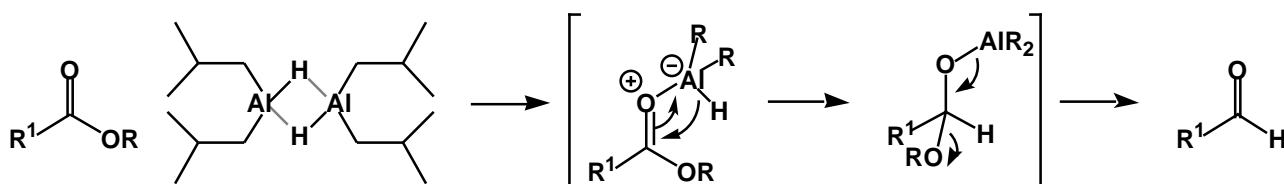


- Nitriles to aldehydes



MECHANISM FOR DIBAL-H REDUCTIONS

- The mechanism of the DIBAL-H reduction different to that of other metal hydride reagents
- Primarily because it is a Lewis acid. This means it needs to coordinate to a Lewis base first before it is activated then it delivers the hydride intramolecularly
- Unlike the other metal hydrides it is an electrophilic reagent



	NaBH ₄	BH ₃	LiAlH(OtBu) ₃	LiAlH(OMe) ₃	LiAlH ₄	LiBEt ₃ H	DIBAL-H	Hydrog.
RCHO RCH ₂ OH	✓	✓	✓	✓	✓	✓	✓	✓
RCOR' RCHOHR'	✓	✓	✓	✓	✓	✓	✓	✓
RCOCl RCH ₂ OH	✓	✗	✓	✓	✓	✓	✓	✓
Lactone diol	✗	✓	✓ / ✗	✓	✓	✓	✓	✓
Epoxide alcohol	✗	✓	✓ / ✗	✓	✓	✓	✓	✓
RCO ₂ R' RCH ₂ OH / R'OH	✗	✓ / ✗	✓ / ✗	✓	✓	✓	✓	✓
RCO ₂ H RCH ₂ OH	✗	✓	✗	✓	✓	✗	✓	✗
RCONR' ₂ RCH ₂ NR' ₂	✗	✓	✗	✓	✓	✓	✓	✓
RC N RCH ₂ NH ₂	✗	✓	✗	✓	✓	✓ / ✗	✓	✓
RNO ₂ RN ₂	✗	✗	✗	✓	✓	✗	✓	✓
RCH=CHR' RCH ₂ CH ₂ R'	✗	✓	✗	✗	✗	✓	✗	✓

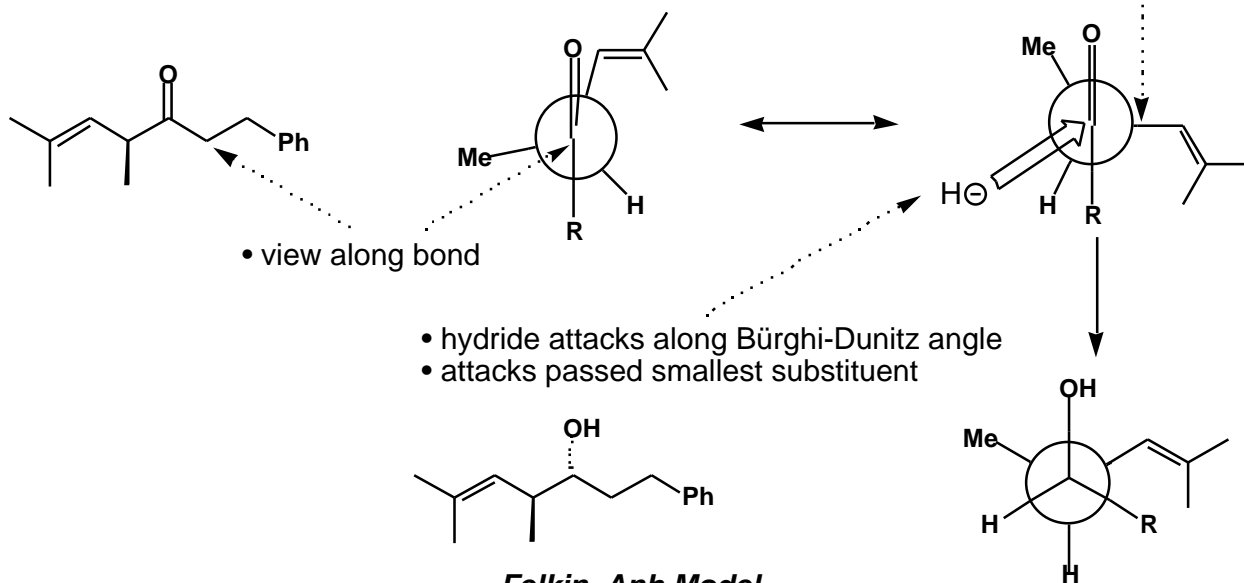
STEREOSELECTIVITY

- The stereocontrol of carbonyl reduction is of great importance
- A number of ways to control it

SUBSTRATE CONTROL

- If the substrate contains a chiral centre -to the carbonyl this can control the approach of the hydride

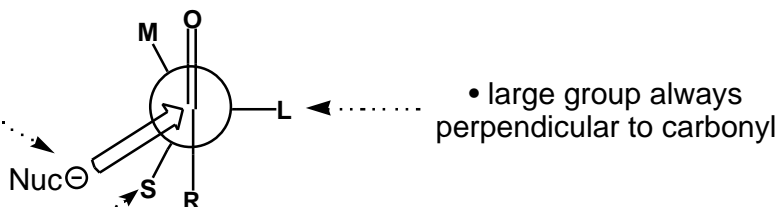
- rotate until largest substituent perpendicular to carbonyl



- nucleophile attacks carbonyl passed smallest group

- Represents transition state

- smallest group eclipses Bürgi-Dunitz angle

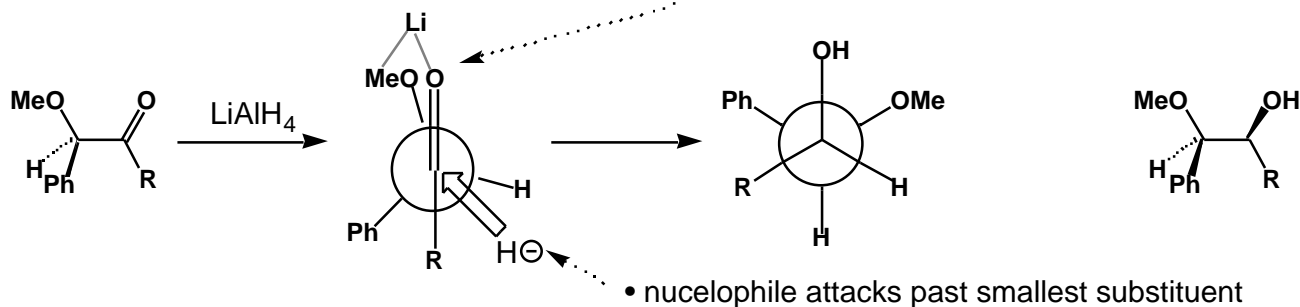


- **Note:** the larger the hydride source the better the selectivity
- Hence the usefulness of the **Selectrides**

Cram-Chelation Control

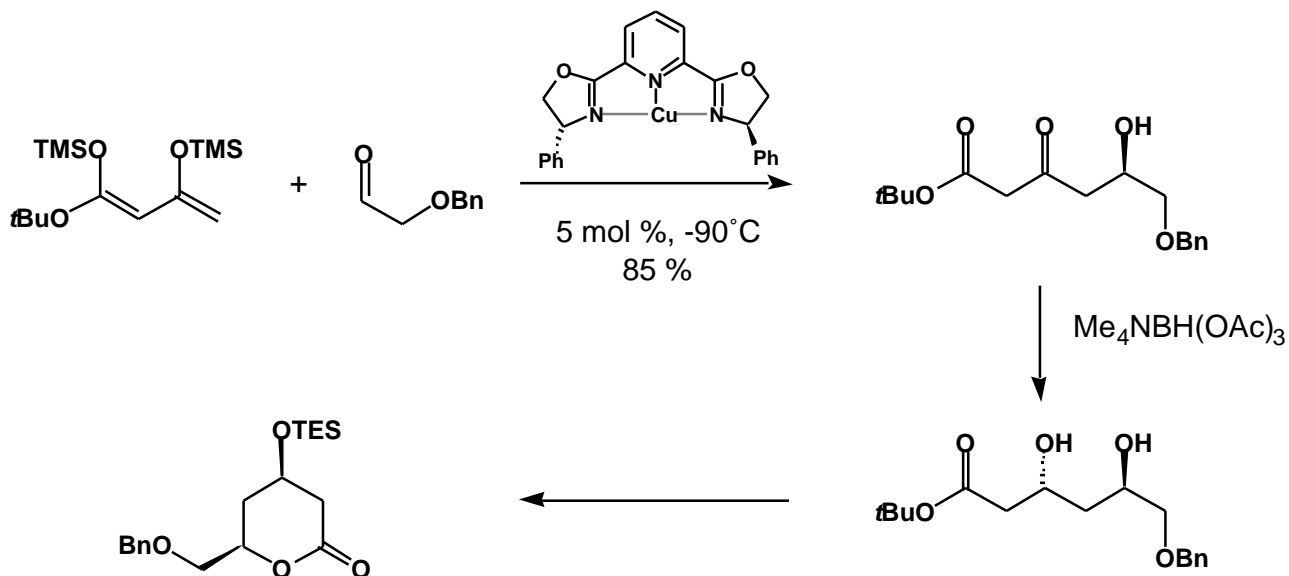
- If a heteroatom is present **chelation** is possible and the transition state conformation is changed.
- Predicted by **Cram-chelation model**

- chelation controls conformation

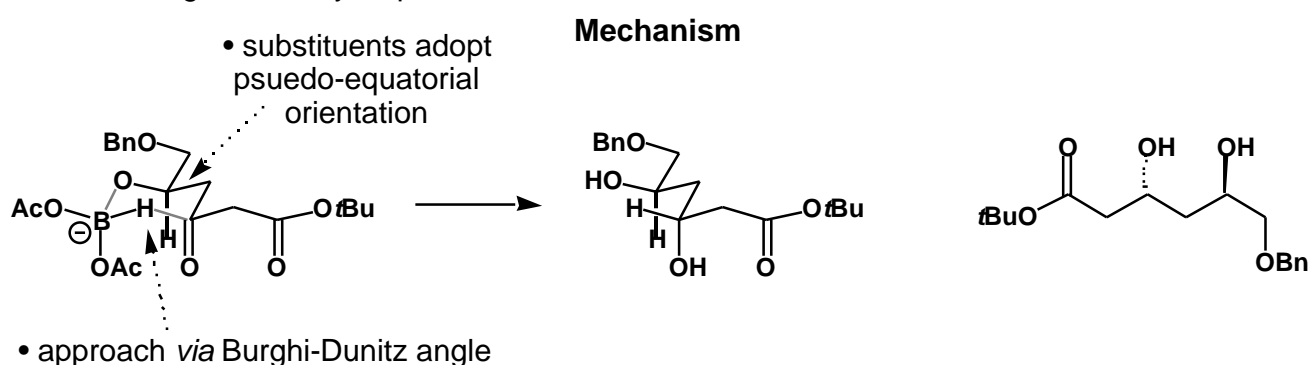


1,3-Stereochemical Induction

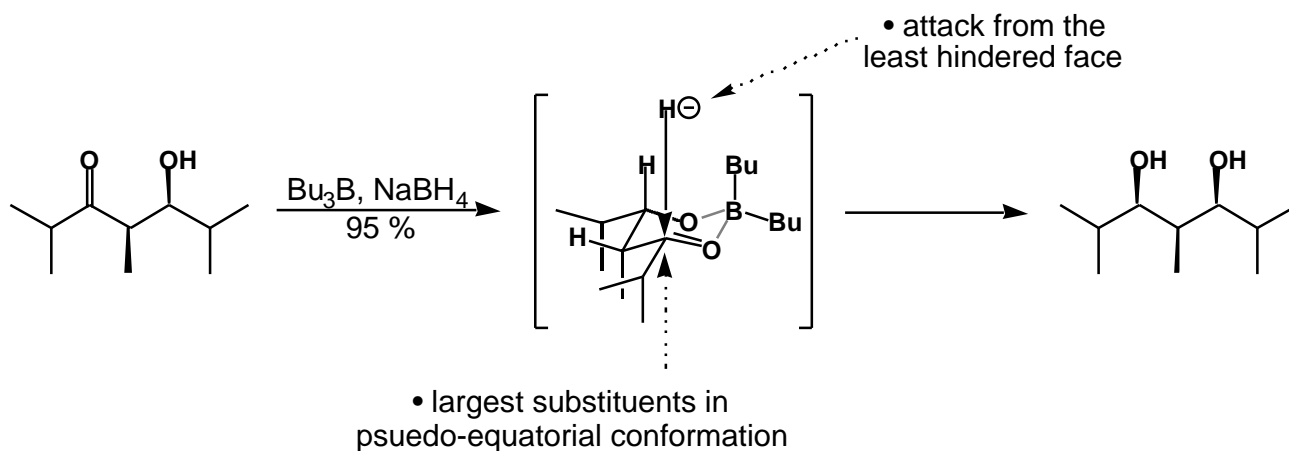
- Very useful transfer of stereochemical information
- Use in conjunction with *stereoselective aldol reaction* allows a powerful entry to 1,3-diols



- Diastereoselectivity achieved by **internal delivery of the hydride**
- The *borohydride* reagent has a very poor counter-ion so *rapidly* co-ordinates to the oxygen lone-pair
- Acetate ligand readily displaced



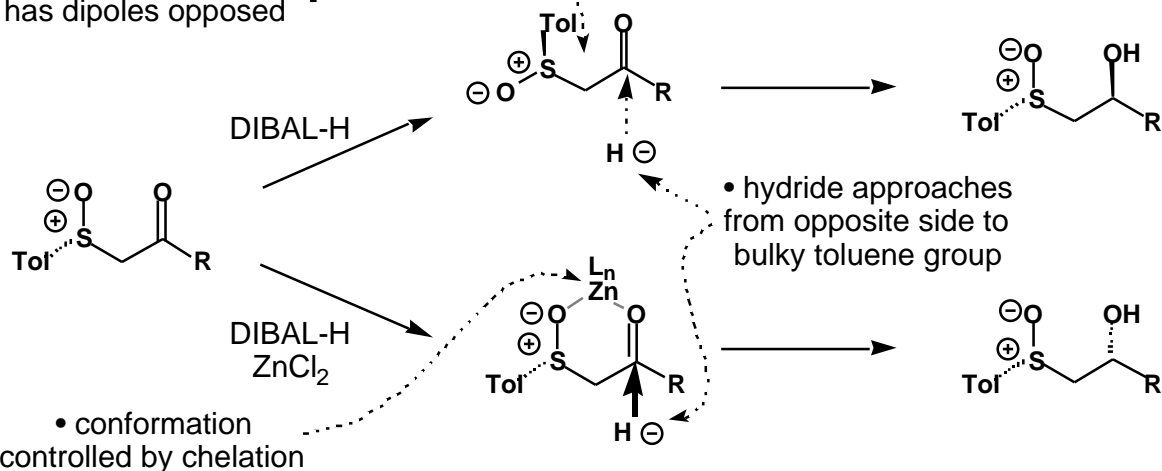
- A powerful extension of this methodology allows the *reversal* of diastereoselectivity
- **Preco-ordination** with a Lewis acid results in **external hydride delivery**



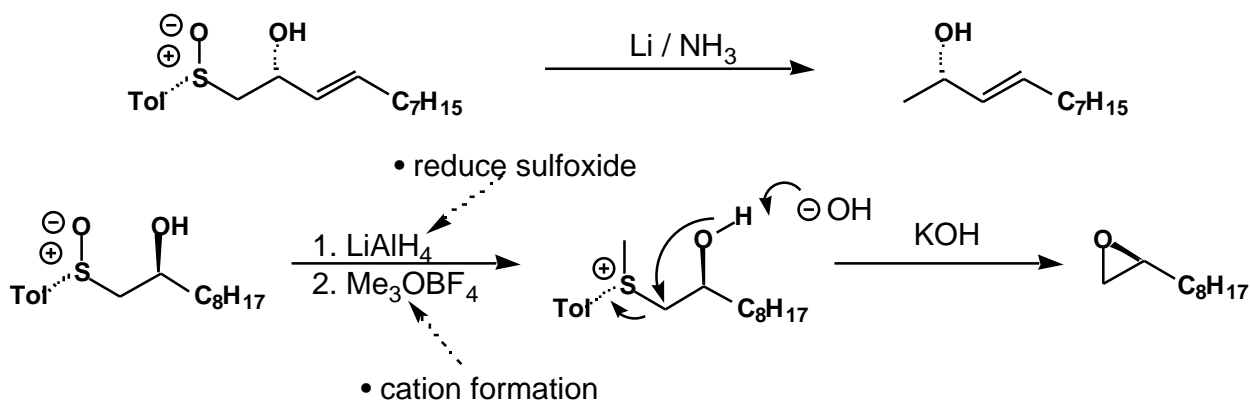
Chiral Auxiliary

- Really a more specific example of *substrate control*
- A chiral unit is introduced into a prochiral molecule to induce a **diastereoselective** reaction
- The unit can then be removed at later stage to give an *optically enhanced* product

- preferred conformation has dipoles opposed

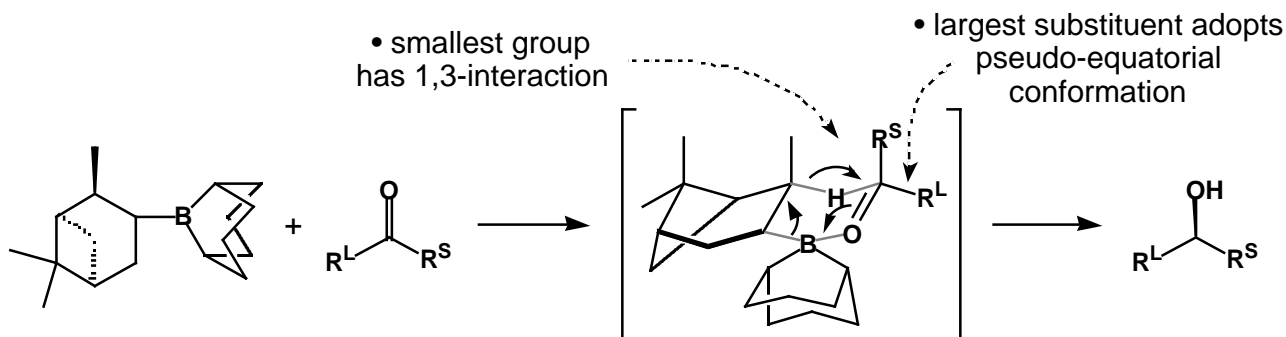


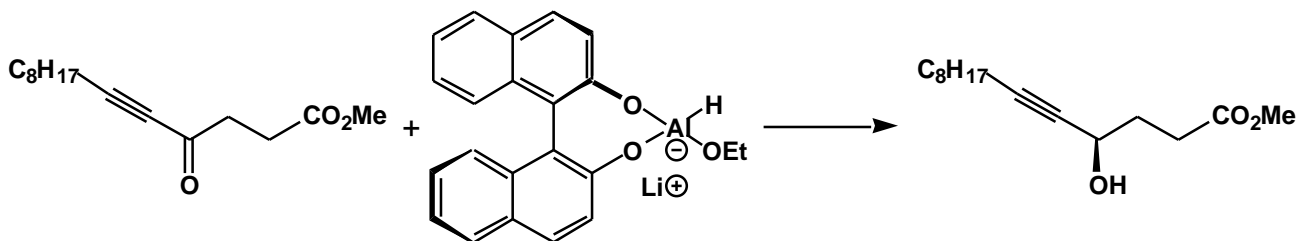
- Auxiliary removal



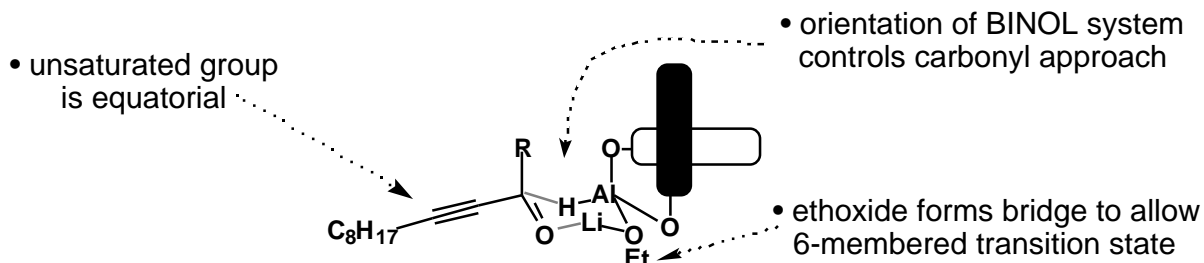
Chiral Reagents

- Sometimes substrate has no chiral centre and / or chiral auxiliary introduction / removal incompatible with existing functionality
- To overcome these short-comings **chiral reagents** introduced



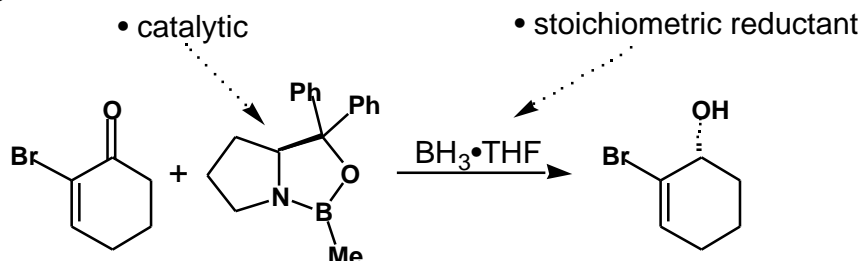


- Proposed transition state model



Chiral Catalysis

- Ultimate goal is to generate *enantiopure* material from only a *catalytic* source of chirality
- Possibly the most successful general catalyst for the reduction of ketones is the CBS oxazaborolidines



Mechanism

