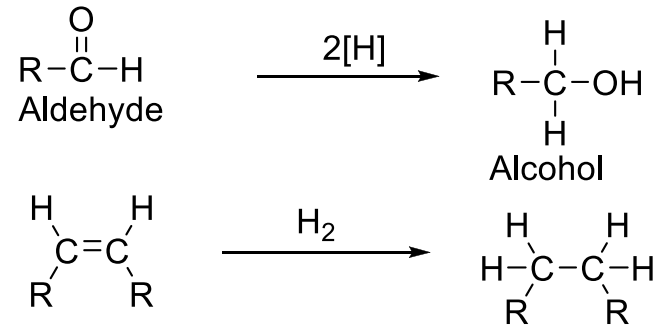


REDUCTIONS AND REDUCING AGENTS

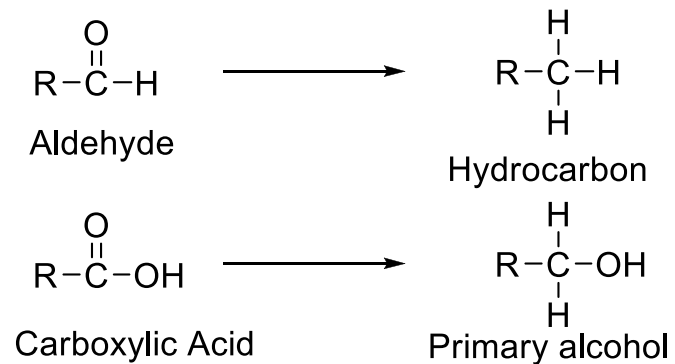
Reductions and Reducing Agents

- Basic definition of reduction: Addition of hydrogen or removal of oxygen
- Addition of electrons

Addition of Hydrogen

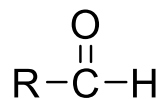


Removal of Oxygen

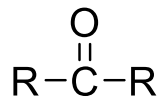


Reducible Functional Groups

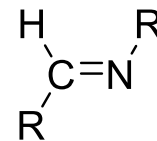
Polar Reducible Groups



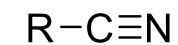
Aldehydes



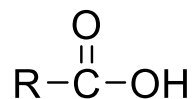
Ketones



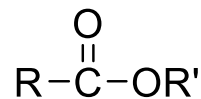
Imines



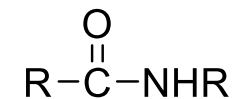
Nitriles



Carboxylic acids

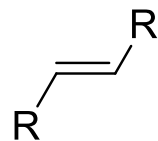


Esters

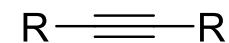


Amides

Non-Polar Reducible Groups



Alkenes



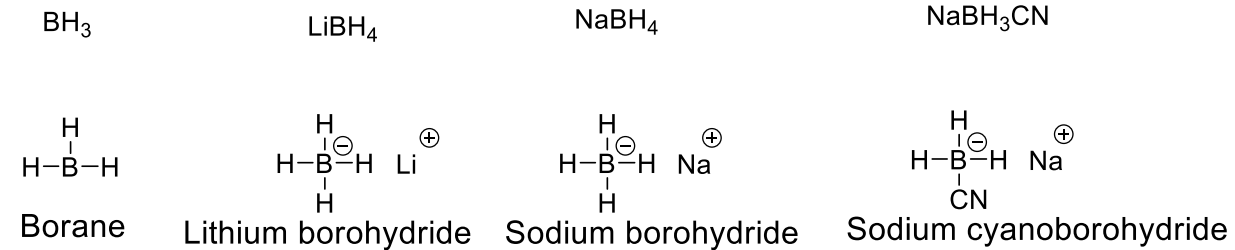
Alkynes

Categories of Common Reducing Agents

Polar Reducing Reagents

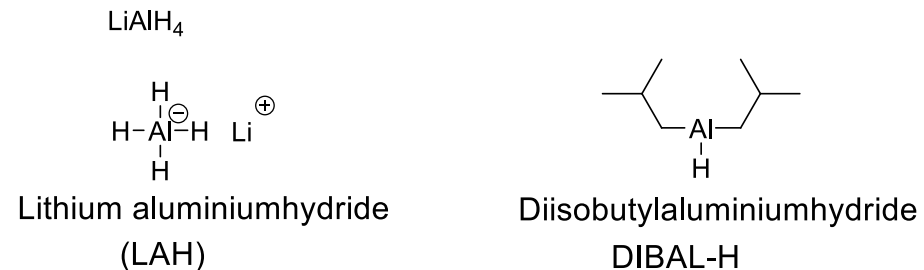
Most of the polar reducing agents are covalent metal hydrides

(a) Borohydride reducing agents



cf: Compare this with LiH and NaH: These are ionic hydrides. Since they are very reactive, they are sources of basic hydrides (act as bases) and not nucleophilic hydrides (covalent hydrides are sources of nucleophilic hydrides).

(b) Aluminium hydride reducing agents



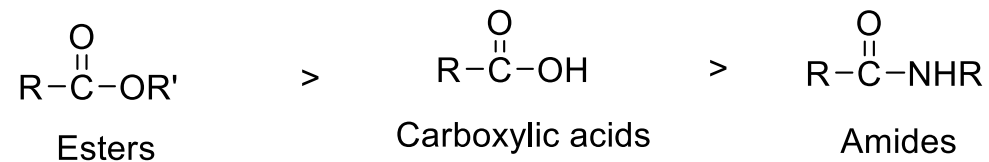
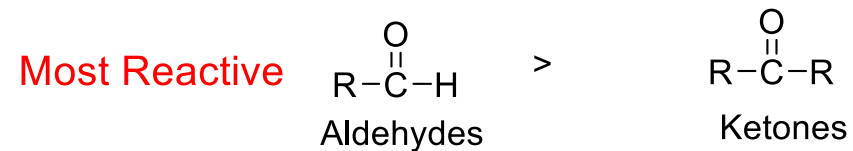
Nonpolar Reducing Reagents

Most reducing conditions employ H_2 adsorbed on a metal catalyst. Mainly used for the reduction of alkenes and alkynes

Relative Reactivity of Nucleophiles at the Reducible Functional Groups

In the absence of any secondary interactions, the carbonyl compounds exhibit the following order of reactivity at the carbonyl

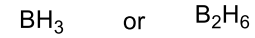
Pecking Order of Reactivity to Nucleophiles



This order may however be reversed in the presence of unique secondary interactions inherent in the molecule; interactions that may be activated by some property of the reacting partner

Common Reducing Agents (Borohydrides)

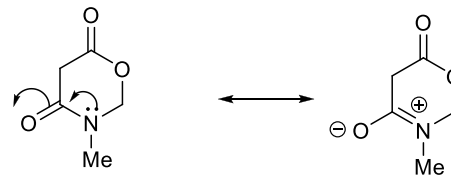
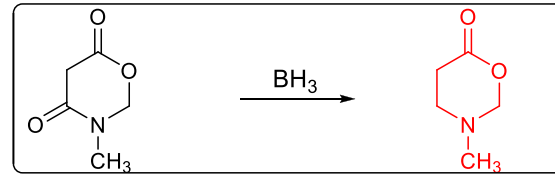
Borane or Diborane



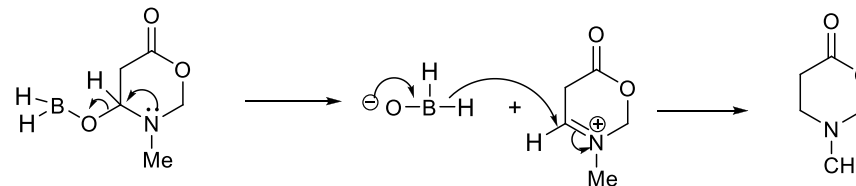
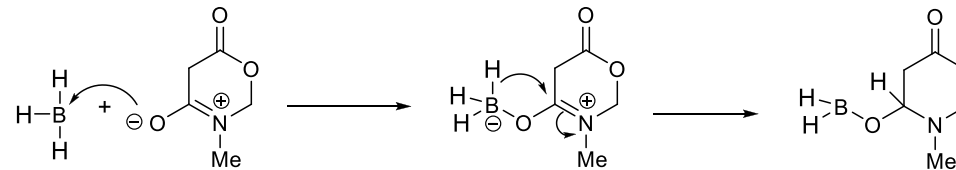
Borane is a strong Lewis acid that reacts fastest with nucleophilic carbonyl groups

The more nucleophilic amides are reduced much faster than the more reactive ester groups

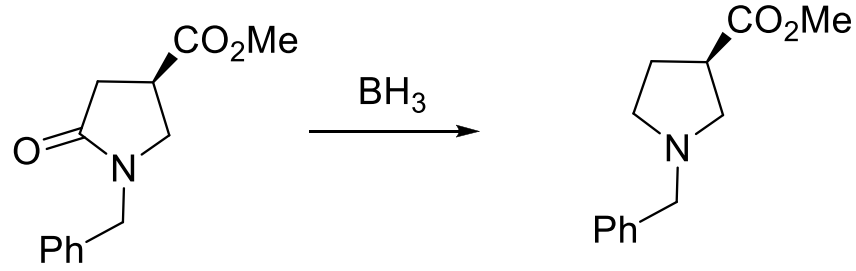
Reduction of Amides to Amines



Amides, unlike esters, exist principally in the imidate form



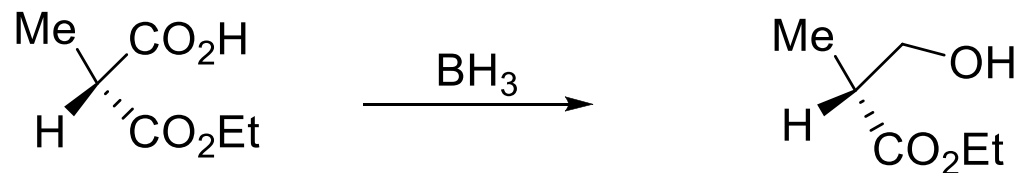
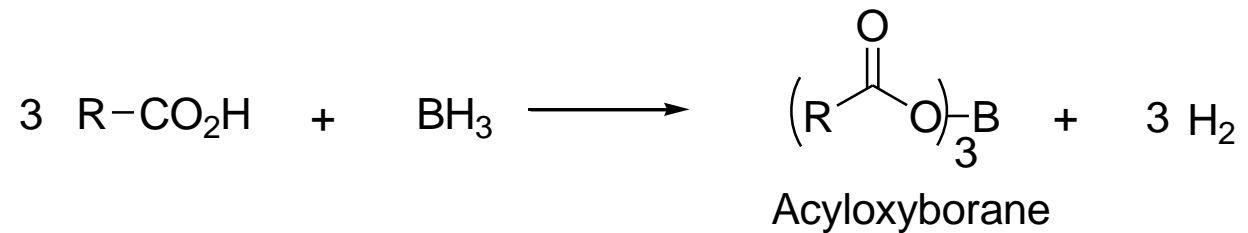
Common Reducing Agents (Borohydrides)



Reduction of Carboxylic Acids to Primary Alcohols

Borane is also effective in the reduction of carboxylic acids to primary alcohols

Reduces carboxylic acids selectively in the presence of the more reactive ester groups
The reduction is presumed to occur through the initial formation of an acyloxyborane.



Common Reducing Agents (Sodium Borohydride)

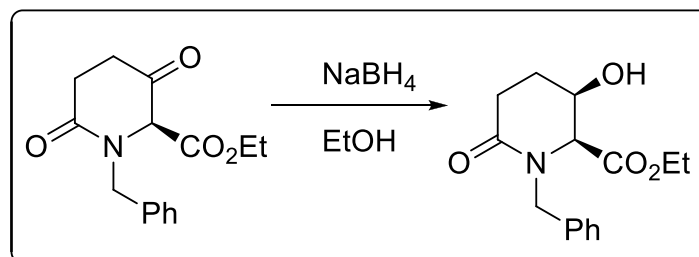
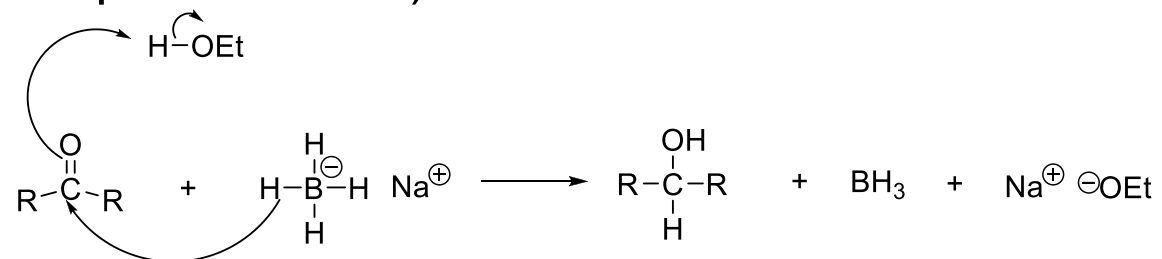


Sodium borohydride is a mild reducing agent for aldehydes and ketones (the most reactive of the carbonyls) to alcohols.

Whereas BH_3 is a Lewis acid, NaBH_4 (Octet on boron) is not a Lewis acid.

Carboxylic acids, esters and amides are immune to NaBH_4 reduction

The reductions with NaBH_4 are commonly carried out in EtOH (Serving as a protic solvent)



Note that nucleophilic attack occurs from the least hindered face of the carbonyl

Common Reducing Agents (Lithium Borohydride)



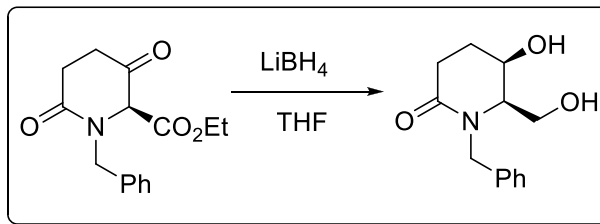
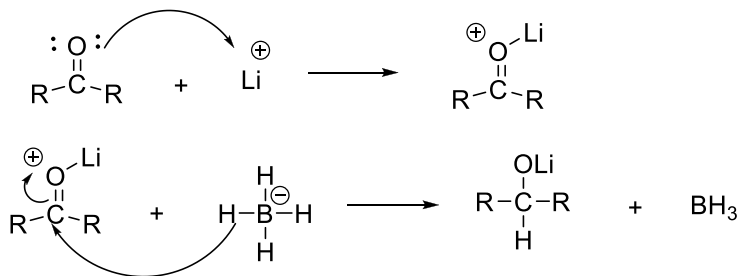
Lithium borohydride is a more reactive reducing agent than sodium borohydride.

Whereas Na^+ in NaBH_4 is a large cation and therefore not a Lewis acid, Li^+ of LiBH_4 is a small cation and hence Lewis acidic and co-ordinates better to the carbonyl oxygen, activating it to nucleophilic attack.

LiBH_4 reduces aldehydes, ketones and ester to alcohols

Carboxylic acids and amides are immune to LiBH_4 reduction

The reductions with LiBH_4 are commonly carried out in THF or ether

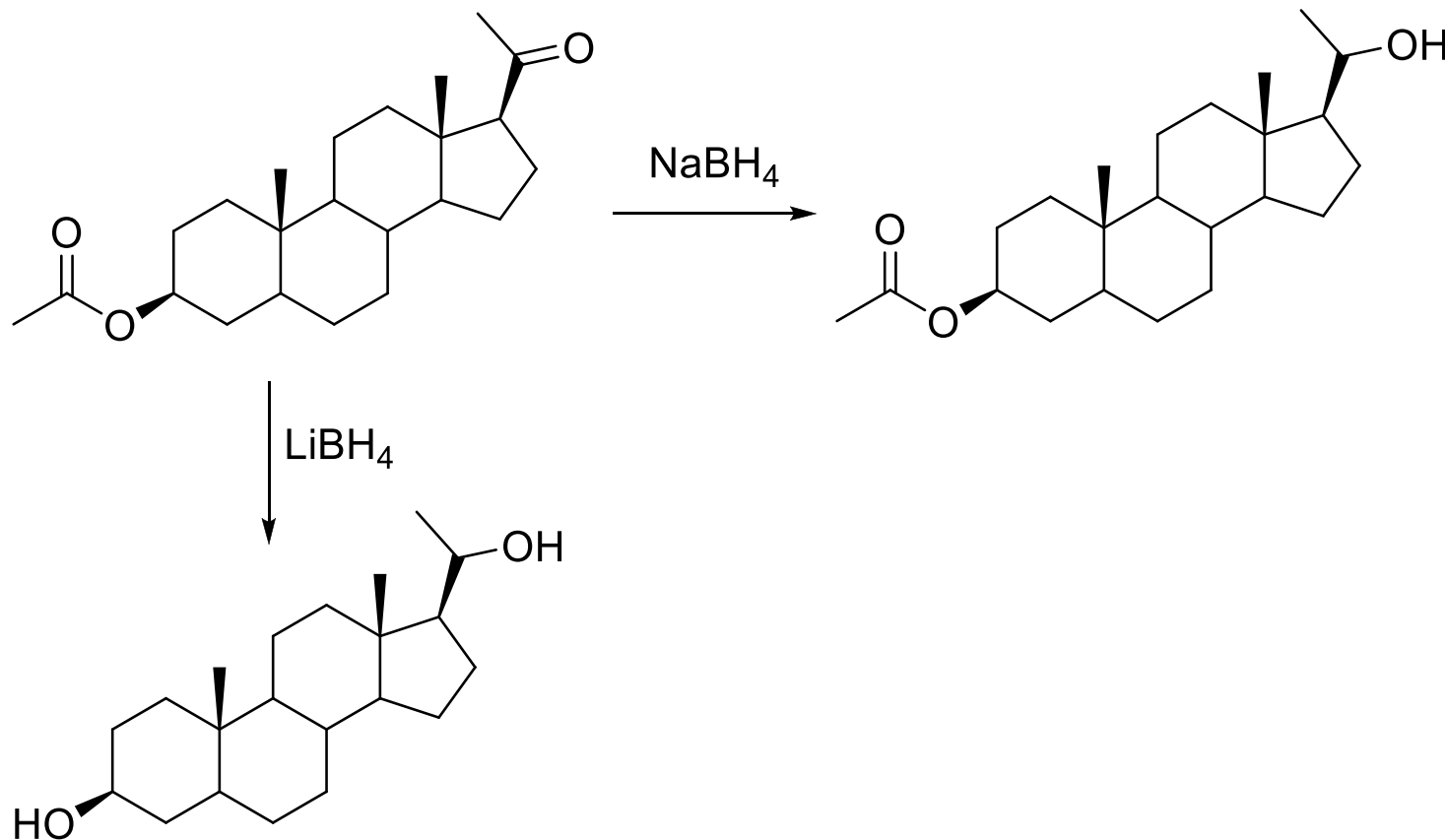


Note that nucleophilic attack occurs from the least hindered face of the carbonyl.

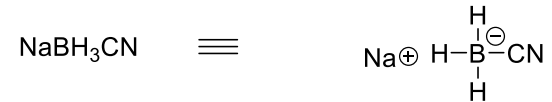
Common Reducing Agents (Borohydrides)

The Influence of Metal Cations on Reactivity

As a result of the differences in reactivity between sodium borohydride and lithium borohydride, chemoselectivity of reduction can be achieved by a judicious choice of reducing agent.



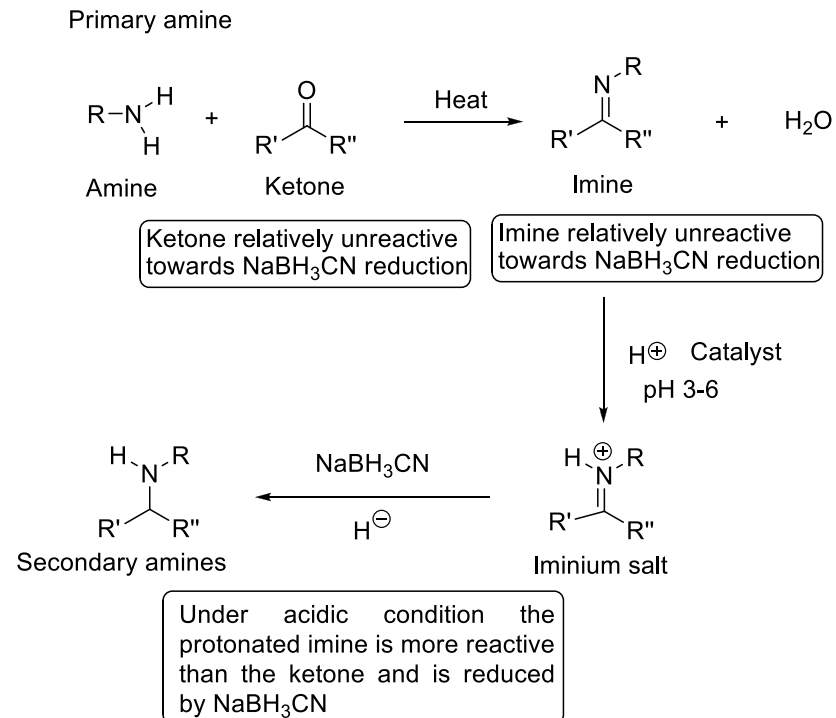
Common Reducing Agents (Sodium Cyanoborohydride)



Since CN is a stronger electron withdrawing group than the H it replaces in NaBH_4 , sodium cyanoborohydride is a more deactivated borohydride reducing agent. It is much less reactive than NaBH_4 .

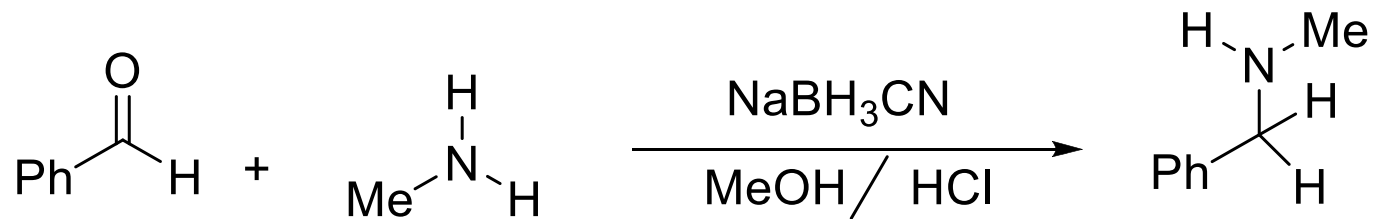
It is compatible with reductions between pH 3-6. Reduces only imines to amines. Although less reactive than ketones to reduction in neutral media, imines are more basic and at pH 3-6 get protonated and activated at the expense of aldehydes and ketones at this pH.

Aldehydes, ketones, esters, carboxylic acids and amides are resistant to reduction by NaBH_3CN since they don't get protonated at pH 3-6.



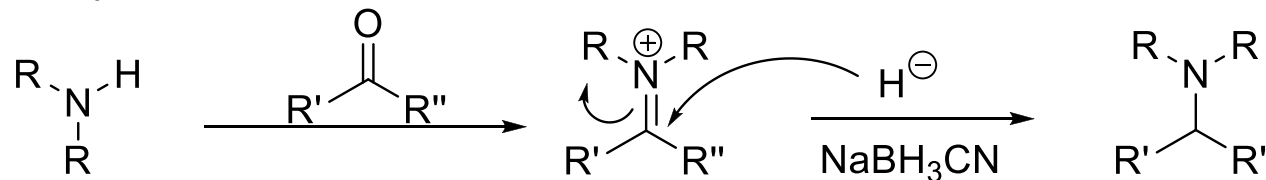
Common Reducing Agents

(Reductive Amination with Sodium Cyanoborohydride)



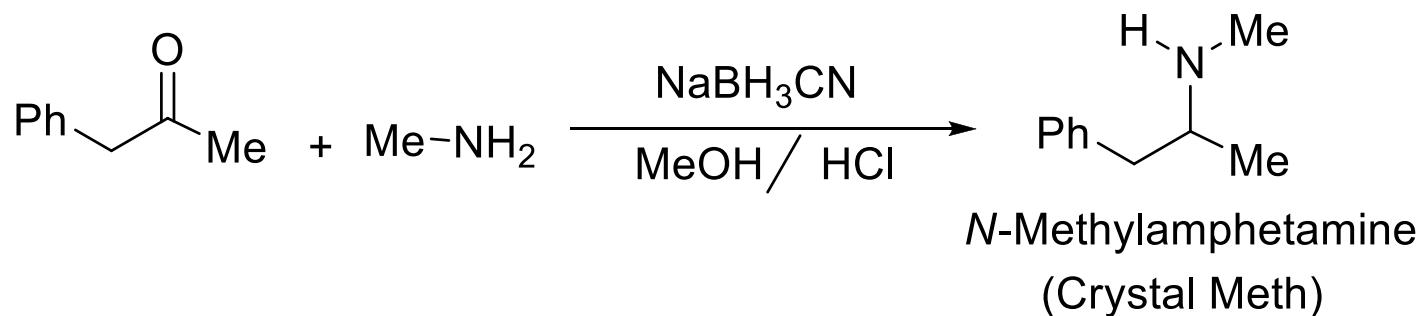
Secondary amine

Tertiary amine



Ketone relatively unreactive towards NaBH_3CN

The iminium ion is more reactive than the ketone and is reduced by NaBH_3CN



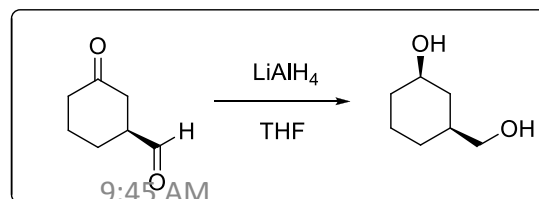
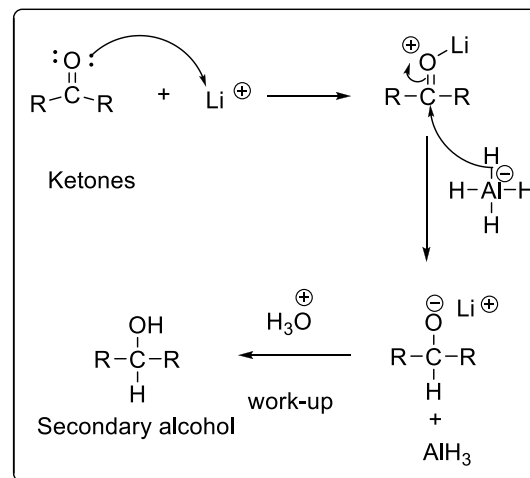
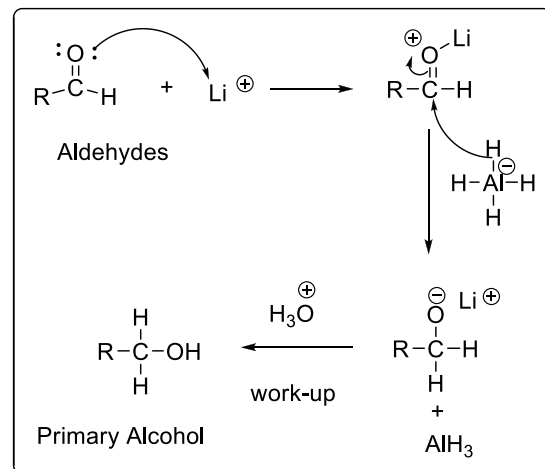
Lithium Aluminium Hydride

Lithium aluminiumhydride reacts the same way as lithium borohydride. It is however a much more reactive reducing agent than lithium borohydride. It is the strongest of the hydride reducing agents.

Note that the Al-H bond is more polarized than B-H bond. Consequently the hydride in Al-H has greater hydride character and therefore more nucleophilic than the hydride in B-H.

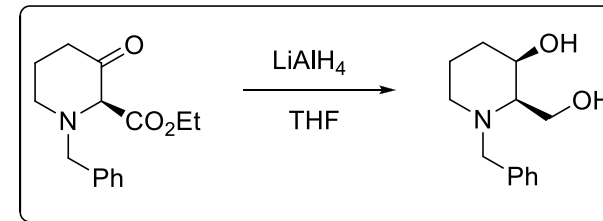
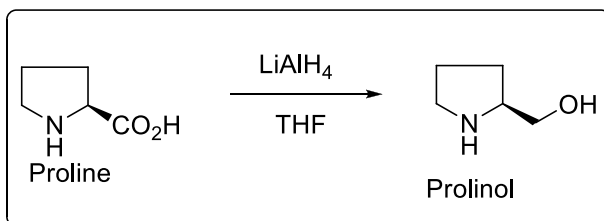
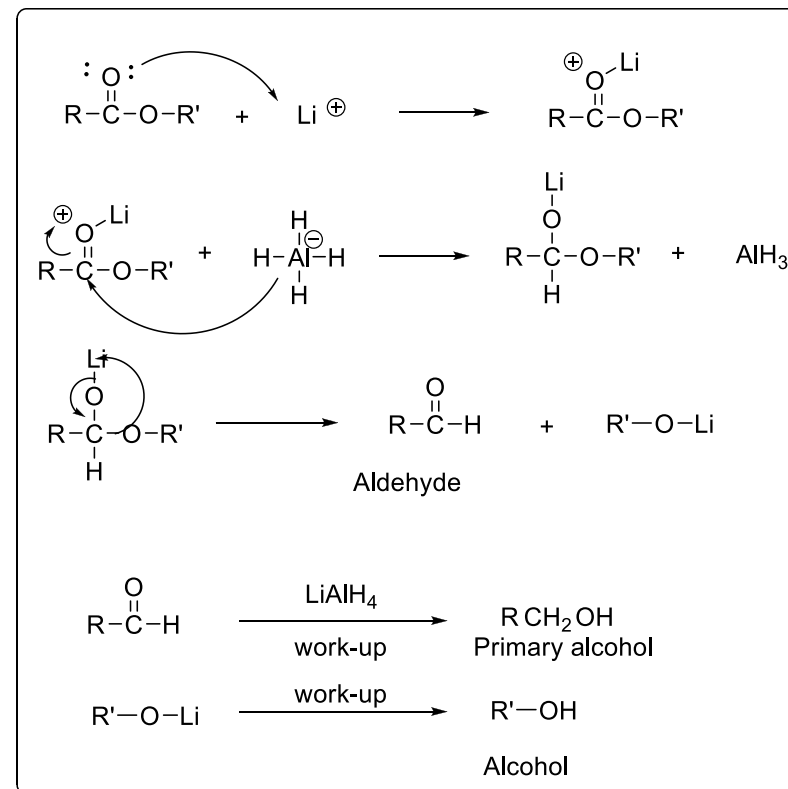
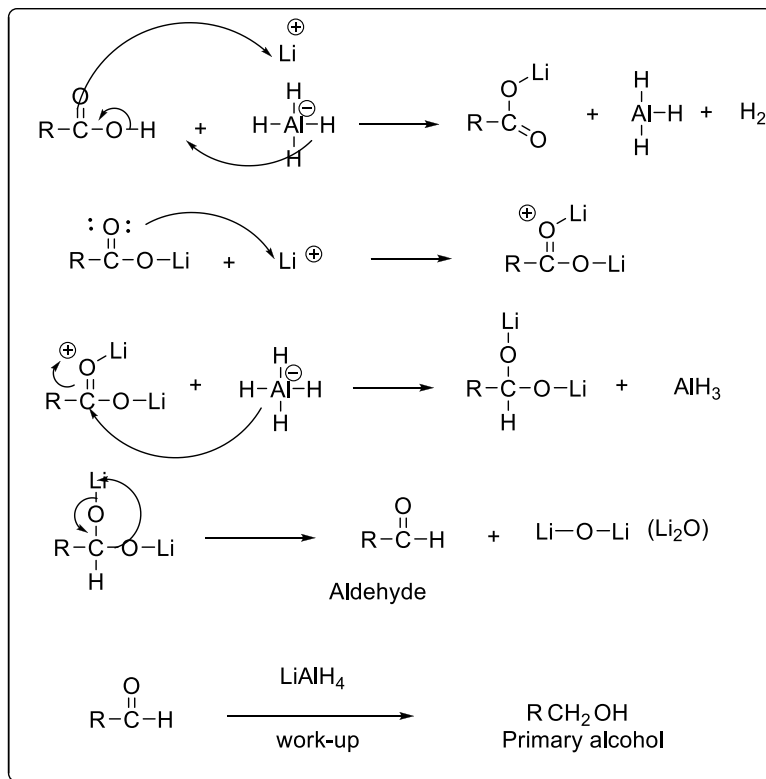
Note that unlike Na^+ , Li^+ is a Lewis acid that co-ordinates better to the carbonyl oxygen, activating the carbonyl to nucleophilic attack.

It reduces both aldehydes and ketones to alcohols



Common Reducing Agents (Lithium Aluminium Hydride)

Carboxylic acids and esters are reduced by LiAlH_4 to primary alcohols

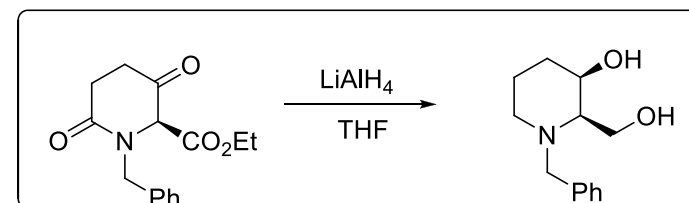
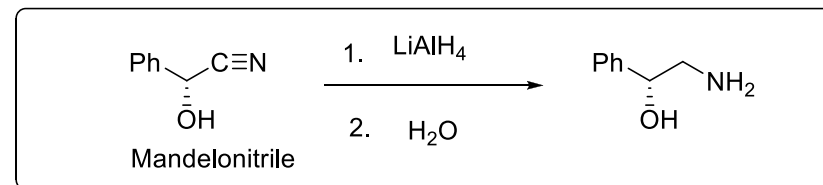
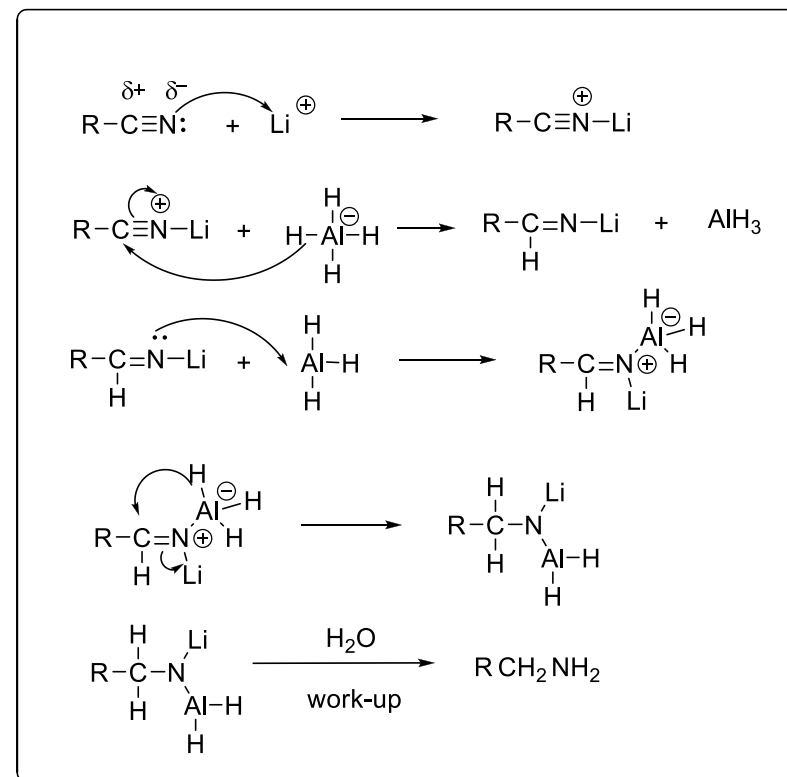
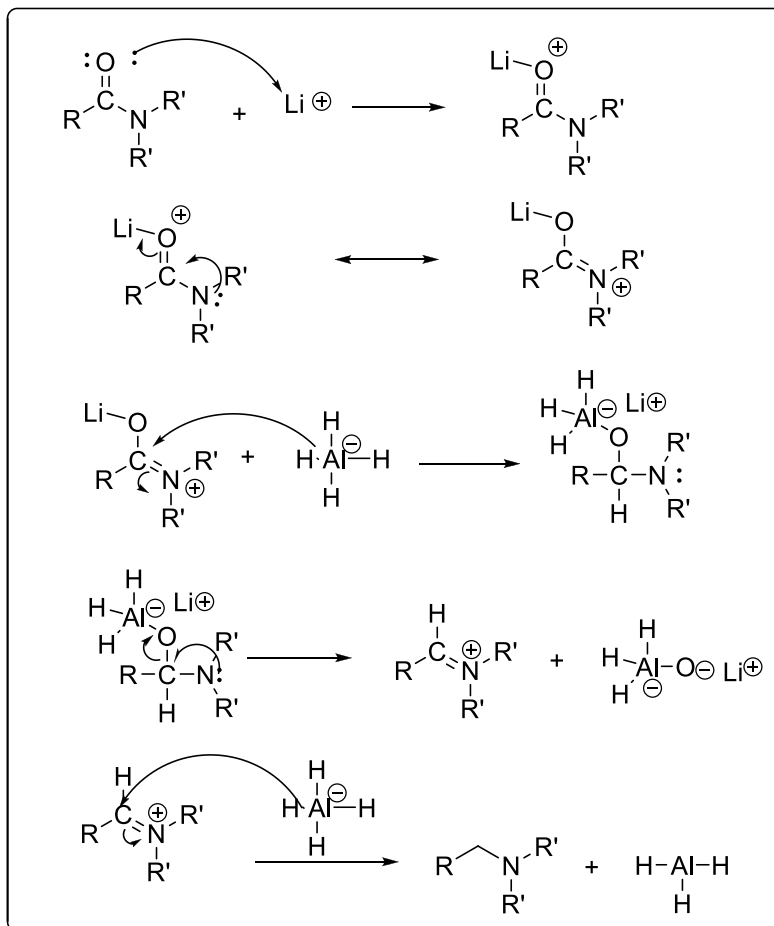


Note that nucleophilic hydride attacks from the least hindered face

Common Reducing Agents (Lithium Aluminium Hydride)

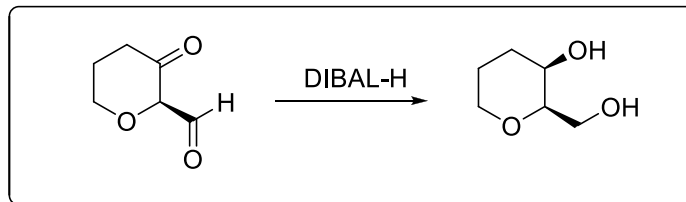
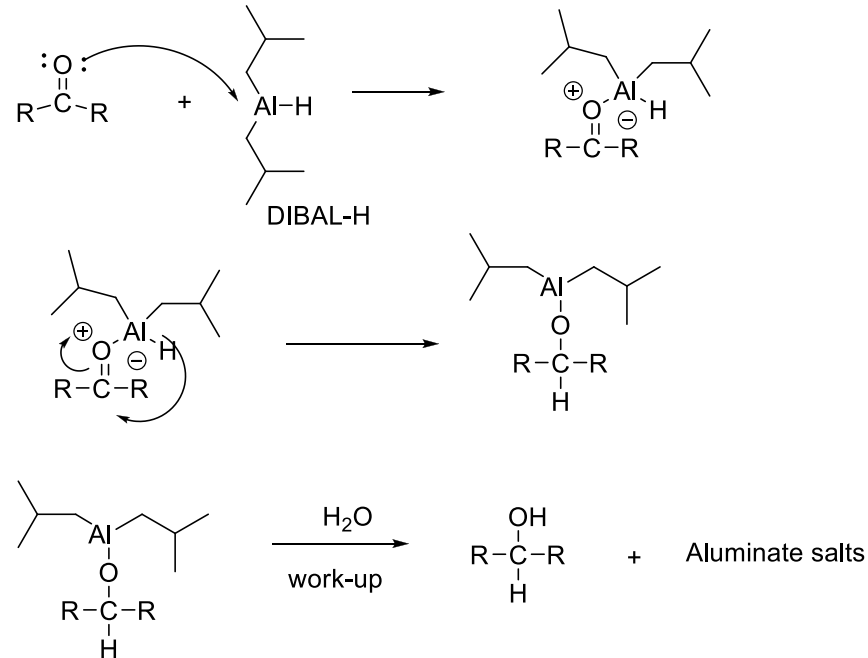
Reduction of Amides and Nitriles to Amines

Amides and nitriles are reduced by LiAlH_4 to amines.



Common Reducing Agents (Diisobutylaluminiumhydride)

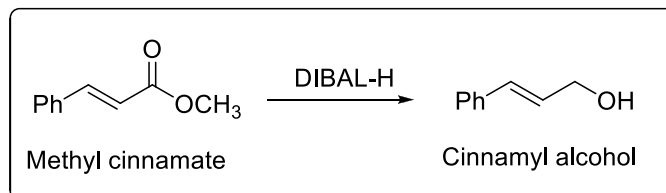
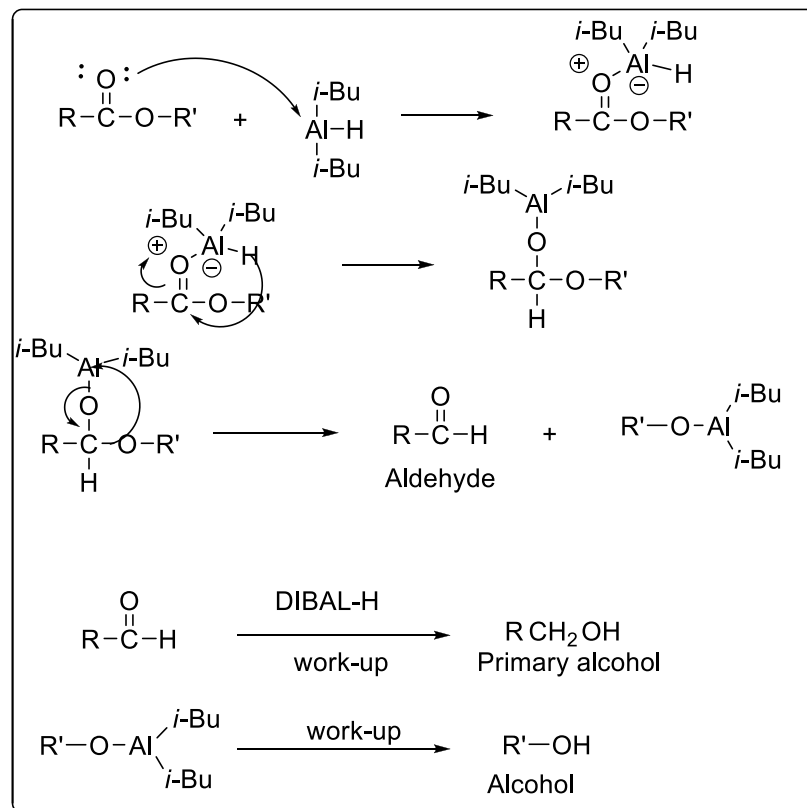
Reduction of Aldehydes and Ketones to Alcohols



DIBAL-H has a tendency of effecting chelation controlled reductions

Common Reducing Agents (Diisobutylaluminiumhydride)

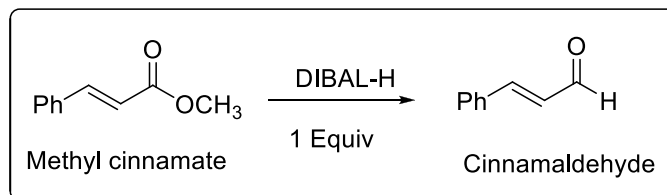
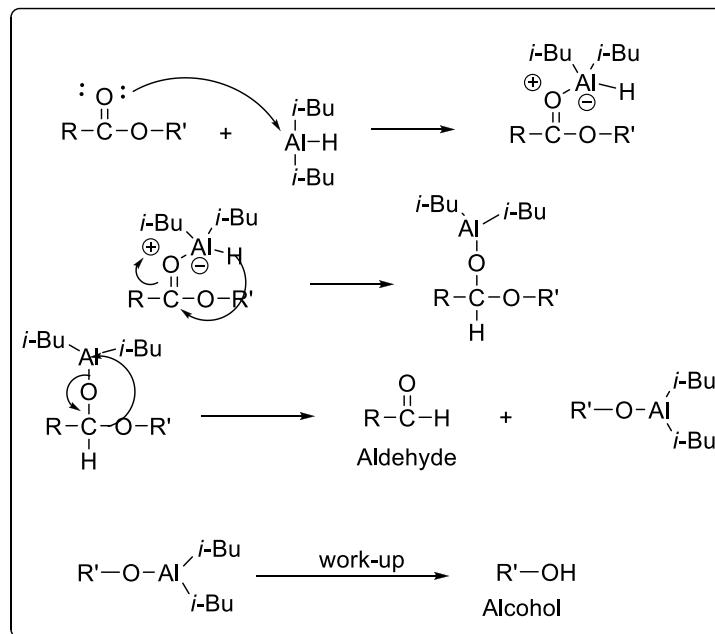
Reduction of Esters to Alcohols



Reduction of esters with at least 2 equivalents of DIBAL-H provides alcohols.

Common Reducing Agents (Diisobutylaluminiumhydride)

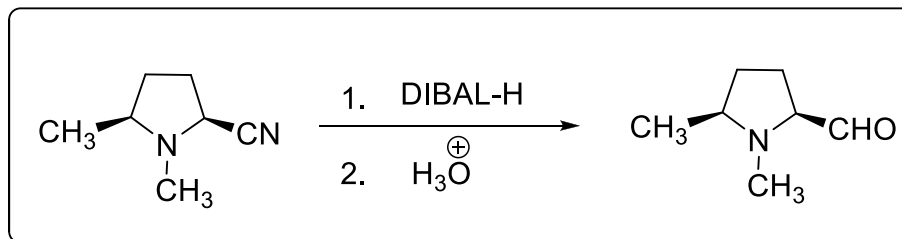
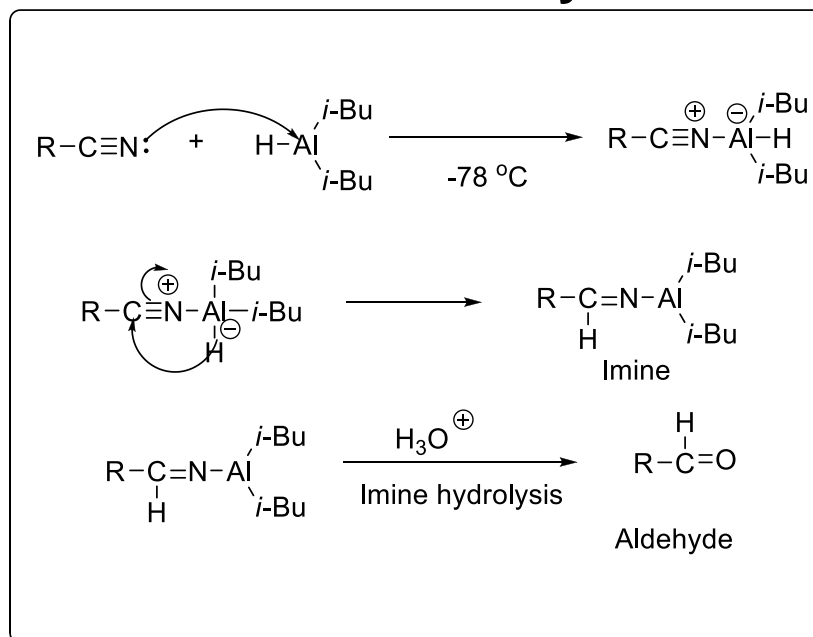
Partial Reduction of Esters to Aldehydes



Half reduction of esters to aldehydes can be accomplished with 1 equivalent of DIBAL-H.

Common Reducing Agents (Diisobutylaluminiumhydride)

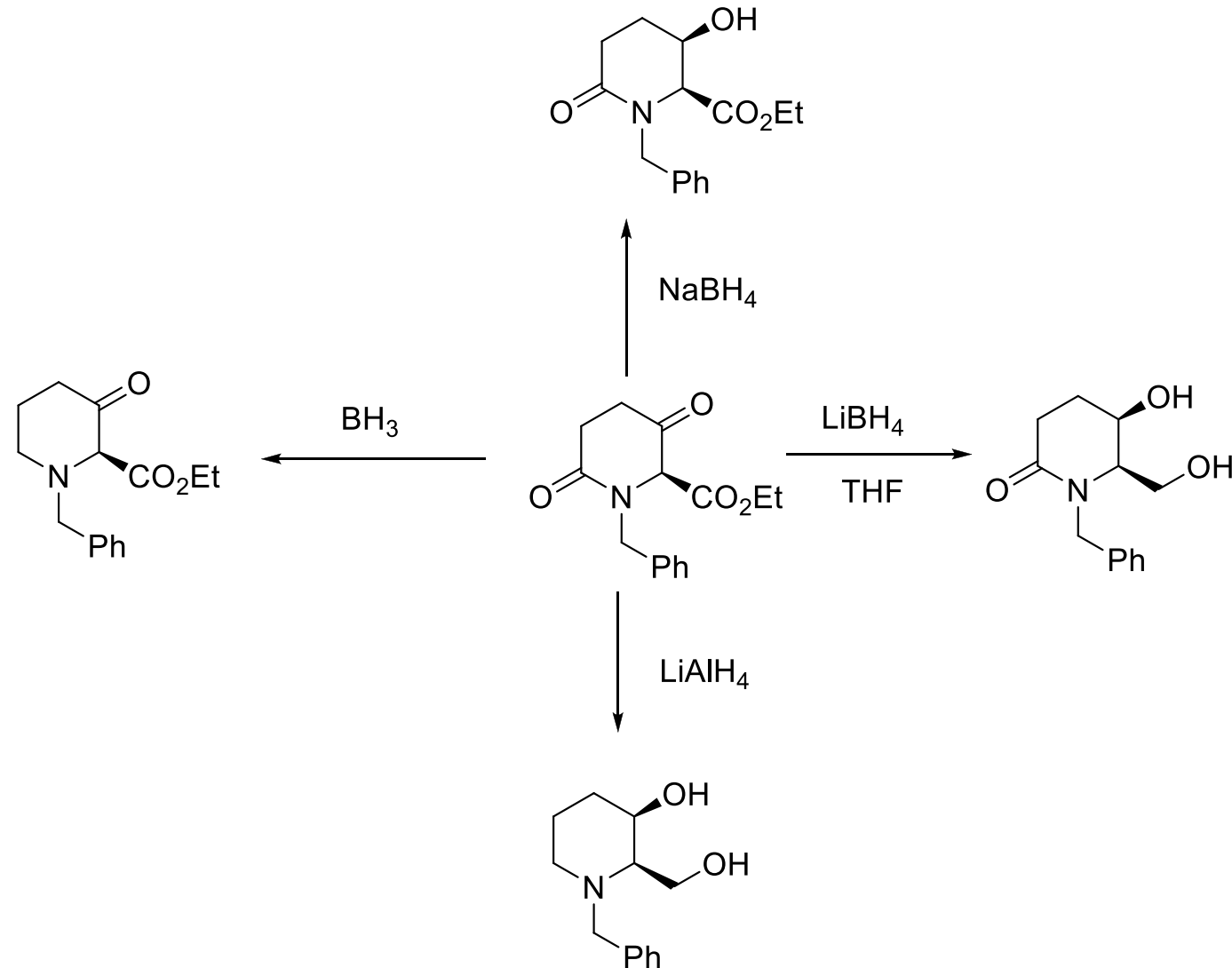
Partial Reduction of Nitriles to Aldehydes



Half reduction of a nitrile with 1 equiv of DIBAL-H followed by hydrolysis provides an aldehyde.

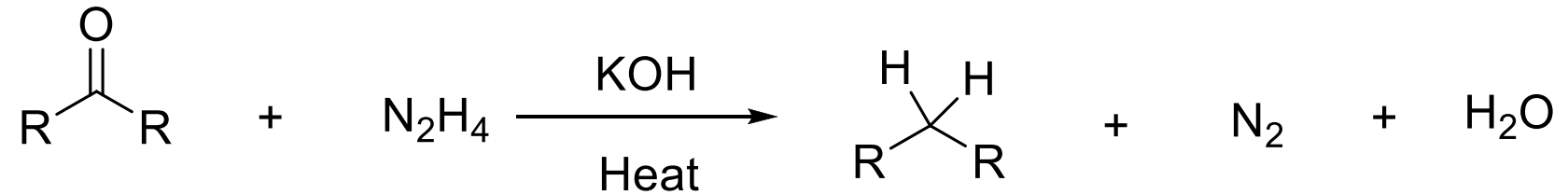
Common Hydride Reducing Agents

A Comparative Analysis among the Reducing Agents



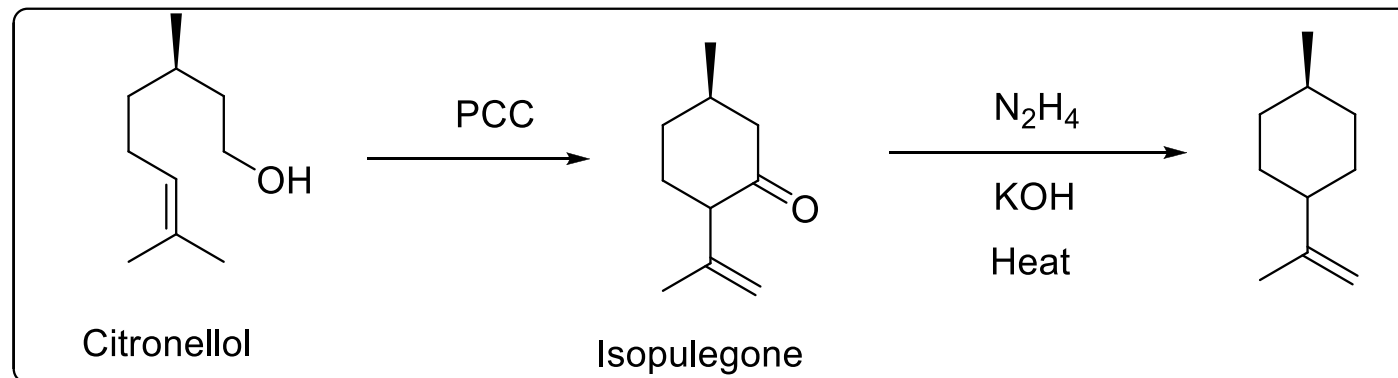
Reductive Deoxygenation (Wolff-Kishner Reduction)

Reductive Deoxygenation of Aldehydes and Ketones to Hydrocarbons



High temperatures are required to effect the reduction
The Basic media may however be incompatible with other functional groups

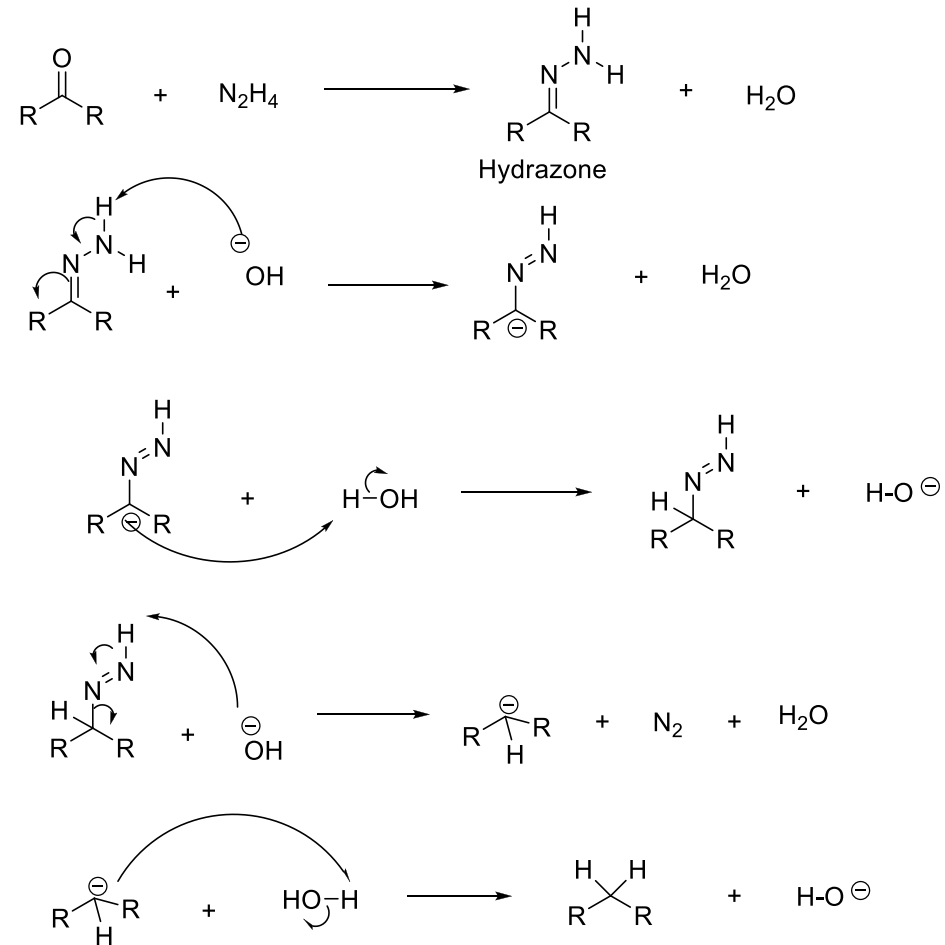
Example



Non-Metal Reducing Agents (Wolff-Kishner Reduction)

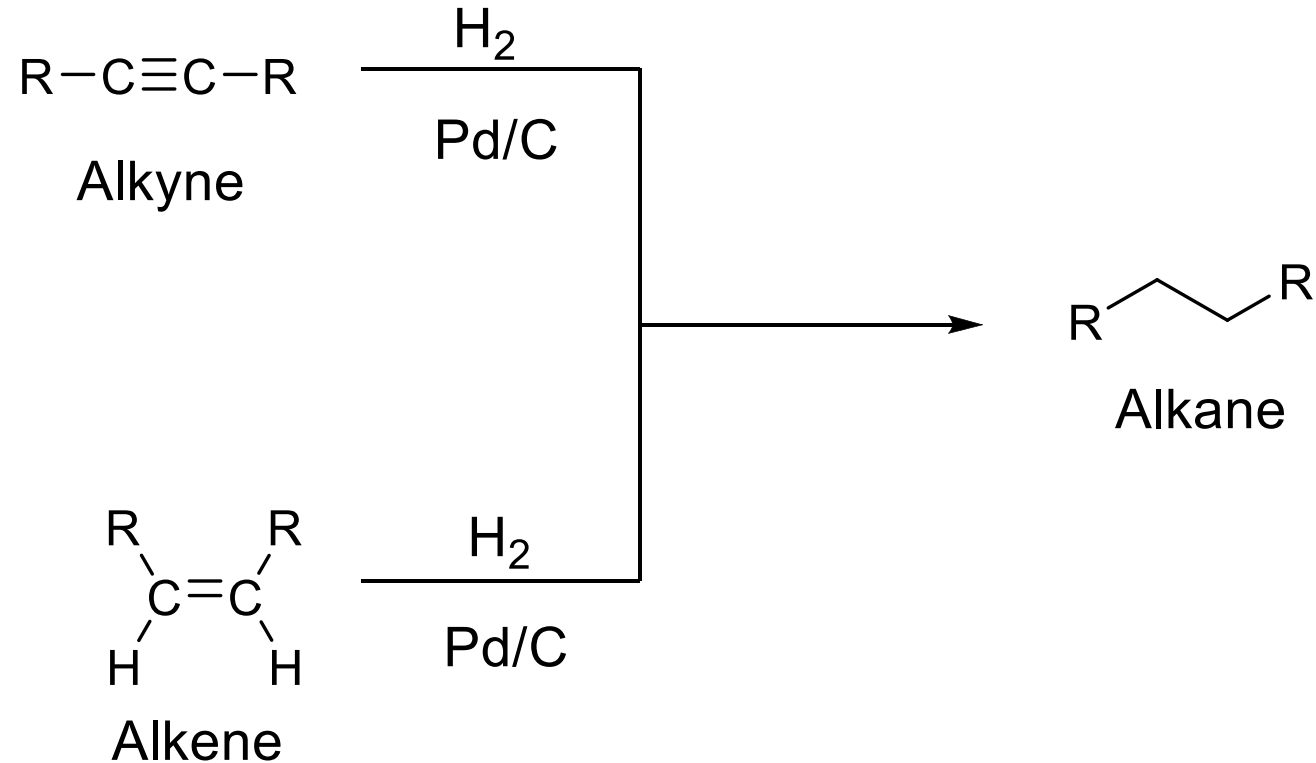
Mechanism of Wolff-Kishner Reduction

Reaction begins with initial formation of a hydrazone



Common Reducing Agents (Catalytic Hydrogenation)

Reduction of Alkynes and Alkenes to Alkanes

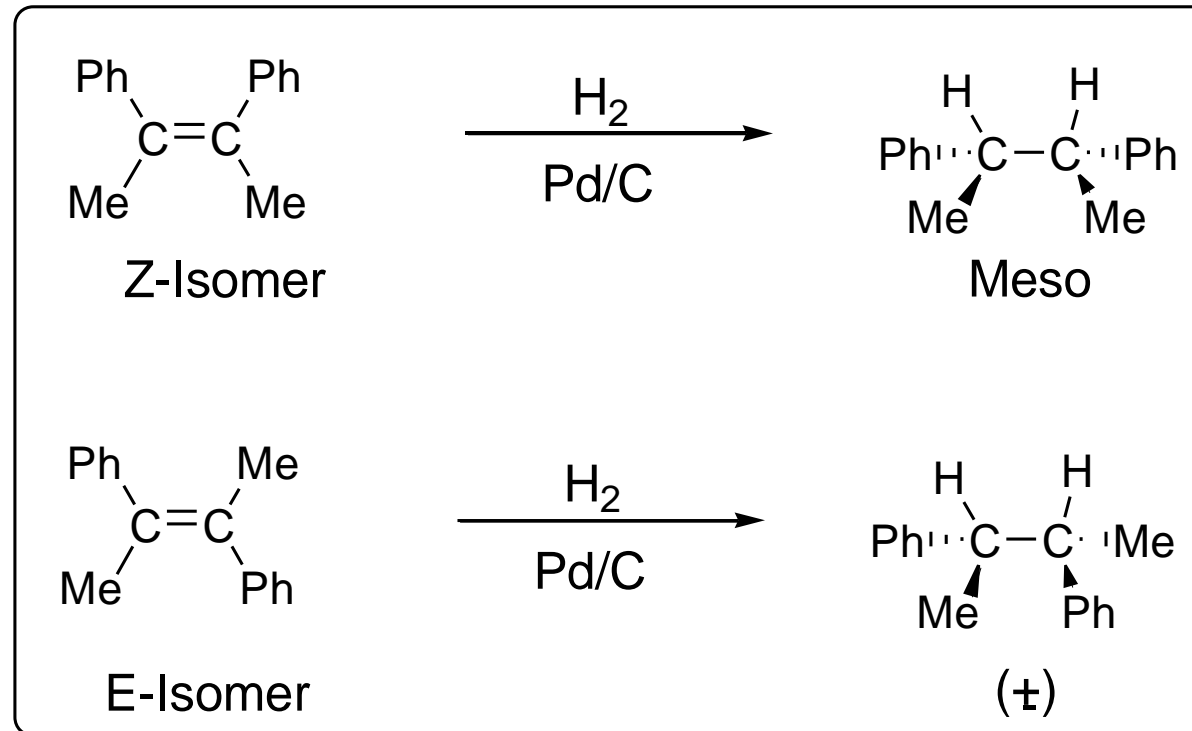


Alkynes and alkenes readily undergo complete hydrogenation on metal catalysts, commonly palladium and nickel, provide alkanes.

Common Reducing Agents (Catalytic Hydrogenation)

Reduction of Alkynes and Alkenes to Alkanes

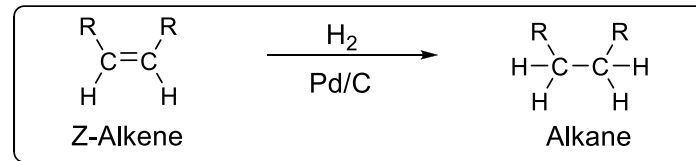
Example



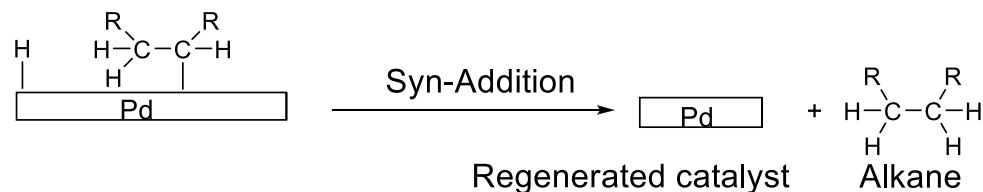
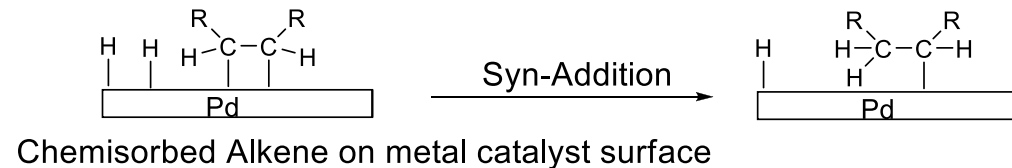
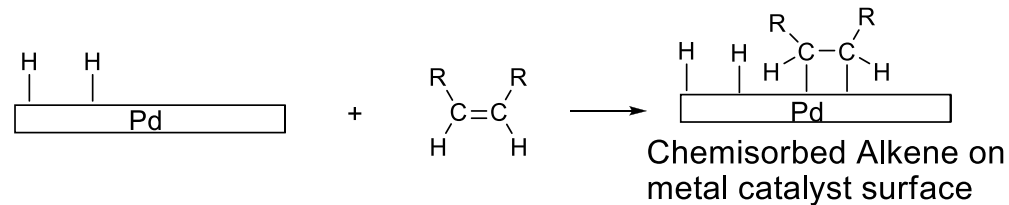
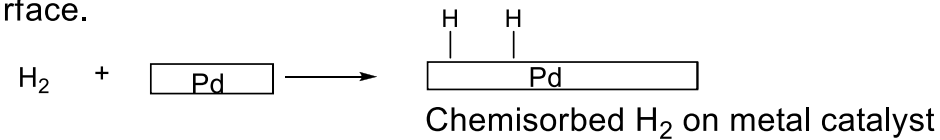
The stereospecific reduction of *E* and *Z*-isomers of an alkene shows that the addition of hydrogen occurs in a *syn* fashion. This is an indication that a highly organized transition state is involved.

Common Reducing Agents (Catalytic Hydrogenation)

Mechanism of Reduction of Alkenes to Alkanes

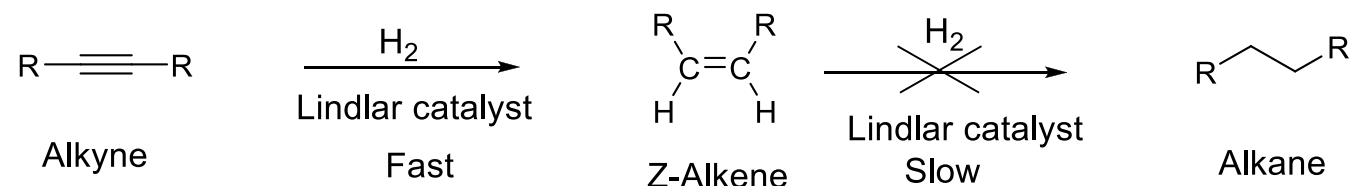


Since hydrogenation takes place on a metal (Pd) surface both the hydrogen and the alkene are first adsorbed on the metal catalyst surface.



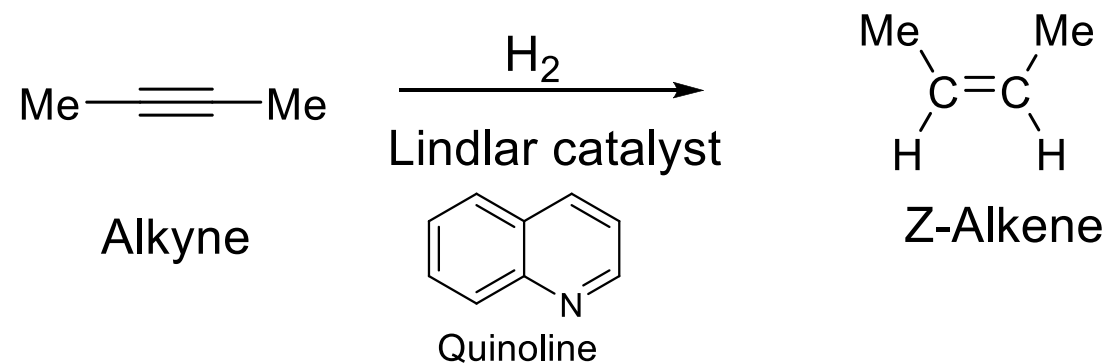
Common Reducing Agents (Catalytic Hydrogenation)

Partial Reduction of Alkynes to (Z)-Alkenes



Since alkynes are more reactive to catalytic hydrogenation than alkenes, controlled reduction of alkynes to alkenes without over-reduction is possible by employing a poisoned palladium catalyst (Lindlar's catalyst) to deter the reduction of the intermediate alkene to a saturated alkane.

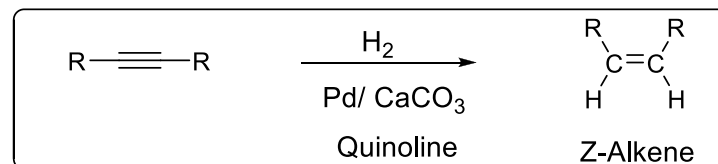
Example



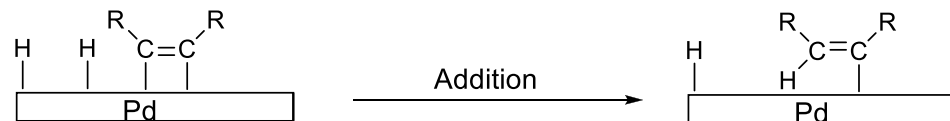
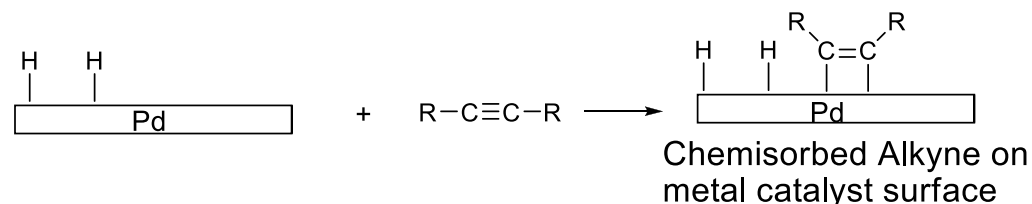
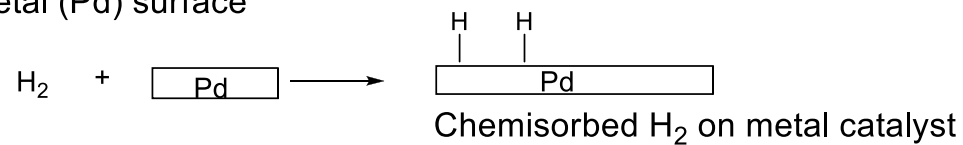
Lindlar's catalyst consists of palladium on a calcium carbonate support poisoned with lead acetate and a small amount of quinoline.

Common Reducing Agents (Catalytic Hydrogenation)

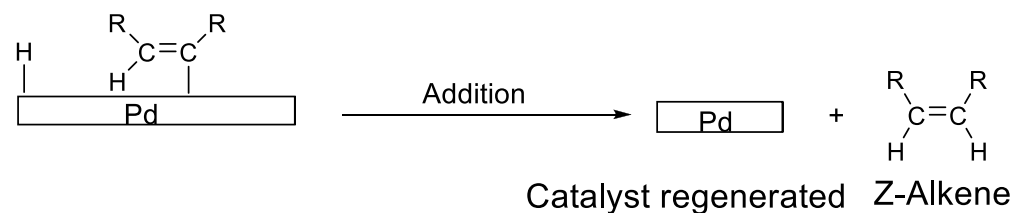
Mechanism of the Partial Reduction of Alkynes to (Z)-Alkenes



Chemisorption of the hydrogen and the alkyne takes place first on a metal (Pd) surface

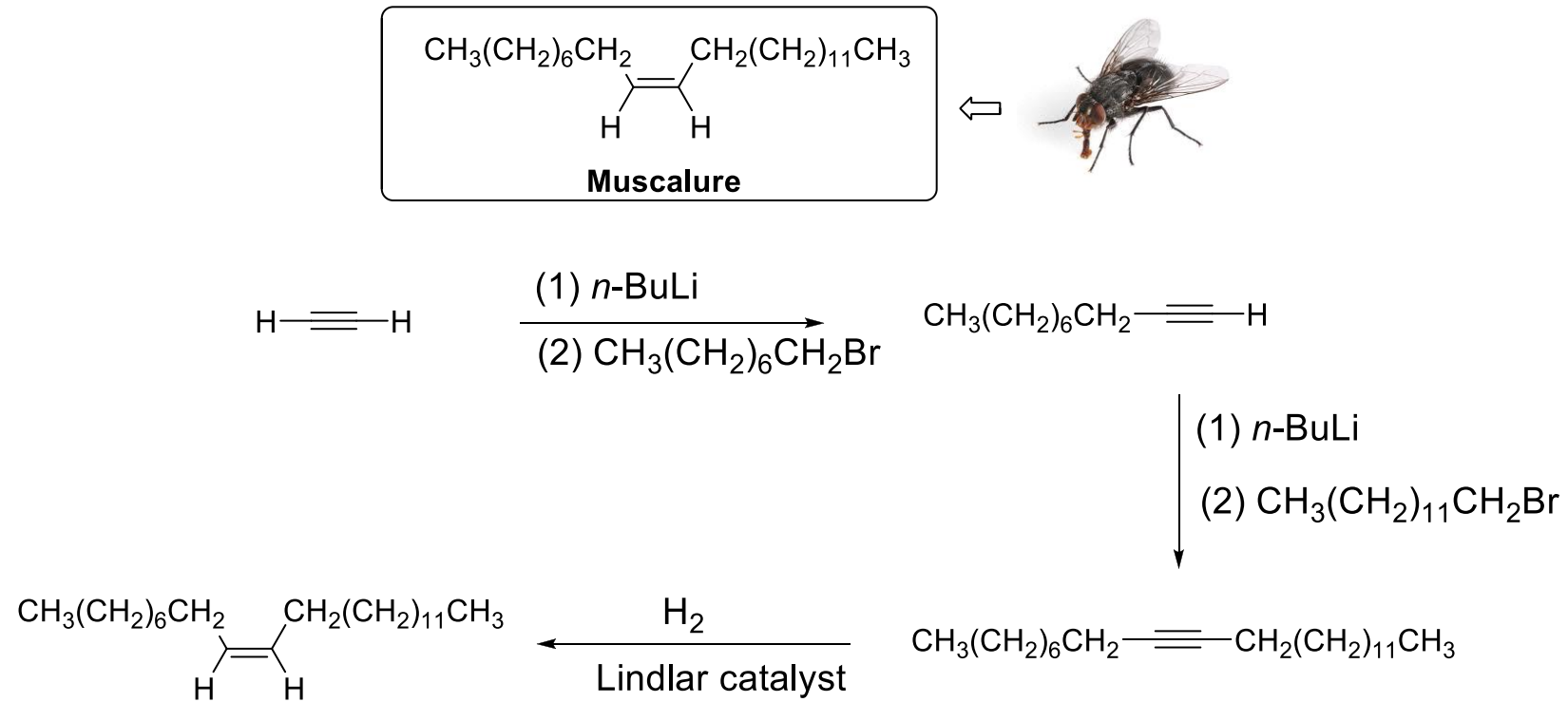


Chemisorbed Alkyne on metal catalyst surface



Common Reducing Agents (Catalytic Hydrogenation)

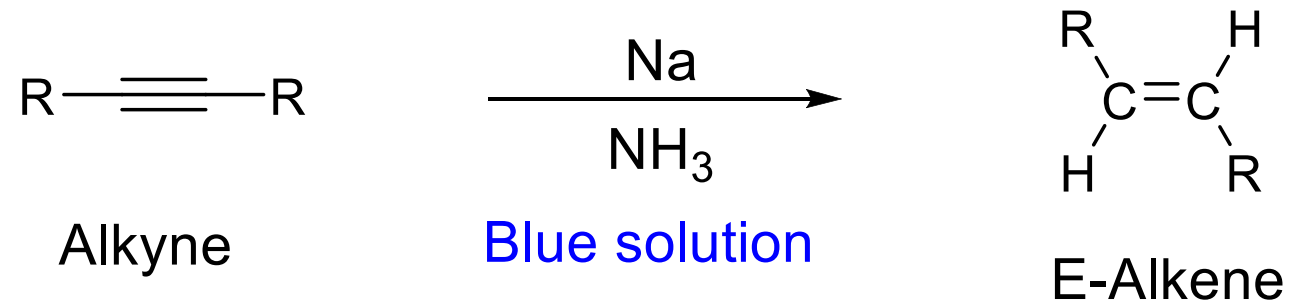
Synthetic Applications of Partial Reduction of Alkynes to Alkenes



The synthesis of Muscalure ((Z)-9-tricosene), the sex pheromone of the female housefly *Musca domestica*, was accomplished through a stereospecific partial reduction of an appropriate alkyne.

Common Reducing Agents (Dissolving Metal Reduction)

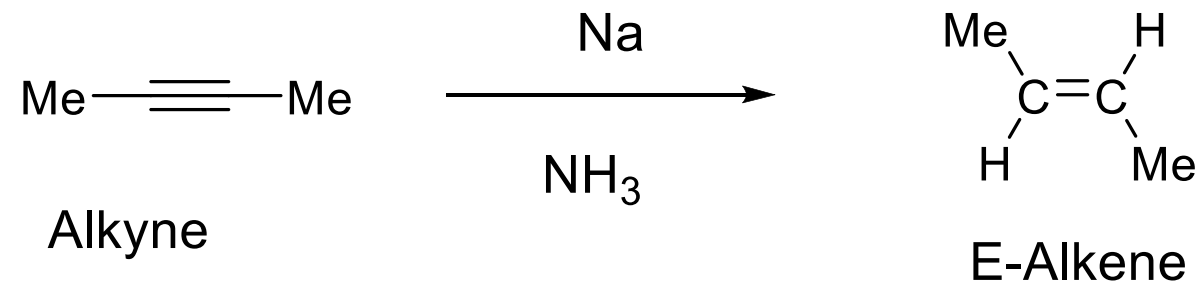
Stereospecific Partial Reduction of Alkynes to (*E*)-Alkenes



The reduction of alkynes under dissolving-metal conditions occurs through radical anion intermediates initiated by successive electron and proton-transfer processes.

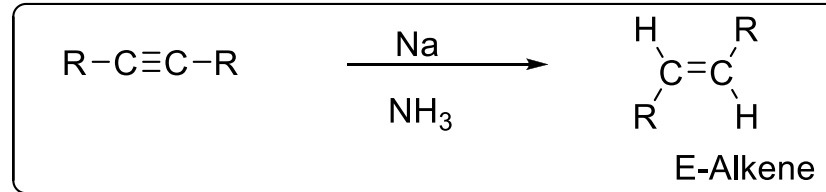
Solutions of group 1 metals (Na or Li or K) in ammonia are used as the reducing mixture. Bright blue electron-rich solutions are obtained.

Example

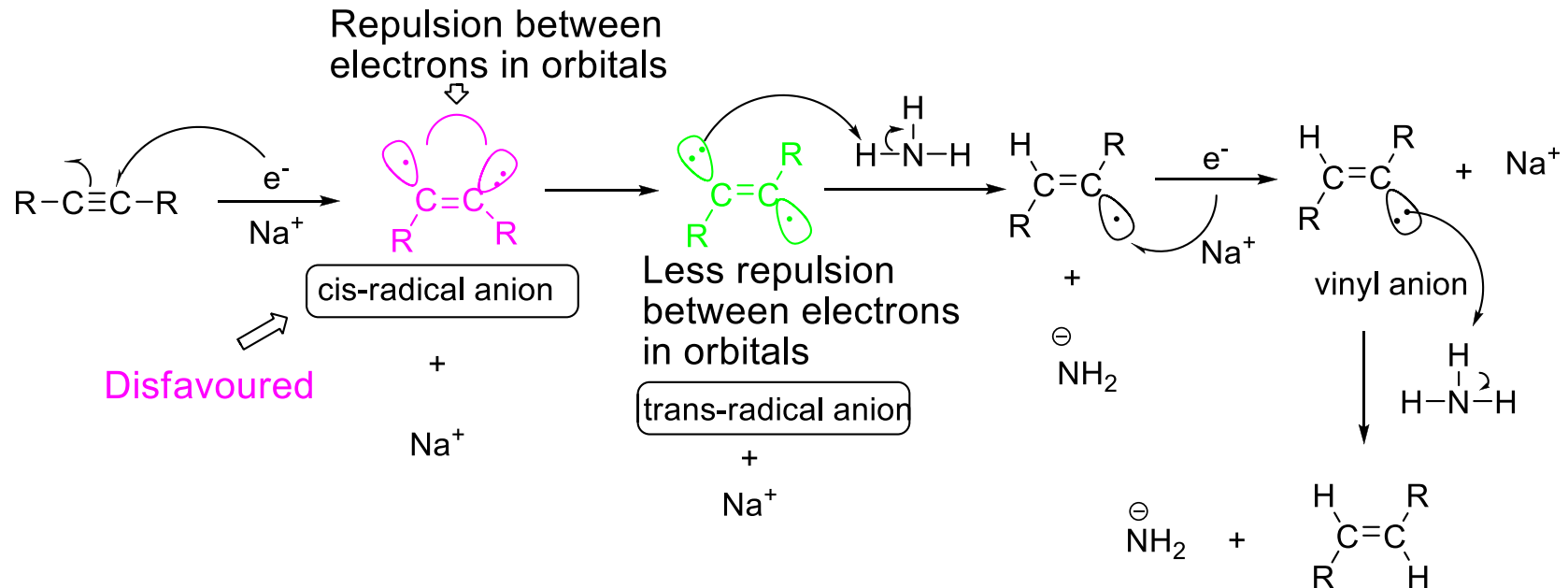


Common Reducing Agents (Dissolving Metal Reduction)

Mechanism of Stereospecific Partial Reduction of Alkynes to (E)-Alkenes

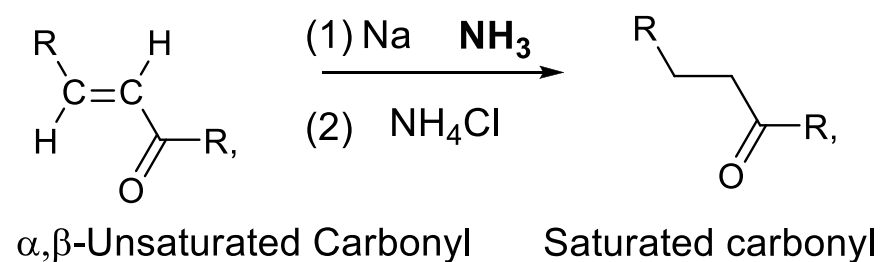


Mechanism

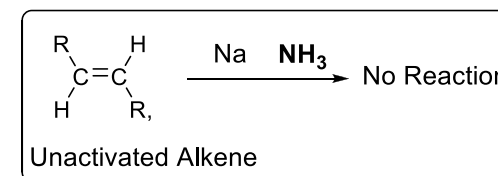


Common Reducing Agents (Dissolving Metal Reduction)

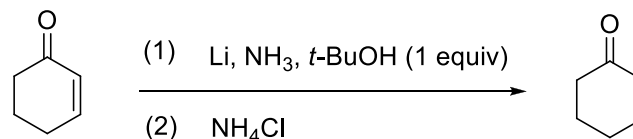
Reduction of Electron Deficient Alkenes



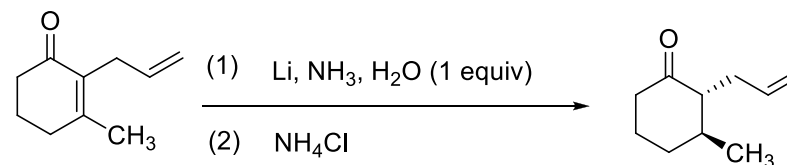
Recall



α,β -unsaturated carbonyl aldehydes and ketones can be cleanly reduced to the enolate of the corresponding saturated aldehyde or ketone with lithium or sodium in liquid ammonia at low temperature. Usually one equivalent of an alcohol or NH_4Cl is added to the reaction medium at the end to serve as a proton source / donor to the enolate.

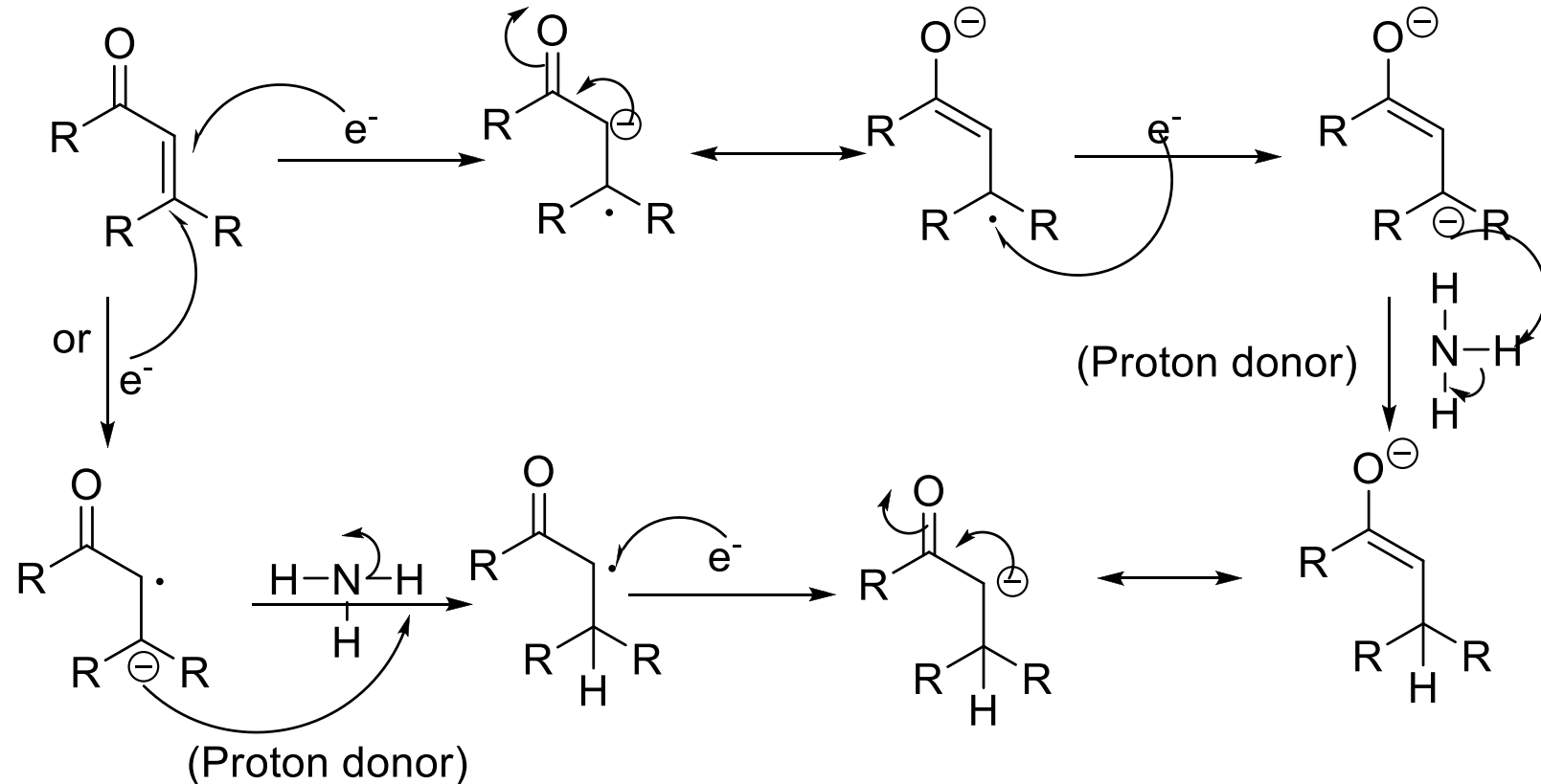


Example



Common Reducing Agents (Dissolving Metal Reduction)

Mechanism of Reduction of Electron Deficient Alkenes

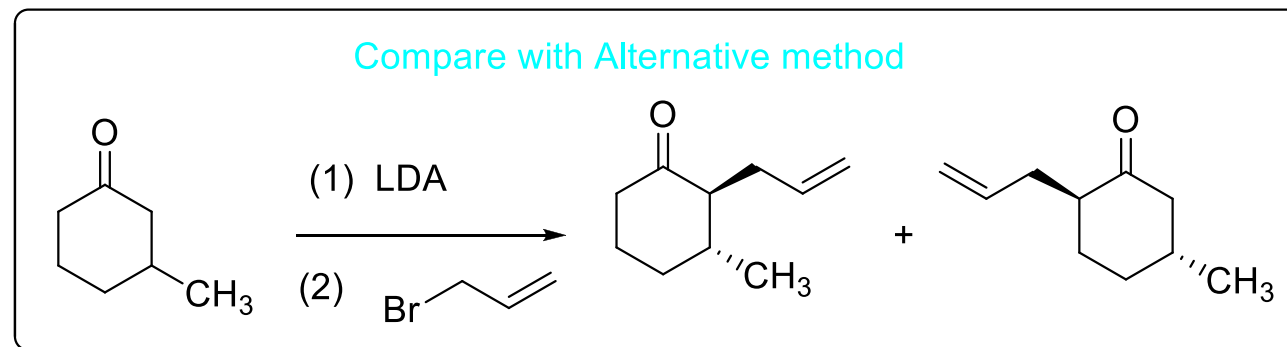
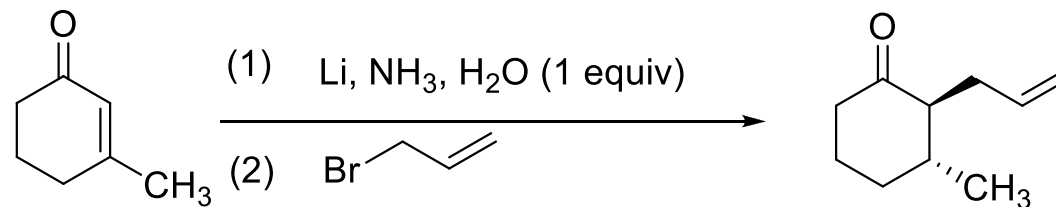


Regiospecific generation of enolates can be achieved

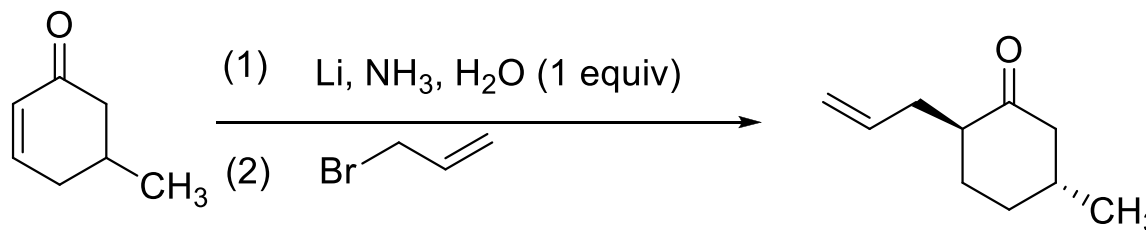
Common Reducing Agents (Dissolving Metal Reduction)

Synthetic Applications of Reduction of Electron Deficient Alkenes

Alkylation of the regioselectively generated enolate can be exploited.



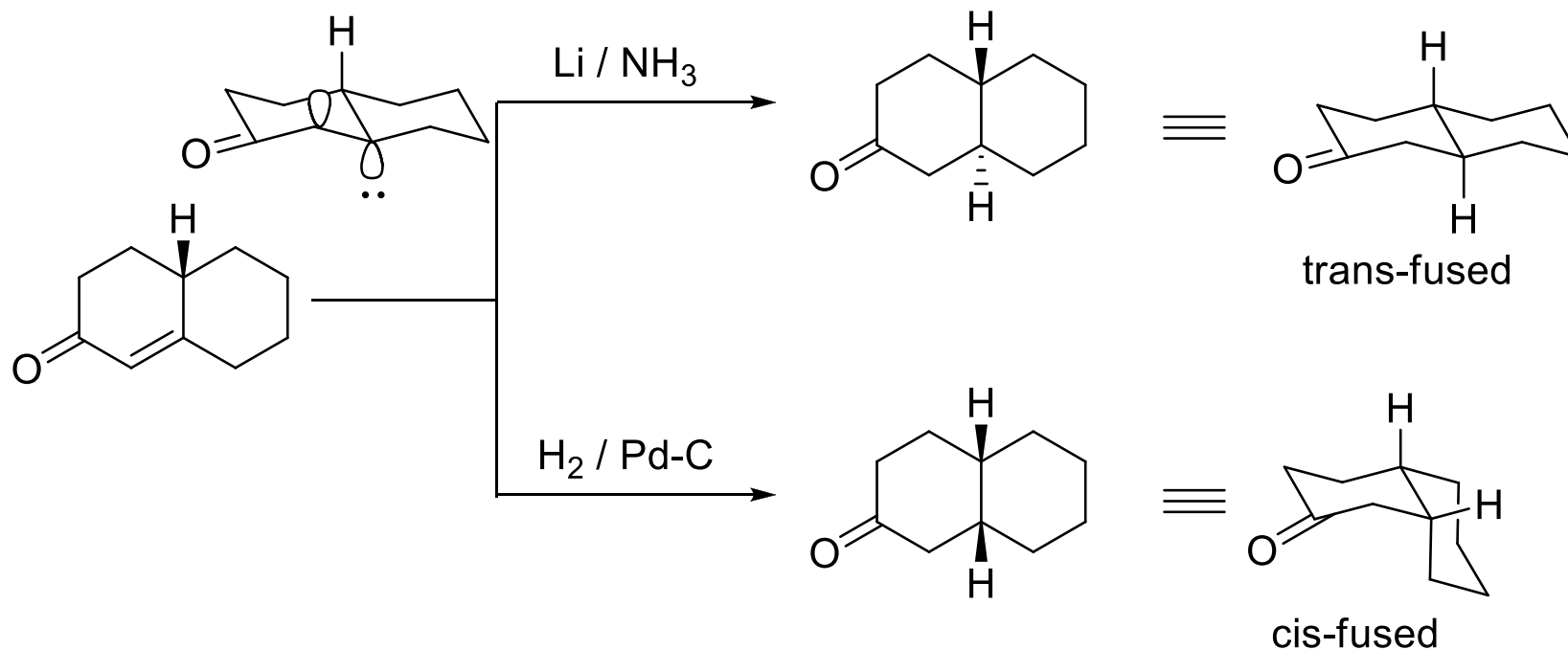
Regioisomers obtained



Common Reducing Agents

(Catalytic Hydrogenation vs Dissolving Metal Reduction)

Stereochemical Consequences of Catalytic Hydrogenation vs Dissolving Metal Reduction

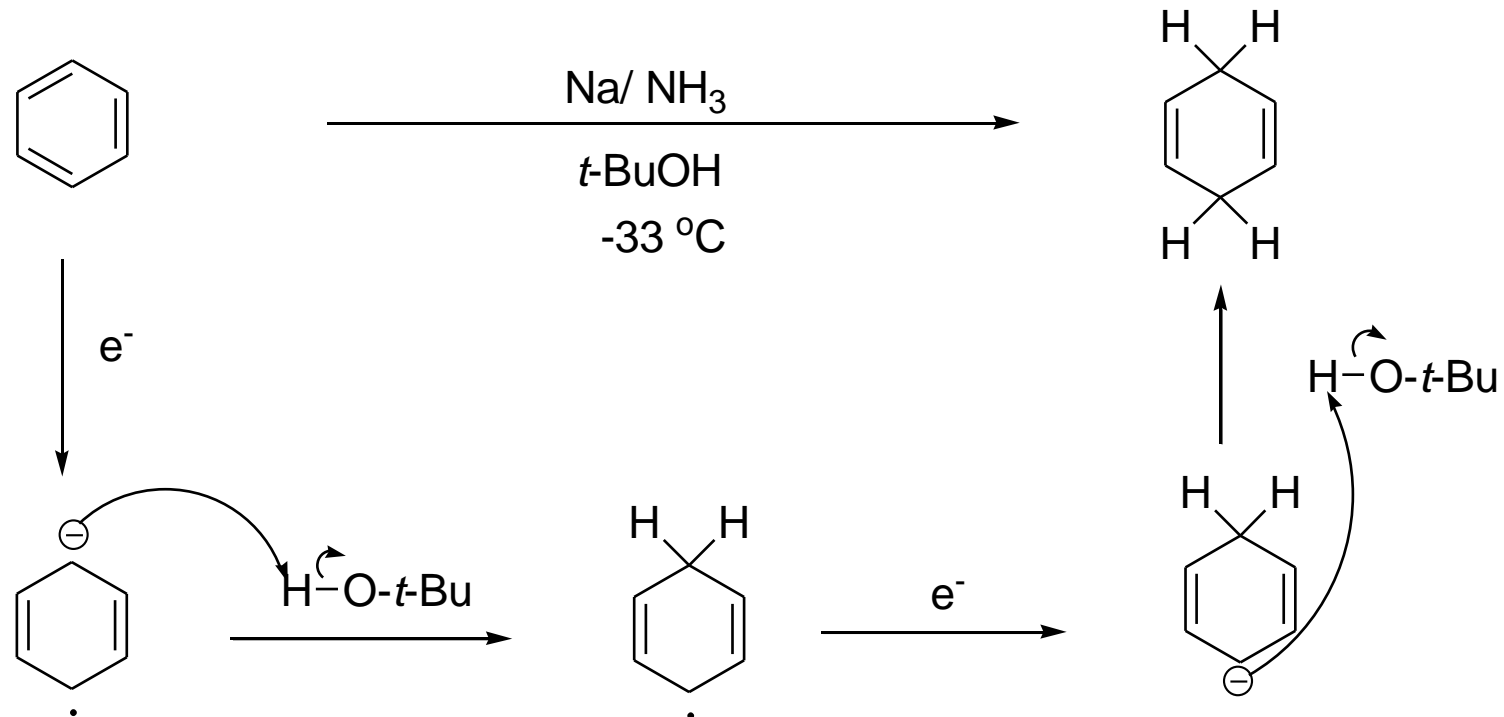


With judicious choice of reducing conditions either trans or cis fused decalone systems can be accessed.

Partial Reduction of Aromatic π -Systems (Birch Reduction)

Dissolving Metal Reduction of Aromatic systems

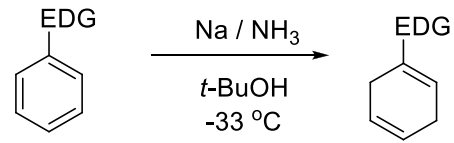
Dissolving-metal systems are synthetically useful for the partial reduction of aromatic rings. The reaction is called Birch reduction. Electrons are the reducing agent and these come from the group 1 metals sodium, lithium or potassium in liquid ammonia.



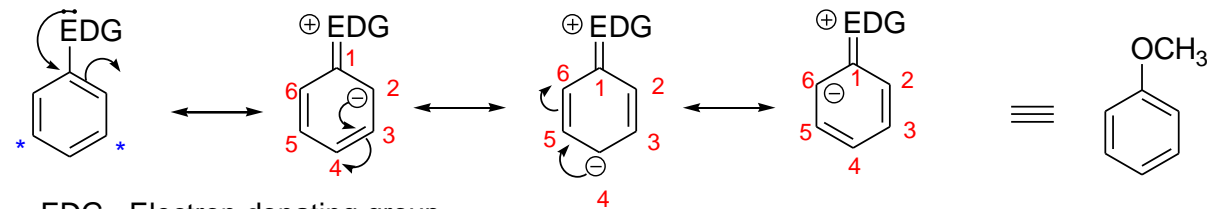
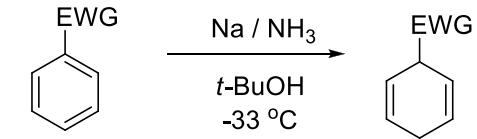
Partial Reduction of Aromatic π -Systems (Birch Reduction)

Regiochemistry of Reduction in Substituted Aromatic systems

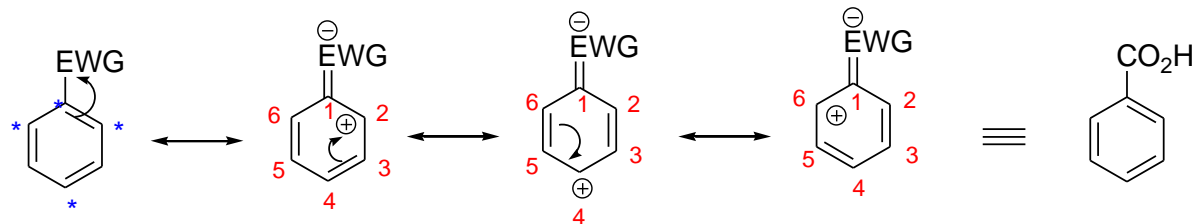
(Electron donating groups)



(Electron withdrawing groups)



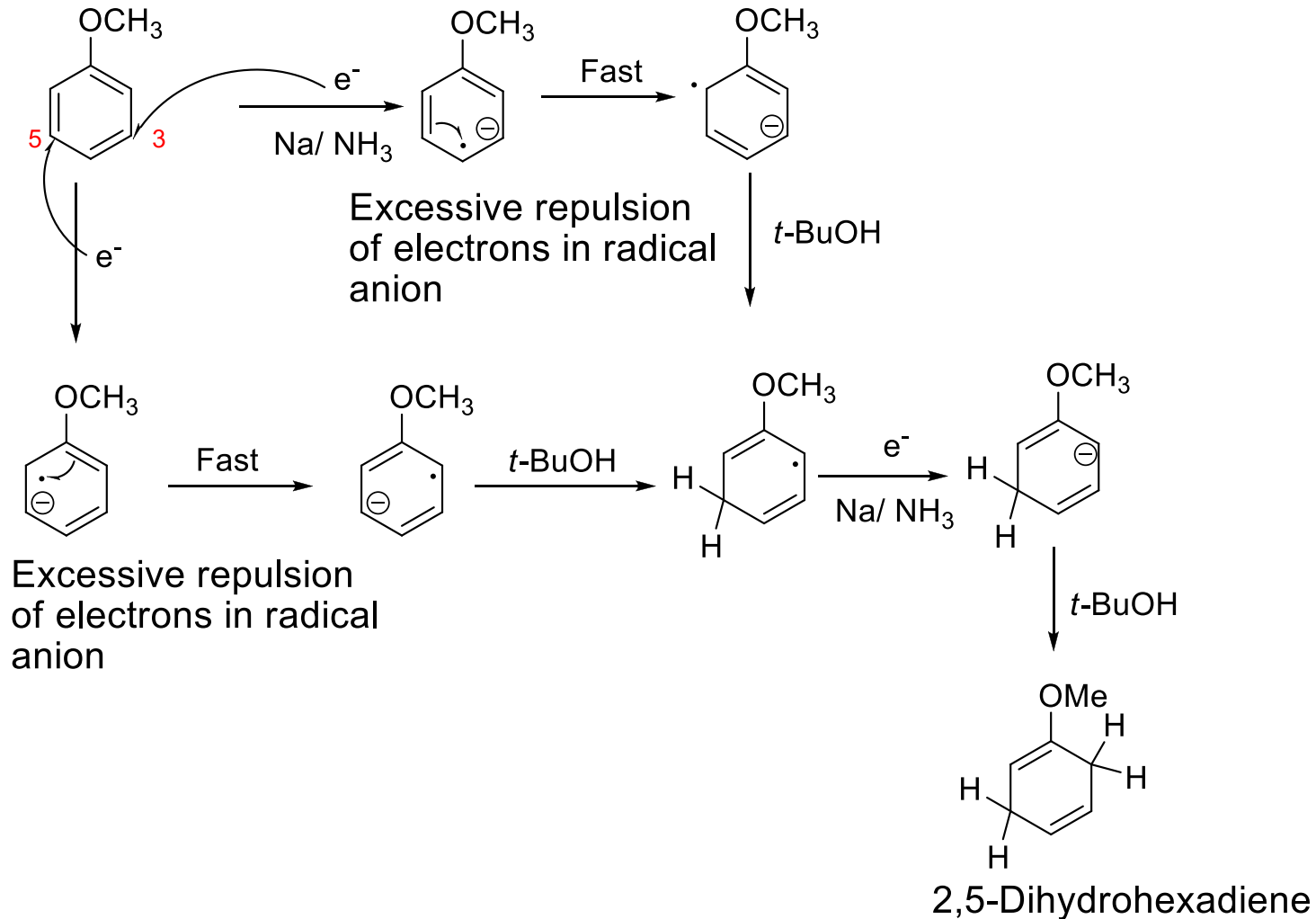
In systems with EDG: C-1, C-2, C-4 and C-6 are electron rich, consequently C-3 and C-5 are electron deficient)



In systems with EWG: C-1, C-2, C-4 and C-6 are electron deficient, consequently C-3 and C-5 are electron rich)

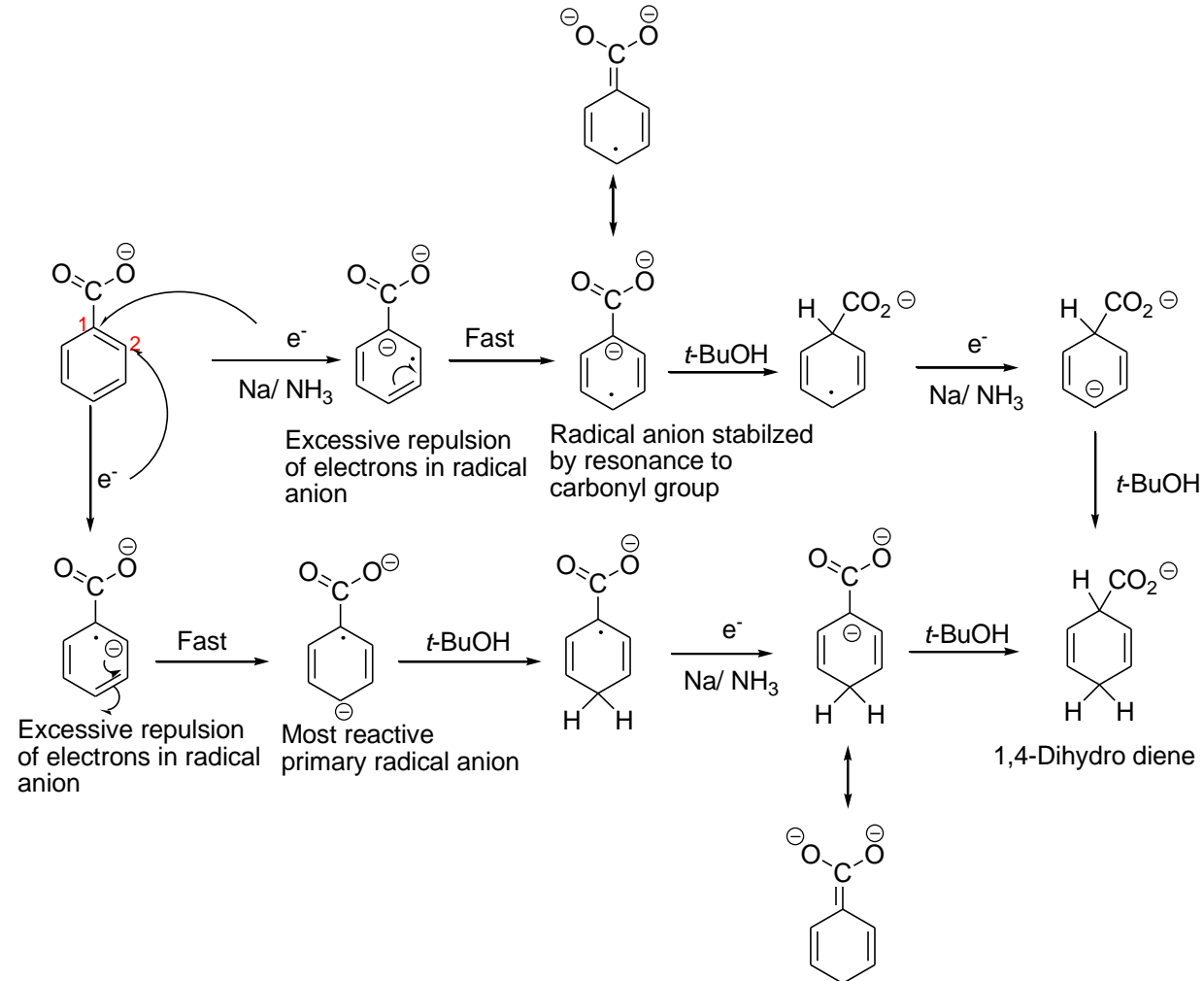
Partial Reduction of Aromatic π -Systems (Birch Reduction)

Mechanism of Reduction in Electron-Donating Substituted Aromatic systems



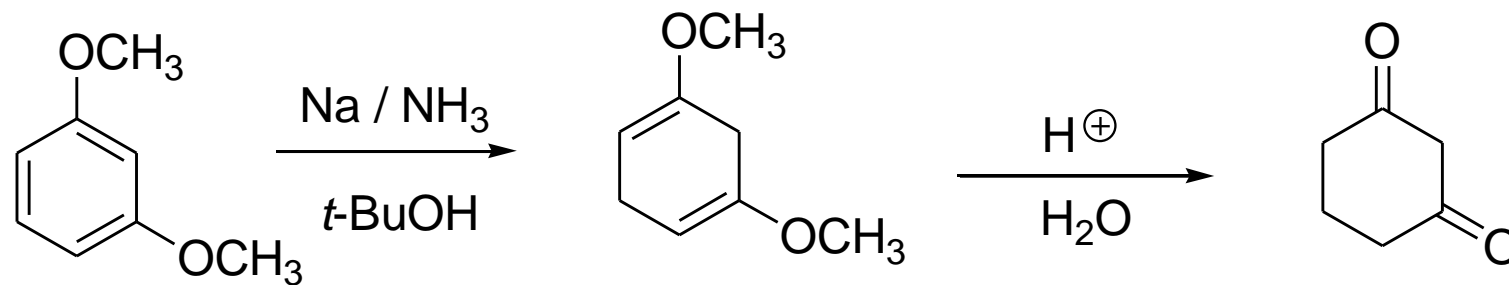
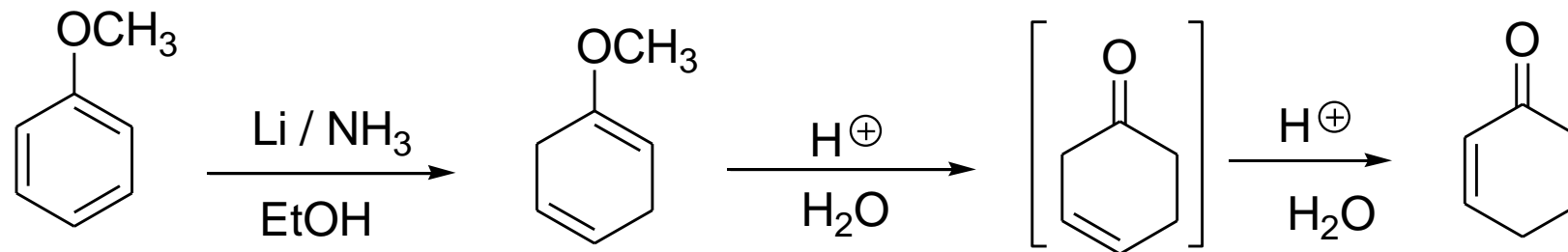
Partial Reduction of Aromatic π -Systems (Birch Reduction)

Mechanism of Reduction in Electron-Withdrawing Substituted Aromatic systems.



Partial Reduction of Aromatic π -Systems (Birch Reduction)

Examples



Electron-donating groups
are conjugated to alkene units

Partial Reduction of Aromatic π -Systems (Birch Reduction)

Examples

