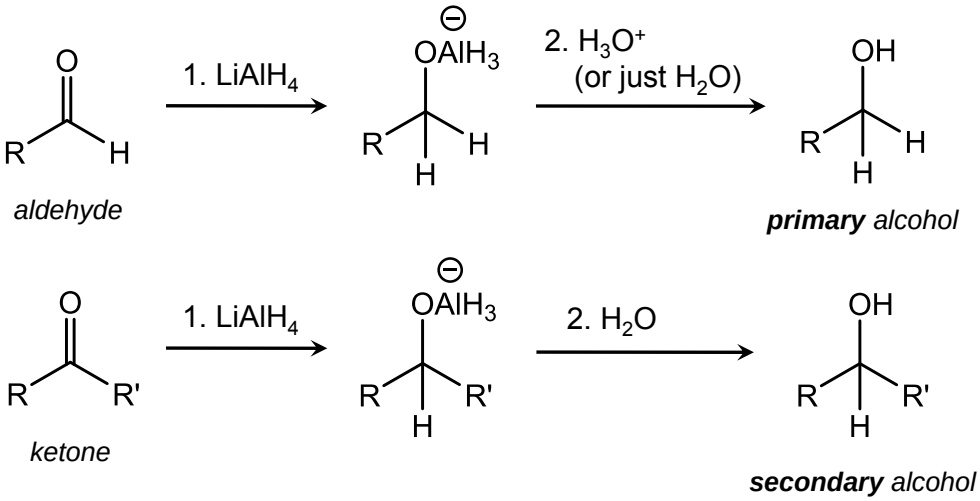
Hydrides as Reducing Agents

Lithium aluminum hydride (**$LiAlH_4$**) is a *strong* reducing agent.
It will donate hydride ("H^-") to <u>any</u> C=O containing functional group.

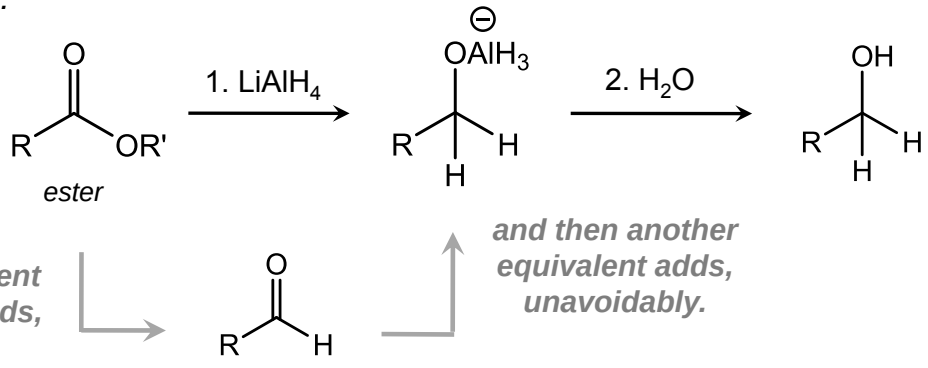
Examples:



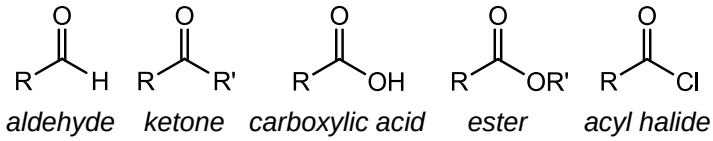
Hydrides as Reducing Agents

Lithium aluminum hydride (**$LiAlH_4$**) is a *strong* reducing agent.
It will reduce almost any C=O containing functional group to an alcohol.

Example:



Reduced by $LiAlH_4$ to an ***alcohol****:*

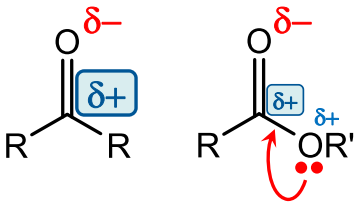


Double Addition of Hydride to Carboxylic Acids and Derivatives

Why?

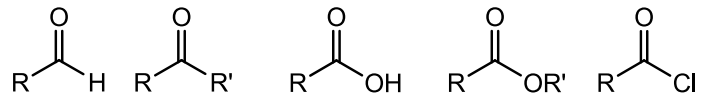
Ketones and aldehydes are more electrophilic than acids, esters and acyl halides.

As soon as a ketone or aldehyde is generated, it is immediately reduced again.



Lone pair donation by oxygen reduces partial positive charge on C=O carbon.

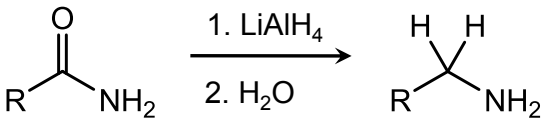
*Reduced by $LiAlH_4$ to an **alcohol**:*

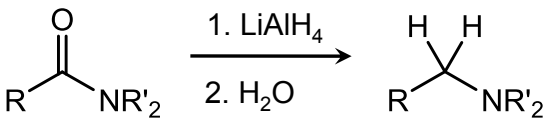


Hydrides as Reducing Agents

Exception: $LiAlH_4$ reduces amides to **amines**.

Examples:

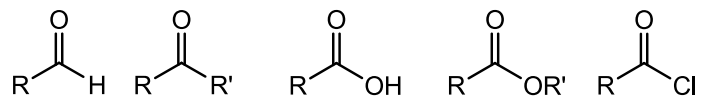




Mechanism depends slightly on whether amide has an N-H or not.

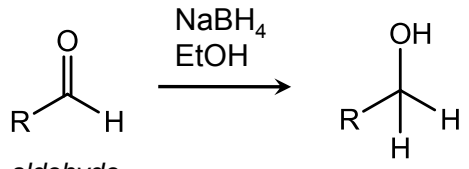
But the result is the same.

*Reduced by $LiAlH_4$ to an **alcohol**:*



Hydrides as Reducing Agents

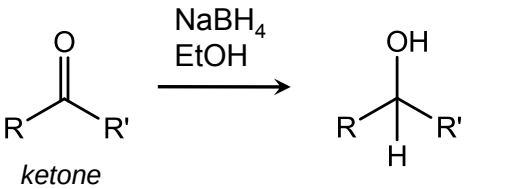
Sodium borohydride (**$NaBH_4$**) is a *mild* reducing agent.
It is only capable of reducing aldehydes and ketones.



aldehyde

***primary** alcohol*

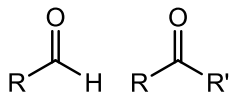
$NaBH_4$ isn't as basic as $LiAlH_4$, so reaction can be conducted in protic solvent, and separate workup step isn't essential.



ketone

***secondary** alcohol*

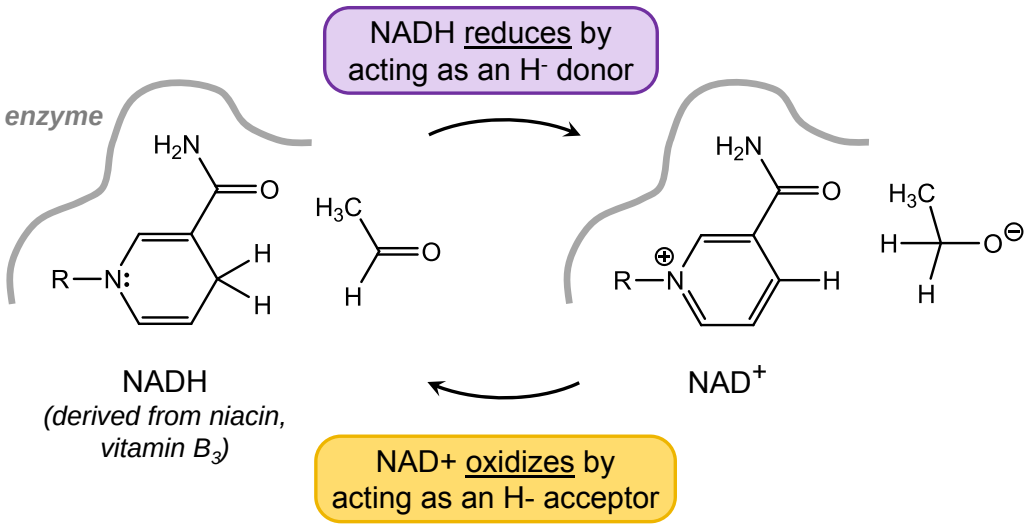
Reduced by $NaBH_4$:



aldehyde *ketone*

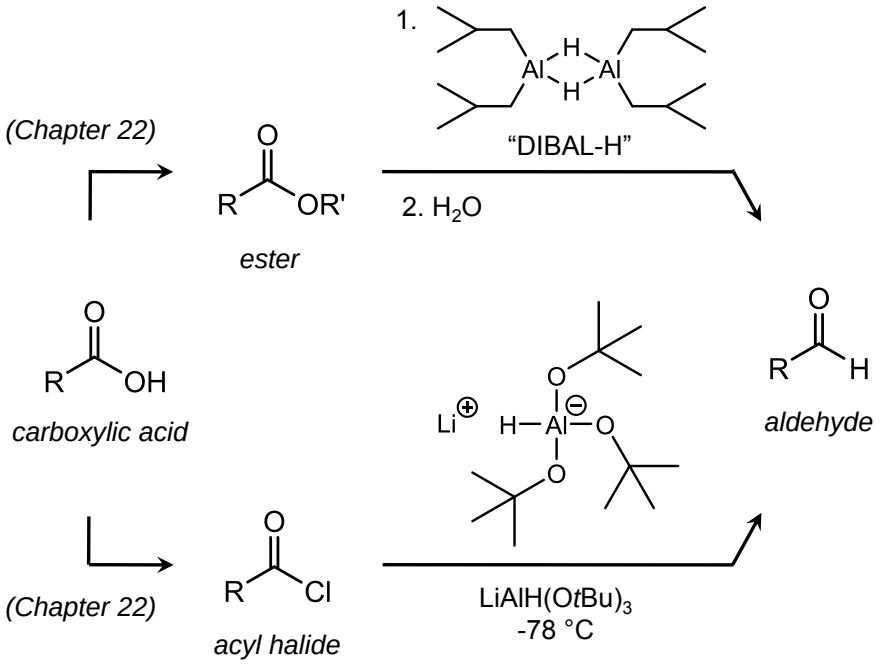
Biological Cofactors as Redox Agents

$LiAlH_4$ isn't used in biology, but biological reductants are mechanistically similar.

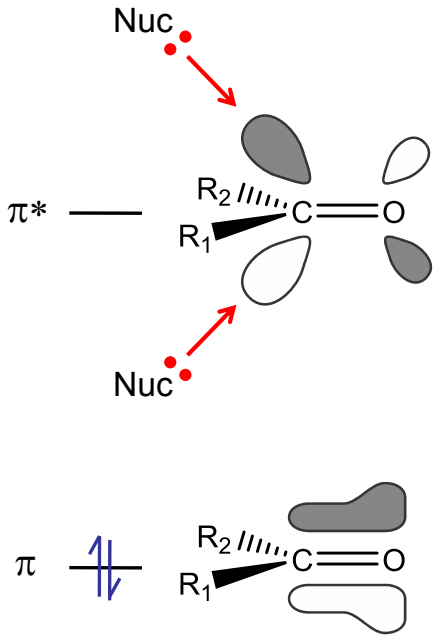


Cofactor: A small-molecule "helper" that is required by an enzyme to catalyze a reaction. Many vitamins are cofactors.

Sterically Hindered Reducing Agents Stop At Aldehyde



Nucleophiles Approach Carbonyl Groups At An Angle

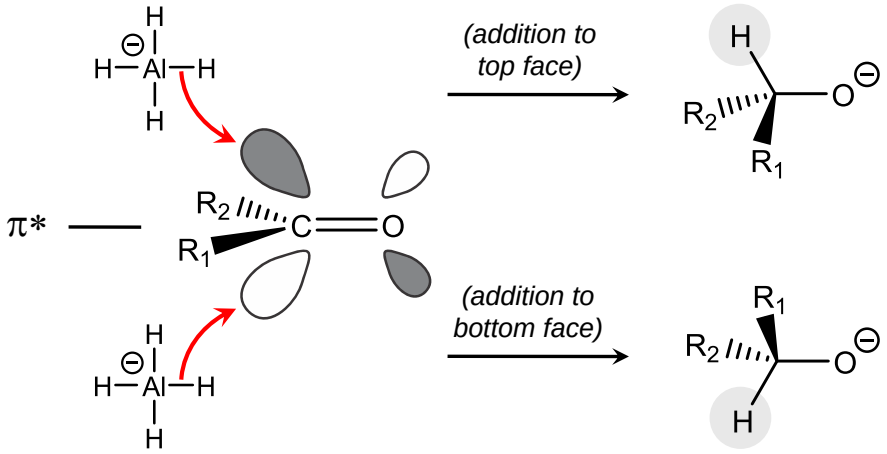


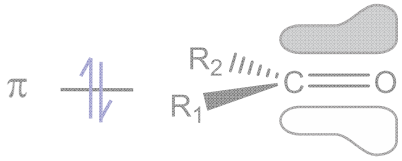
Nucleophiles are electron donors.

As a nucleophile approaches the C=O electrophile, it will donate electrons to the most available, lowest-energy molecular orbital (the LUMO).

Optimal overlap with the π* LUMO is at an angle, above or below the C=O plane.

Nucleophile Additions to Carbonyls Generate Racemic Mixtures



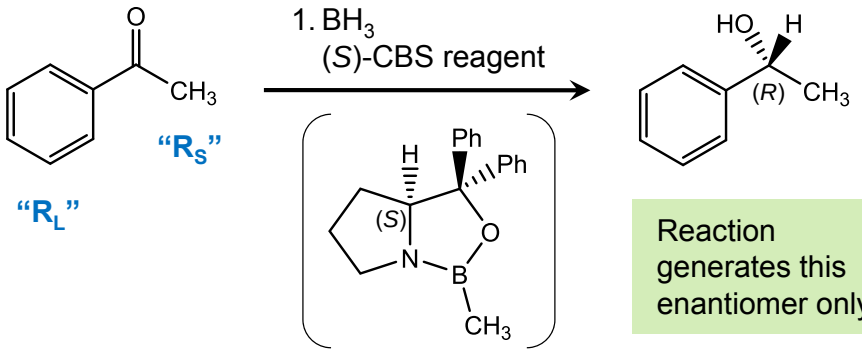


50:50 mixture of top- and bottom-face adduct is observed.

Enantioselective Reduction of Ketones Using Chiral Catalysts

Chiral catalysts bring reactants together in specific geometries, to force the preferential formation of one enantiomer over the other.

Example:



2. H^+ *(workup)*

Reaction generates this enantiomer only.

Enantioselective Reduction of Ketones Using Chiral Catalysts