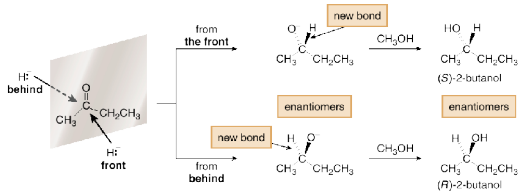
Enantioselective Reduction

Stereochemistry of Carbonyl Reduction

Å Hydride converts a planar *sp*2 hybridized carbonyl carbon to a tetrahedral *sp*3 hybridized carbon.



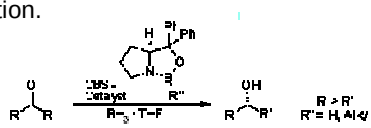
- Conclusion: Hydride reduction of an achiral ketone with $LiAlH_4$ or $NaBH_4$ gives a racemic mixture of two alcohols when a new stereogenic center is formed.

Enantioselective Carbonyl Reduction

- Selective formation of one enantiomer over another can occur if a chiral reducing agent is used.
- A reduction that forms one enantiomer predominantly or exclusively is an enantioselective or asymmetric reduction.
- An example of chiral reducing agents are the enantiomeric Coreyï Bakshiï Shibata (CBS) reagents.

Coreyï Bakshiï Shibata Reduction

- This is a chemical reaction in which an achiral ketone is enantioselectively reduced to produce the corresponding chiral, non-racemic alcohol.
- It is also known as The Coreyï Itsuno reduction.



CBS catalyst

- The CBS catalyst or Corey-Bakshi-Shibata catalyst is an asymmetric catalyst derived from proline.
  - It finds many uses in organic reactions such as the CBS reduction, Diels-Alder reactions and (3+2) cycloadditions.
  - Proline, a naturally occurring chiral compound, is readily and cheaply available.
- It transfers its stereocenter to the catalyst which in turn is able to drive an organic reaction enantioselectively to one of two possible enantiomers.
  - This selectivity is due to steric strain in the transition state that develops for one enantiomer but not for the other.

CBS catalyst

Two enantiomers of the chiral CBS reducing agent

(*S*)-2-methyl-**CBS**-oxazaborolidine

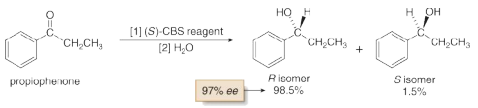
(*S*)-CBS reagent

(*R*)-2-methyl-**CBS**-oxazaborolidine

(*R*)-CBS reagent

CBS catalyst

Å These reagents are highly enantioselective. For example, treatment of propiophenone with the (*S*)-CBS reagent forms the *R* alcohol in 97% *ee*.

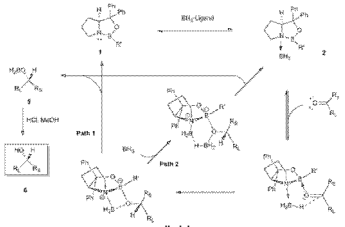


CBS Reaction Mechanism

- The chiral oxazaborolidine, known as the Coreyï Bakshiï Shibata catalyst or the CBS catalyst, is a small molecule with multifunctionality.
- It was proposed that this reduction undergoes a catalytic cycle in four principal steps:
  - The coordination of the nitrogen atom of the Lewis base to borane
  - Complexation of the ketone to the endocyclic boron (functioning as Lewis acid) via the Lewis acidï base interaction
  - Hydride transfer from borane to the carbonyl carbon
  - Dissociation of the alkoxyborane moiety and regeneration of the catalyst.

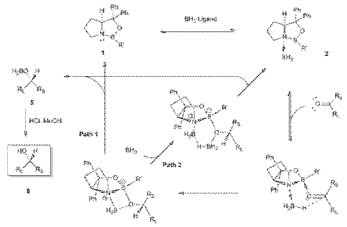
CBS Reaction Mechanism

- The first step of the mechanism involves the coordination of BH_3 to the nitrogen atom of the oxazaborolidine CBS catalyst 1.
  - This coordination serves to activate the BH_3 as a hydride donor and to enhance the Lewis acidity of the catalystÕs endocyclic boron.



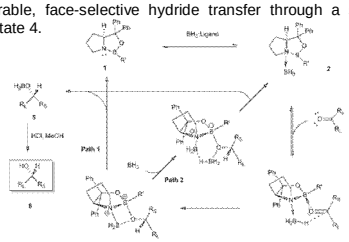
CBS Reaction Mechanism

- Subsequently, the endocyclic boron of the catalyst coordinates to the ketone at the sterically more accessible electron lone pair
  - i.e. the lone pair closer to the smaller substituent (R_S)



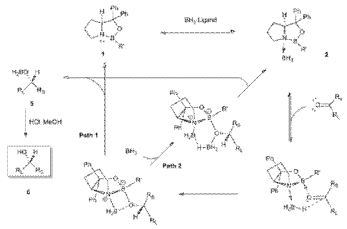
CBS Reaction Mechanism

- This preferential binding in 3 acts to minimize the steric interactions between the ketone (the large R_L substituent directed away) and the RÕ group of the catalyst, and aligns the carbonyl and the coordinated borane for a favorable, face-selective hydride transfer through a six-membered transition state 4.



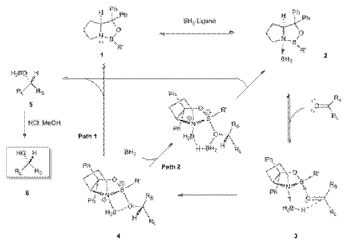
CBS Reaction Mechanism

- Hydride transfer yields the corresponding, chiral boron enolate 5, which upon acidic workup yields the chiral alcohol 6.



CBS Reaction Mechanism

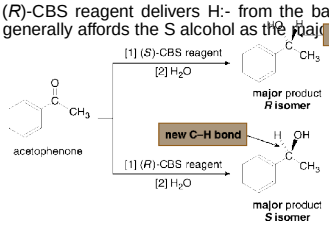
- The last step to regenerate the catalyst may take place by two different pathways (Path 1 or 2)



Coreyï Bakshiï Shibata Reduction

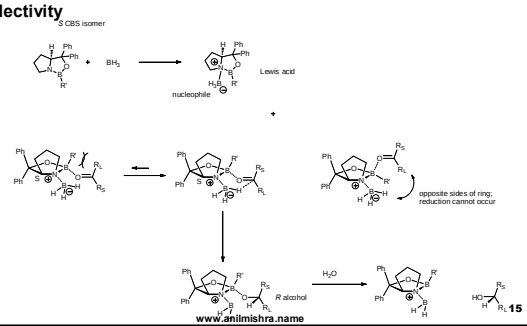
Selectivity

- One Bð H bond serves as the source of hydride in this reduction.
- The (*S*)-CBS reagent delivers H:- from the front side of the C=O. This generally affords the R alcohol as the major product.
- The (*R*)-CBS reagent delivers H:- from the back side of the C=O. This generally affords the S alcohol as the majo



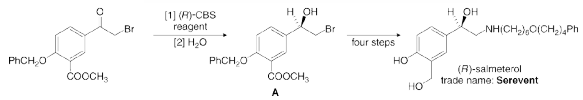
Coreyï Bakshiï Shibata Reduction

Selectivity



Uses of CBS Reduction

Å Enantioselective reductions are key steps in the synthesis of several widely used drugs, including salmeterol, a long-acting bronchodilator.



- (*R*)-Salmeterol is a long-acting bronchodilator used for the treatment of asthma.
- In this example, the (*R*)-CBS reagent adds the new H atom from behind, the same result observed with acetophenone and propiophenone. In this case, however, alcohol **A** has the *R* configuration using the rules for assigning priority in Chapter 5.