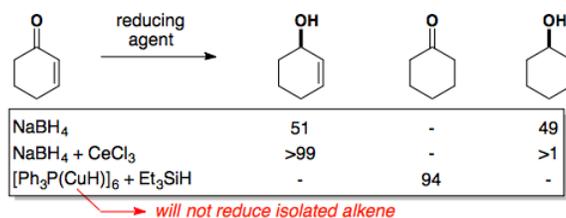


18.6: Enantioselective Carbonyl Reductions

Chemoselective Reductions

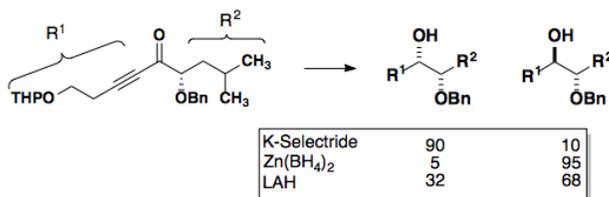
Enones present unique challenges as reducing agents can also attack the alkene giving a mixture of products. Methods to selectively reduce the ketone (Luche Reduction) and the alkene (Stryker Reduction) have been developed.



Diastereoselective Reductions

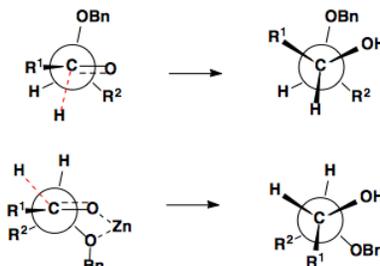
Acyclic Compounds

Reductions of aldehydes and ketones follow the same selectivity models as the addition of unstabilized carbon nucleophiles to these functional groups. Non-chelating reducing agents (NaBH₄, LiAlH₄, etc.) show Felkin-Anh selectivity while reducing agents which can chelate (Zn(BH₄)₂) show Cram Chelate selectivity.



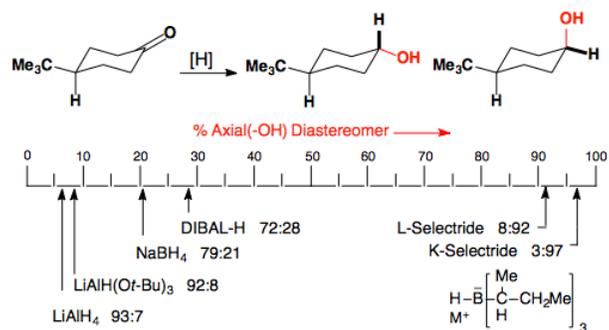
Tetrahedron Lett., **1985**, 26,5139-5142.

As seen in the example above, lithium will sometimes chelate.

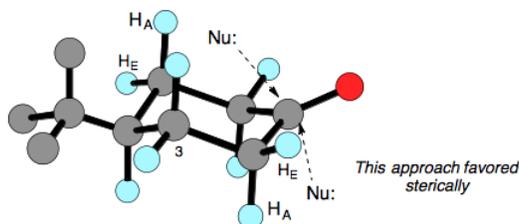


Cyclohexanones

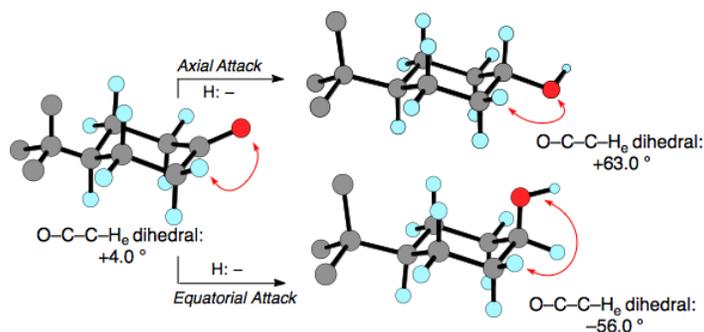
Hydrides can approach cyclohexanones from the axial or equatorial face of the ketone.



It has been observed that increasingly bulky hydride reagents prefer to attack from the equatorial face of the carbonyl. This is rationalized by the increased steric demand of a nucleophile approaching from the axial face of the carbonyl as it encounters the axial substituents (H in this case) at the 3 and 5 positions.

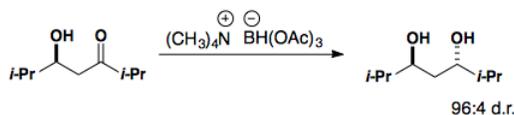


This argument would thus seem to always argue for attack from the equatorial face, but we must also take into consideration any developing torsional strain through the transition state. Attack from the axial face avoids developing eclipsing interactions between the C–O bond and the C–H_E bonds at the 2 and 6 positions. Attack from the equatorial face forces the C–O bond to travel past the C–H_E bonds to sit in the chair conformation. We can see this below as the dihedral angle in the starting cyclohexanone starts as a positive number and ends up as a negative number which shows that the C–O bond must have gone through an eclipsing conformation to reach its final position. Axial attack does not cause a change in sign of the dihedral angle, thus avoiding any eclipsing interactions in the transition state.

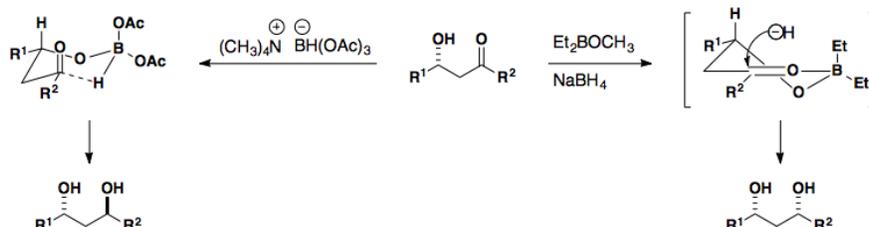
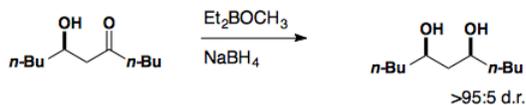


We can thus predict that small hydride reagents, such as LiAlH₄, will prefer to attack from the axial face as the torsional strain in the transition state is the dominant interaction while large hydride reagents, such as H–BR₄, will attack from the equatorial face as the steric interactions from the reagent's approach are now the dominant interaction.

Substrate Directed Reductions



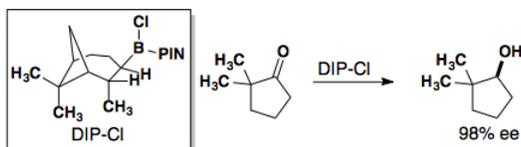
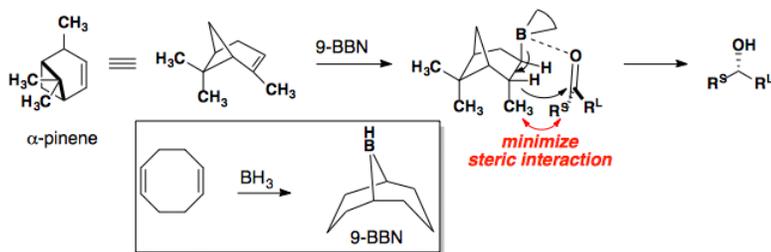
J. Am. Chem. Soc., **1988**, *110*, 3560-3578.



Tetrahedron Lett., **1987**, *28*, 155-158.

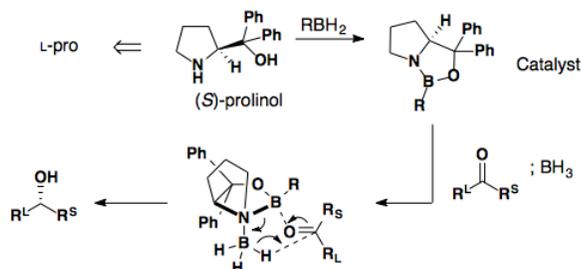
Enantioselective Reductions

Chiral Boronates

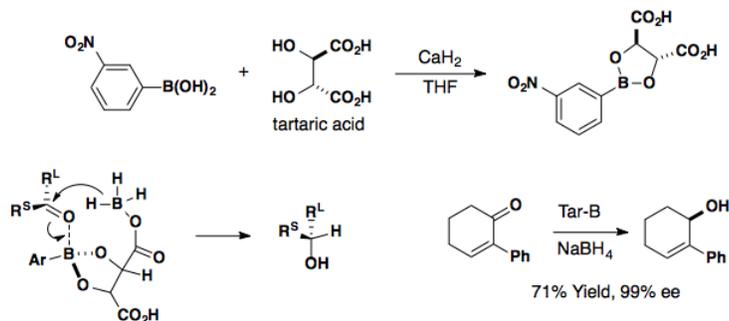


If the selectivity from these reactions is the opposite of your desired product, you can use a Mitsunobu Reaction to invert the stereocenter.

Corey-Bakshi-Shibata (CBS) Reductions

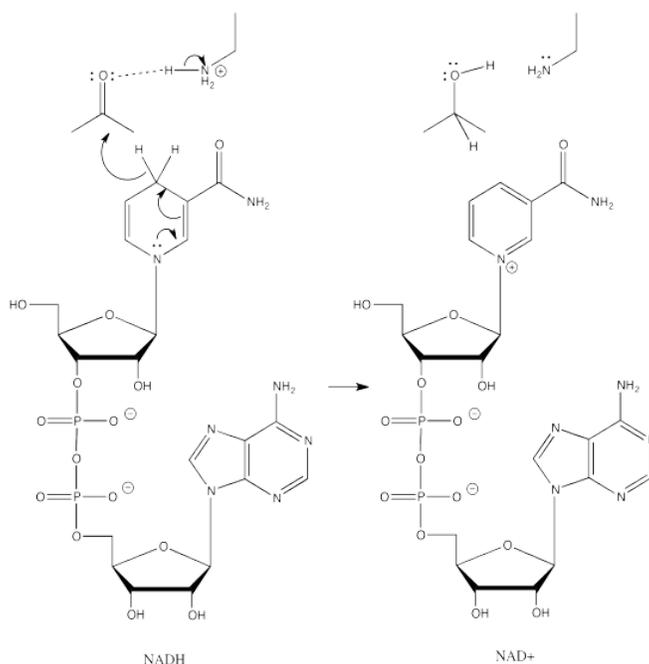


Tar-B



Biological Reduction

Addition to a carbonyl by a **semi-anionic** hydride, such as NaBH_4 , results in conversion of the carbonyl compound to an alcohol. The hydride from the BH_4^- anion acts as a nucleophile, adding H^- to the carbonyl carbon. A proton source can then protonate the oxygen of the resulting alkoxide ion, forming an alcohol.



Formally, that process is referred to as a reduction. Reduction generally means a reaction in which electrons are added to a compound; the compound that gains electrons is said to be reduced. Because hydride can be thought of as a proton plus two electrons, we can think of conversion of a ketone or an aldehyde to an alcohol as a two-electron reduction. An aldehyde plus two electrons and two protons becomes an alcohol.

Aldehydes, ketones and alcohols are very common features in biological molecules. Converting between these compounds is a frequent event in many biological pathways. However, semi-anionic compounds like sodium borohydride don't exist in the cell. Instead, a number of biological hydride donors play a similar role.

NADH is a common biological reducing agent. NADH is an acronym for nicotinamide adenine dinucleotide hydride. Instead of an anionic donor that provides a hydride to a carbonyl, NADH is actually a neutral donor. It supplies a hydride to the carbonyl under very specific circumstances. In doing so, it forms a cation, NAD^+ .

Contributors

- Stephen Laws
- Michael Di Maso (UC Davis)

- Jared Shaw (UC Davis)

18.6: [Enantioselective Carbonyl Reductions](#) is shared under a [CC BY-NC-SA 4.0](#) license and was authored, remixed, and/or curated by LibreTexts.