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Reviews

Asymmetric Reductions Involving Borohydrides: A Practical Asymmetric Reduction of Ketones Mediated by (L)-TarB−NO_2: A Chiral Lewis Acid

Jinsoo Kim,[†] Jeff T. Suri,[‡] David B. Cordes,[§] and Bakthan Singaram*[,†]

Department of Chemistry and Biochemistry, University of California, Santa Cruz, 1156 High Street, Santa Cruz, California 95064, U.S.A., GluMetrix, Inc. 15375 Barranca Parkway, Suite I-108, Irvine, California 92618, U.S.A., and Lawrence Livermore National Laboratory, 7000 East Avenue, Livermore, California 94550, U.S.A.

Abstract:

The asymmetric reduction of prochiral ketones has been achieved through a myriad of different methods. Early reductions gave low to moderate enantiomeric excesses (ee's), but more modern reagents have led to dramatic increases in enantioselectivity. The development of (L)-TarB-NO_2 boronic ester is extensively reviewed in the context of other well-known asymmetric reducing reagents. In combination with $NaBH_4$, the chiral intermediate is able to reduce prochiral ketones to optically active secondary alcohols in ee's as high as 99% and can be easily recovered under basic conditions.

1. Introduction

The chirality of molecules has been known for well over a century. However, the need for enantiomerically pure compounds was not very well defined. Some enantiomers behave identically, others, very differently. This became public knowledge in the 1960s when it was discovered that the (*S*)-enantiomer of the sedative thalidomide was teratogenic.[1] By FDA mandate, pharmaceutical companies must now show activity for both enantiomers of any chiral compound as well as the racemate. Examples of pharmaceuticals that are sold in their optically pure form are shown in Figure 1.

Although the importance of optically pure products has been known for quite some time, it has only been within the past three decades that synthetic methods yielding high enantiomeric excesses (ee's) have been determined.[2] The primary methods employed in the synthesis of chiral nonracemic molecules involve the resolution of a racemate via cocrystallization, use of a chiral natural product as a starting material, or enantioselective reactions.[3] Although it is still heavily used in industry due to its cost efficiency,[4] resolution of isomers from a racemate is not optimal because the maximum yield

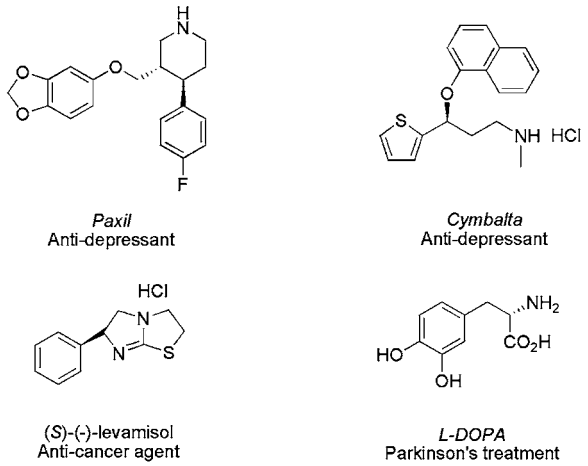

Figure 1. **Optically active pharmaceutical compounds.**

of the reaction is 50%. Natural products are useful as chiral building blocks in stereospecific reactions, but asymmetric methods are often still required to attain high diastereoselectivity. Synthesis of stereochemically complex natural products often requires asymmetric methods.[5] The demand for enantiomerically pure products has led both industry and academia to develop an extensive library of asymmetric synthetic methods.[6−9] An ongoing challenge in asymmetric methodology is the development of cost-effective reactions that can be applied to an industrial scale.[10] Enzymes are often used for this purpose within industrial process chemistry because of their natural selectivity for a particular enantiomer.[11]

Of the asymmetric synthetic methods currently available, stereoselective reductions are among the most widely explored and utilized.[12] A number of asymmetric reducing

* To whom correspondence should be addressed. Fax: + 1 831 459 2935. E-mail: singaram@chemistry.ucsc.edu.
† University of California, Santa Cruz.
‡ GluMetrix, Inc.
§ Lawrence Livermore National Laboratory.

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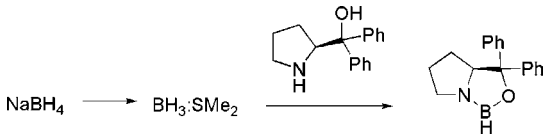
agents utilize the unique reactivity of boron hydrides and their derivatives.[13]

2. CBS Catalyst

Corey became interested in early work by Itsuno,[14] particularly a study in which (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutanol was used as an additive in the reduction of aromatic ketones.[15] The decision to continue exploring this system using tertiary alcohols was based on mechanistic insights that arose from Itsuno's work.[16] Using this tertiary amino alcohol, initial studies were applied to acetophenone and produced results comparable to those of Itsuno. However, subsequent examinations of reaction kinetics led to the postulate that the oxazaborolidine reagent could be used in catalytic rather than stoichiometric amounts. This was readily verified when acetophenone was reduced in 94% ee using 2.5−5 mol % of the reagent.

Further consideration of the reaction mechanism led to the eventual use of a pyrrolidine-based tertiary alcohol, α,α-diphenyl-2-pyrrolidine methanol. This catalyst was determined to be superior to the previous catalyst and was named the CBS (Corey, Bakshi, Shibata) catalyst. The catalyst is synthesized by mixing α,α-diphenyl-2-pyrrolidine methanol with BH_3:SMe_2 (BMS). The relatively expensive BMS is in turn commercially produced from inexpensive sodium borohydride (Scheme 1).

Scheme 1. **Synthesis of CBS catalyst**



The asymmetric induction achieved by the CBS reducing system is highly influenced by the variant group attached to the boron atom. This group can be tuned to fit a particular substrate, although most commonly *B*-hydrogen or *B*-methyl is used. The group on boron directs the ketones to bind in such a way that there is minimal interaction between the *B*-R group and the small substituent of the ketone (Scheme 2).

Scheme 2. **Mechanism of the CBS catalyst**

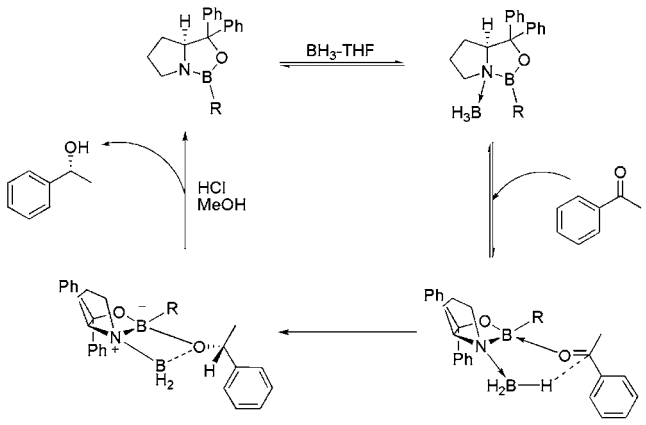
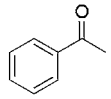
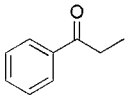
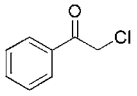
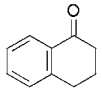
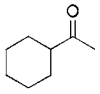


Table 1 summarizes the results of various ketone reductions using *B*-methyl CBS catalyst.[17] A single equivalent of ketone was mixed with 0.1 equiv of catalyst and 0.6 equiv of BH_3·THF for 25 min to yield the optically active secondary alcohols.

Table 1. **Reduction of ketones using CBS catalyst**

Entry	Ketone	%ee[a,b]
1		97 (*R*)
2		97 (*R*)
3		95 (*S*)
4		97 (*R*)
5		86 (*R*)
6		84 (*R*)

[a] All reactions gave >99% conversion to the alcohol according to GC. [b] Absolute configuration determined by gas chromatography.

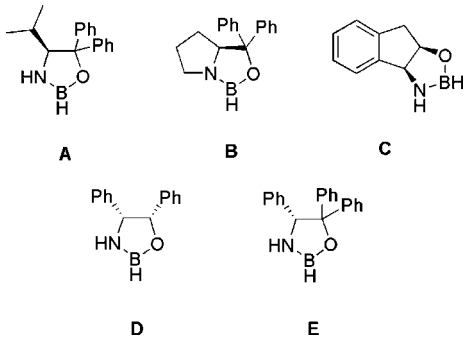


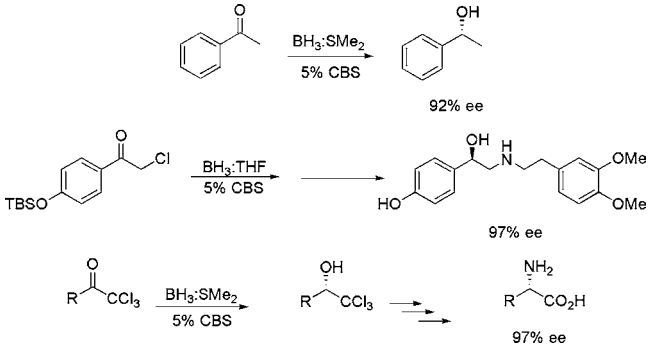
Figure 2. **Oxazaborolidines used in asymmetric reduction. (A) Itsuno,[15] (B) Corey,[18] (C) Hong,[19] (D) Quallich,[20] (E) Berenguer.[21]**

Several optimizations have been explored, including variation of the geminal carbinol substituents, alternative reducing agents such as catecholborane, and variation of the oxazaborolidine ring system (Figure 2).

The versatility of CBS catalyst has been shown in a variety of syntheses, all stemming ultimately from its stereoselective reduction of a ketone to the corresponding optically active alcohol (Scheme 3).[16,22,23]

Use of CBS and other oxazaborolidine catalysts in industrial processes is well documented.[24−29] Pfizer's development of the antidepressant Zoloft involved the exploration of several asymmetric synthetic methods, including a reduction using an oxazaborolidine catalyst. However, it is not cost efficient at an industrial scale so the current synthesis involves resolution of the racemate.[30]

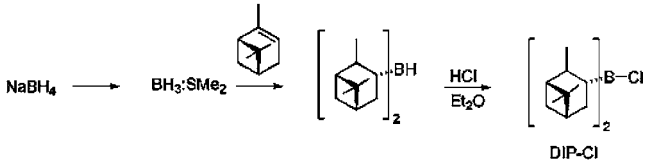
Scheme 3. **Use of CBS catalyst in organic syntheses**



3. *B*-Chlorodiisopinocampheylborane (DIP-Cl)

Another well-known and highly explored asymmetric reducing system is the α-pinene derivative *B*-chlorodiisopinocampheylborane (DIP-Cl).[31,32] DIP-Cl is also able to convert a variety of ketones into secondary alcohols with excellent enantioselectivity. Its synthesis is simple and cost-effective, making it an attractive reagent in asymmetric reductions (Scheme 4).

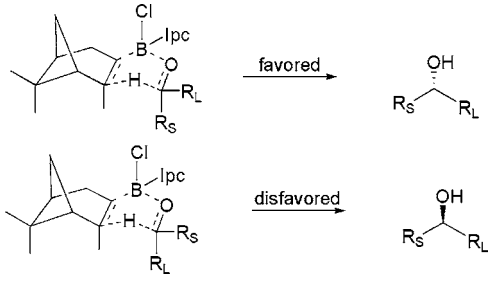
Scheme 4. **Synthesis of DIP-Cl**



Like CBS catalyst, DIP-Cl is also synthesized from the relatively expensive BMS. Mixture of BMS and BCl_3:SMe_2 in a 2:1 ratio yields BH_2Cl:SMe_2, which was subsequently mixed with α-pinene to give the diisopinocampheyl haloborane (DIP-Cl). DIP-Cl is effective and, though used in stoichiometric amounts, it generates the same number of equivalents of chiral alcohol per mole of BMS as CBS catalyst.

DIP-Cl effects its asymmetric induction via a six-membered transition state. The larger group flanking the carbonyl of the ketone prefers to sit in the pseudoequatorial position. This steric preference creates facial selectivity for delivery of the hydride. Transfer of the β-hydrogen affords the secondary alcohol with good enantioselectivity (Scheme 5).

Scheme 5. **Mechanism of DIP-Cl**



DIP-Cl has been used to reduce a variety of hindered ketones, including aryl ketones, cyclic aliphatic ketones, and α,β-acetylenic ketones with high ee (Table 2).

DIP-Cl has also been successfully incorporated into industrial syntheses.[33,34] An early step in the total synthesis of Prozac is an asymmetric reduction, which has been achieved using DIP-Cl.[35]

Table 2. **Enantioselective reduction of hindered ketones by DIP-Cl**

Entry	Ketone	Yield	%ee
1		72	98
2		60	91
3		71	98
4		65	95
5		50	95

Although CBS and DIP-Cl are excellent asymmetric reducing agents that have achieved widespread use, they are made from the somewhat expensive BMS, which is derived from sodium borohydride. Consequently, asymmetric reducing systems utilizing chirally modified sodium borohydride would be more attractive. Sodium borohydride is more stable and does not require special handling procedures. Over the past few decades, chirally modified sodium borohydride has been used for the asymmetric reduction of ketones with

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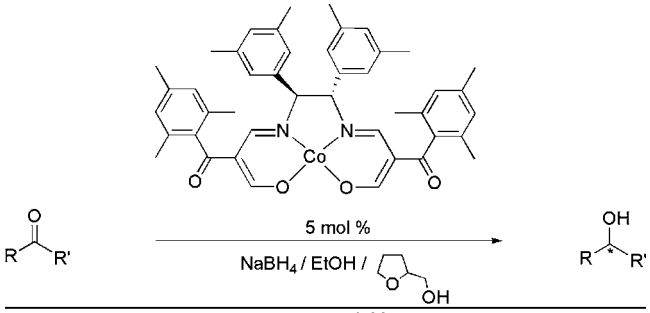
varying degrees of success and under a wide range of experimental conditions.

4. Asymmetric Reducing Agents Using Sodium Borohydride

Sodium borohydride ($NaBH_4$) has found limited use in conjunction with chiral metal catalysts in asymmetric reductions. Mukaiyama developed a cobalt(II)-based chiral catalyst that has proven effective in asymmetric reduction of aromatic ketones.[36] Using 5 mol % of catalyst and a stoichiometric amount of alcohol to activate the $NaBH_4$, aromatic ketones were reduced with moderate to high ee's. One of the main advantages of this particular system is that both enantiomers of the catalyst can be synthesized so that generation of both enantiomers of the corresponding alcohol is also possible (Table 3).[37−39]

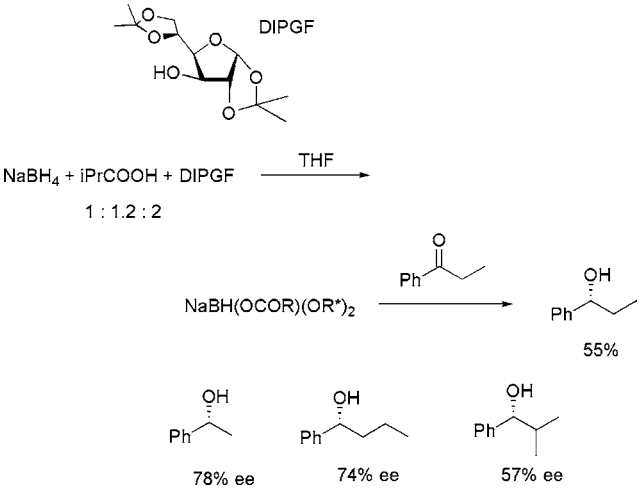
Table 3. **Enantioselective reduction of hindered ketones by Co(II) catalyst**



Entry	Ketone	Yield	%ee
1		95	68
2		92	70
3		99	73
4		95	89
5		94	92
6		76	94

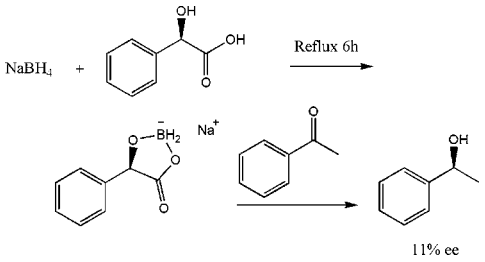
Saccharide modification of sodium borohydride offers yet another route of asymmetric induction. Upon mixing with carboxylic acid and di-*O*-isopropylidene glucofuranose (DIPGF) the borohydride is transformed into a reagent that is able to selectively reduce hindered ketones with moderate to good selectivity (Scheme 6).[40−42]

Scheme 6. **Saccharide modification of sodium borohydride in asymmetric reduction**



Sodium borohydride can be reacted with optically active α-hydroxy carboxylic acids, such as mandelic acid, to create a chiral five-membered borolidine species (Scheme 7).

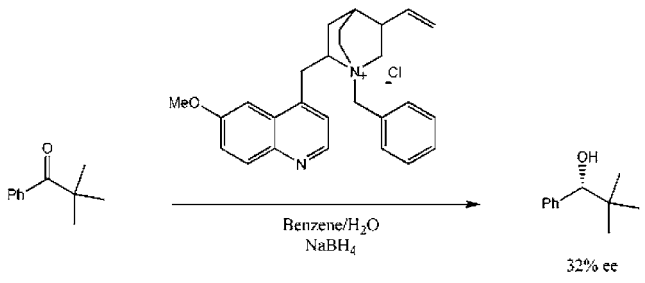
Scheme 7. **Use of chiral α-hydroxy carboxylic acids in asymmetric reduction with $NaBH_4$**



However, these systems often produce low conversions with low to moderate enantioselectivity for the reduction of prochiral ketones.[43]

Phase transfer catalysts in combination with sodium borohydride offer another route to asymmetric reduction of prochiral ketones. In a biphasic system such as water and benzene, phase transfer catalysts can selectively reduce hindered ketones with sodium borohydride.[44] The main limitation is that the ketone must be hindered or chiral at the α-position for optimal results. Still, reduction of *tert*-butyl phenyl ketone with the benzylquininium chloride catalyst gave the product alcohol in low (32%) ee (Scheme 8).

Scheme 8. **Phase transfer catalysts in asymmetric reduction**



Attempts were made to modify sodium borohydride with amino acids to produce a chiral reducing agent.[45] Initial

(36) Nagata, T.; Yorozu, K.; Yamada, T.; Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2145−2147.
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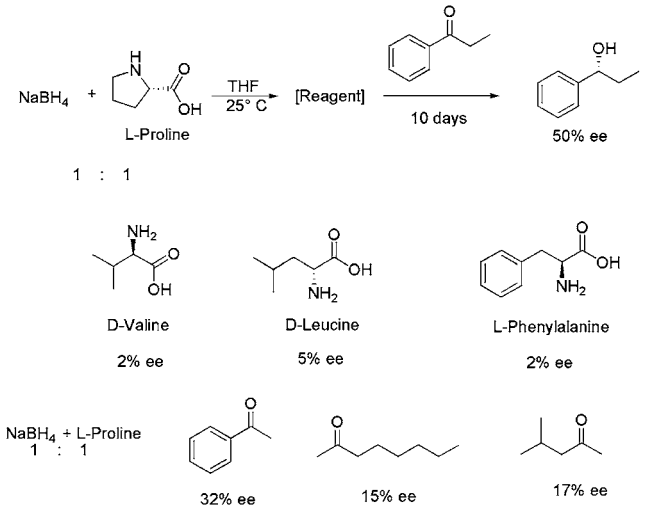
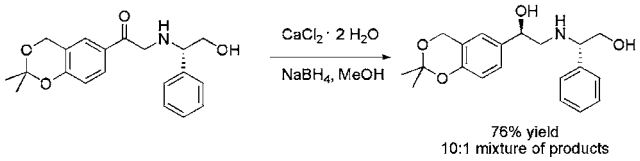
studies conducted with L-proline-modified reagent gave an asymmetric induction of 50% ee when reducing propiophenone. These reactions are slow and can take up to 10 days for complete reduction. D-Valine, D-leucine, and L-phenylalanine showed significantly decreased enantioselectivity with the same substrate. L-Proline/$NaBH_4$ was used to reduce other substrates, but none showed the same selectivity as propiophenone (Scheme 9).

Scheme 9. **Amino acid-modified $NaBH_4$ systems in asymmetric reduction**



Chelation control has been effectively used in the asymmetric reduction of a prochiral ketone using unmodified sodium borohydride. Ley et al. used an elegant reductive strategy in their synthesis of (*R*)-salmeterol using calcium chloride and sodium borohydride.[46] The calcium chloride enhances the solubility of the ketone in methanol and allows for selective reduction, yielding a 10:1 anti:syn mixture of diastereomers (Scheme 10).

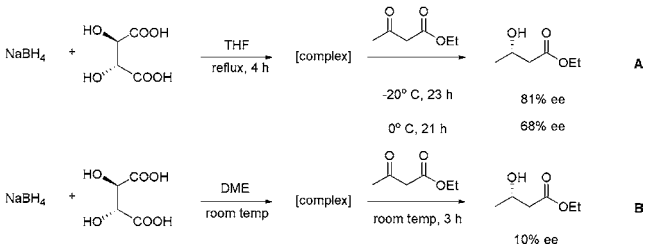
Scheme 10. **Asymmetric reduction using metal chelator**



5. Use of Tartaric Acid with $NaBH_4$ in Asymmetric Reduction

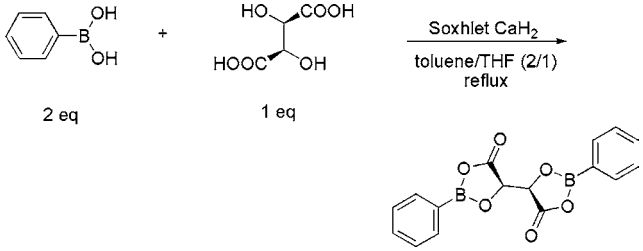
Yatagai reported the use of (L)-tartaric acid and sodium borohydride in asymmetric reductions.[47] This is attractive since both enantiomers of tartaric acid are readily available natural products. According to Yatagai the $NaBH_4$/tartaric acid complex was able to selectively reduce hindered ketones such as α-ketoesters, β-ketoesters, and functionalized acetophenones with good ee. Polyak, however, was unable to reproduce Yatagai's results and achieved much lower ee's using the same reagents (eq 1).[48]

$NaBH_4$/tartaric acid reduction of β-ketoesters by A) Yatagai and B) Polyak.



Nozaki combined (L)-tartaric acid and boronic acid to form a chiral Lewis acid reducing agent.[49] The bisboronate ester showed promising results in the reduction of amino-substituted aryl ketones. Using a series of reducing agents it was discovered that the best results were obtained using a stoichiometric amount of $LiBH_4$. Although used in stoichiometric amounts, the chiral auxiliary was inexpensive and the reagents could be recycled (Scheme 11).

Scheme 11. **Synthesis of Nozaki's bisboronate ester**



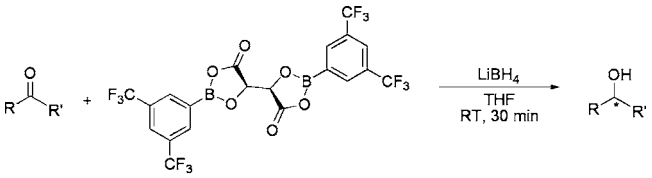
Substitution of the aryl group on the boronic ester produced varying results, with 3,5-CF_3-aryl substitutions showing the best enantioselectivity (Table 4).

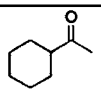
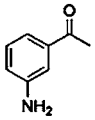
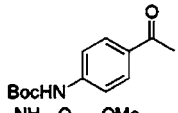
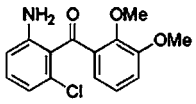
6. TarB-X-$NaBH_4$, A New Asymmetric Reducing System

Synthesis. Our attempts at duplicating the synthesis of Nozaki's catalyst produced only decomposition product. It was deduced that the high-temperature reflux necessary to azeotropically remove water with toluene caused degradation of tartaric acid due to its lability at temperatures above 100°C. To rectify this problem, milder reaction conditions were employed. An alternative synthesis was developed with the use of refluxing THF and CaH_2 to remove the water generated in the condensation of phenylboronic acid with tartaric acid.[50,51] This method can be applied to other syntheses requiring formation of a boronic ester under mild conditions.[52]

(41) Hirao, A.; Nakahama, S.; Mochizuki, H.; Itsuno, S.; Yamazaki, N. *J. Org. Chem.* **1980**, *45*, 4231−4233.
(42) Hirao, A.; Itsuno, S.; Owa, M.; Nagami, S.; Mochizuki, H.; Zoorov, H. H. A.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 900−905.
(43) Nasipuri, D.; Sarkar, A.; Konar, S. K.; Ghosh, A. *Indian J. Chem., Sect. B* **1982**, *21*, 212−215.
(44) Colonna, S.; Fornasier, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 371−373.
(45) Umino, M.; Iwakuma, T.; Itoh, N. *Chem. Pharm. Bull.* **1979**, *27*, 1479−1481.
(46) Bream, R. N.; Ley, S. V.; McDermott, B.; Procopiou, P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2237−2242.
(47) Yatagai, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1826−1990.
(48) Polyak, F. D.; Solodin, I. V.; Dorofeeva, T. V. *Synth. Commun.* **1991**, *21*, 1137−1142.
(49) Nozaki, K.; Kobori, K.; Uemura, T.; Tsutsumi, T.; Takaya, H.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1109−1113.
(50) Suri, J. T.; Vu, T.; Hernandez, A.; Congdon, J.; Singaram, B. *Tetrahedron Lett.* **2002**, *43*, 3649−3652.
(51) Cordes, D. B.; Nguyen, T. M.; Kwong, T. J.; Suri, J. T.; Luibrand, R. T.; Singaram, B. *Eur. J. Org. Chem.* **2005**, *24*, 5289−5295.
(52) Broutin, P.-E.; Colobert, F. *Eur. J. Org. Chem.* **2005**, *6*, 1113−1128.

Table 4. **Enantioselective reduction of ketones by Nozaki's bisboronate ester**

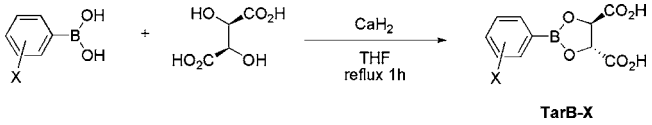


Entry	Ketone	%ee[a,b]
1		82 (*R*)[c]
2		56 (−)[d,e]
3		99 (+)[d,e]
4		90 (+)[d,e]
5		85 (*S*)[e]

[a] Absolute configuration shown in parentheses. [b] All reactions gave 100% conversion to the alcohol. [c] Determined by ^{19}F NMR of (*R*)-MPTA ester. [d] Absolute configuration not determined. [e] Configuration determined by chiral HPLC (Daicel, CHIRALCEL OD).

In a surprising development, it was discovered that just one equivalent of phenylboronic acid produced an active reagent that gave identical results to those of Nozaki's in the reduction of acetophenone. This prompted us to investigate the synthesis and utility of our new chiral agent, which we call "TarB-X". Equimolar amounts of phenylboronic acid and the appropriate isomer of tartaric acid were refluxed in THF over 2 equiv of CaH_2 to yield active reagent in near quantitative yield. The solution was cooled after an hour, filtered, and stored in an ampule (Scheme 12).

Scheme 12. **Synthesis of TarB-X**

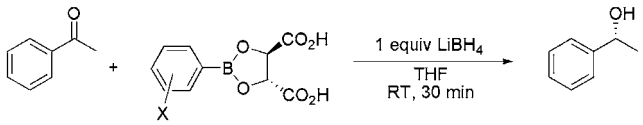


TarB-X

Structural Elucidation. Structural elucidation was carried out to ensure that the chiral reducing agent we had synthesized was, in fact, novel.[53] ^{1}H NMR of (L)-tartaric acid gives a singlet at approximately 4.3 ppm, representative of the methine protons. ^{1}H NMR of TarB-X indicated that the singlet had shifted to 5.0 ppm. This confirmed not only conjugation of tartaric acid to the electron-withdrawing boron but also maintenance of the C_2 symmetry of the tartaric acid.[50] This was further confirmed by integration of the aromatic protons to the methine protons, which gave a 2:1 ratio. ^{13}C NMR and ^{11}B-NMR[54] also provided supporting data. FT-IR showed a carbonyl stretch at 1736 cm^{-1} and an OH stretch at 3427 cm^{-1}, characteristic shifts of carboxylic acids. Additional proof of free carboxylic acids was provided by active hydride estimation. Addition of $LiBH_4$ to *m*-nitro-TarB produced 2 equiv of H_2 gas.[55] We found that the free carboxylic acids are necessary to achieve high enantioselectivities through the formation of acyloxyborohydrides.

Substituent Effects. We varied the substituents on the aromatic ring of TarB-X to study their effect on the enantioselectivity achieved in the reduction of ketones. A summary of these data with acetophenone as the representative ketone is shown in Table 5. An unsubstituted phenyl group gave moderate enantioselectivity (entry 1). Electron-withdrawing groups such as halides and trifluoromethyl groups at the ortho and para positions show noticeable improvement (entries 2, 3, 5, and 7). However, these same electron-withdrawing groups in meta positions (entries 4 and 6) seem to hinder the ability of TarB-X to effectively promote asymmetric reduction. A nitro group at the 3-position of the phenyl ring gave the best enantioselectivity and was selected for the subsequent asymmetric reduction projects (Table 5).

Table 5. **Substituent effects in reduction of acetophenone using TarB-X**



entry	X	% ee[b,c,d]
1	H	71
2	2-F	90
3	4-F	90
4	2,3,4,5,6-F	13
5	4-CF_3	91
6	3,5-CF_3	76
7	4-Cl	90
8	3-NO_2	94

[a] Determined by GC analysis on Supelco Beta-Dex 120 column. [b] All products were of the (*R*) configuration as determined by chiroptical comparison. [c] All reactions gave 100% conversion to the alcohol according to GC.

Reduction of Aromatic Alkyl Ketones with $NaBH_4$. Optimal reaction conditions were explored using acetophenone as the representative substrate. Neither increasing nor decreasing the temperature provided better enantioselectivity compared to reactions carried out at 25 °C. Acetonitrile and diethyl ether were examined as possible replacement solvents for THF, but neither produced superior results (Table 6). The best results were obtained using 2 equiv of TarB-NO_2, 1 equiv of $LiBH_4$, and 1 equiv of acetophenone.

We used these optimized conditions to probe the generality of this new asymmetric reducing system. Reduction of aromatic ketones using TarB-NO_2 and $LiBH_4$ proved to be very effective, giving the corresponding alcohols in high enantiomeric purity (Table 7).

Although effective in reductions, the highly reactive nature of lithium borohydride makes it somewhat difficult to handle. A less reactive hydride source, such as sodium borohydride, was an ideal replacement due to its stability to air and moisture. Additionally, it is also significantly cheaper than most boron reagents, at a cost of $8 per mole. In contrast,

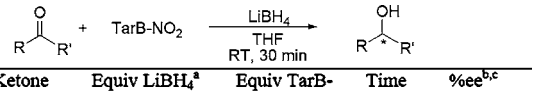
(53) Nozaki's bisboronate adduct contains no free carboxylic acid.[49]

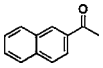
Table 6. **Reduction of acetophenone using TarB-X under different conditions**

X	TarB-X (mmol)	$LiBH_4$[a] (mmol)	acetophenone (mmol)	solvent	°C	% ee[b,c]
4-Cl	3	6	6	THF	25	50
4-Cl	6	3[d]	6	THF	25	88
4-Cl	6	6	6	Et_2O	25	32
4-Cl	6	6	6	CH_3CN	25	90
4-Cl	12	6	6	THF	25	99
3-NO_2	6	6	6	THF	−15	74
3-NO_2	6	6	6	THF	0	83
3-NO_2	6	6	6	THF	40	85
3-NO_2	12	6	6	THF	25	99

[a] All reactions gave 100% conversion to the alcohol according to GC unless otherwise noted. [b] Determined by GC analysis on a Supelco Beta-Dex 120 column. [c] All products were of the (*R*) configuration as determined by chiroptical comparison. [d] Only 50% conversion to alcohol according to GC.

Table 7. **Enantioselectivity of aromatic ketones by TarB-NO_2 and $LiBH_4$**



Entry	Ketone	Equiv $LiBH_4$[a]	Equiv TarB-NO_2	Time h	%ee[b,c]
1		1	2	0.5	99 (99)
2		1	2	0.5	(90)[d]
3		1.5	2	1	94 (94)
4		2	2	1.5	99 (99)
5		1	2	0.5	88
6		1	2	0.5	99 (99)

[a] All reactions gave 100% conversion to the alcohol according to GC. [b] Determined by GC analysis on a Supelco Beta-Dex 120 column. [c] Values in partentheses were determined via optical rotation; all products were of the (*R*) configuration. [d] Enantiomers did not separate on GC.

lithium borohydride is $130 per mole[56] and must be handled with care because it is pyrophoric. Sodium borohydride also lends itself to modifications that can prove useful in a variety of synthetic transformations.[57]

The primary concern in replacing $LiBH_4$ with $NaBH_4$ was the change from a homogeneous system to a heterogeneous system, due to the solubility of $NaBH_4$ in ethereal solvents. To examine their respective efficiencies, acetophenone was reduced using $NaBH_4$ and TarB-NO_2 in both homogeneous and heterogeneous systems. In the homogeneous system the ketone and TarB-NO_2 were premixed in solvent A, and $NaBH_4$ was dissolved in solvent B (Table 8). Solvent B containing $NaBH_4$ was added dropwise to the solvent A solution.

(54) In THF, two peaks are observed relative to BF_3:Et_2O: a broad peak at 32 ppm and another smaller peak at 10 ppm. 3-Nitrophenylboronic acid gives a broad peak at 28 ppm.

(55) H_2(g) measured in a hydride meter as described in: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975; Chapter 9.

Due to the susceptibility of TarB-NO_2 to hydrolysis the range of solvents was limited to aprotic solvents of low polarity.

Table 8. **Reduction of acetophenone with TarB-NO_2 and $NaBH_4$ in a homogeneous system**

entry	solvent A	solvent B	% ee[a,b]
1	NMP	NMP	0
2	THF	THF/NMP (3:1)	92
3	THF	diglyme	97
4	diglyme	diglyme	88
5	tetraglyme	tetraglyme	78

[a] All reactions gave 100% conversion to the alcohol according to GC unless otherwise noted. [b] Determined by GC analysis on a Supelco Beta-Dex 120 column.

Although the solubility of $NaBH_4$ in *N*-methylpyrrolidone is good, only racemic alcohol product was observed. Use of diglyme and tetraglyme provided good enantioselectivities, but isolation of the alcohols proved somewhat problematic due to their high boiling points. THF produced the most promising results.

A survey of the literature suggested that use of $NaBH_4$ in a heterogeneous system with THF as a solvent had potential to yield good enantioselectivity.[58−61] $NaBH_4$ is essentially insoluble in THF and is unable to fully reduce ketones even after several hours. However, introduction of a carboxylic acid allows the $NaBH_4$ to form a conjugate that is soluble in THF. This is fortuitous because it prevents achiral hydride delivery to the ketone.[51]

On the basis of these results, we used a suspension of sodium borohydride in THF. The ketone/TarB-NO_2 solution was then transferred in a single aliquot to the $NaBH_4$/THF mixture. This heterogeneous TarB-NO_2 solution still gave excellent enantioselectivity and full conversion of the ketone in 30 min.

The efficiency of homogeneous and heterogeneous systems was examined in the reduction of aromatic ketones. Results are summarized in Table 9.

Table 9. **Enantioselective reduction of acetophenone using TarB-NO_2 in homogeneous and heterogeneous systems**

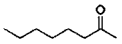
Entry	Ketone	%ee		
		$LiBH_4$-THF homogeneous	$NaBH_4$-Diglyme homogeneous	$NaBH_4$-THF heterogeneous (yield)[a]
1		99	97	98 (90)
2		96	95	97 (85)
3		88	97	98 (79)
4		85	90	93 (76)
5		78	64	95 (65)
6		99	96	98 (93)
7		94	78	97 (84)

[a] Isolated yields.

The costly reagent in our methodology is the arylboronic acid. Although used in stoichiometric amounts, it was efficiently recovered by a simple extraction with aqueous NaOH (3 M). After quenching the reaction mixture with HCl, the solution was brought to pH 12 using NaOH (3 M) and extracted with diethyl ether to separate the product alcohol from the sodium salt of the arylboronic acid. Acidification of the aqueous layer followed by extraction with diethyl ether afforded recovered arylboronic acid in essentially quantitative yield.

Reduction of Aliphatic Ketones. While several asymmetric reducing agents have produced high enantioselectivity in the reduction of aromatic ketones, enantioselective reduction of aliphatic ketones still remains challenging.[62] It was previously reported that TarB-NO_2 was able to effectively reduce the aliphatic substrates 2-octanone and pinacolone with moderate to excellent enantioselectivity.[51] Recently its ability to reduce a variety of aliphatic ketones, including *tert*-alkyl, *sec*-alkyl, and *n*-alkyl ketones was reported (Table 10).[63] It was found that TarB-NO_2 was able to enantioselectively reduce the aliphatic ketones with results comparable or better than those of CBS and DIP-Cl.

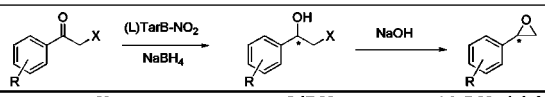
Table 10. **Enantioselective reduction of aliphatic ketones using TarB-NO_2**

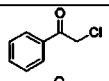
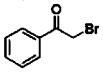
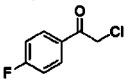
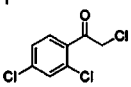
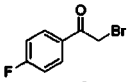
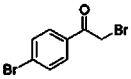
Entry	Ketone	Isolated Yield (%)	% ee
1		80	94 (*R*)[a]
2		—	95 (*R*)
3		80	80 (*R*)
4		86	83 (*R*)
5		62	62 (*R*)
6		82	82 (*R*)
7		65	56 (*R*)
8		83	60 (*R*)

[a] Determined by comparison of optical rotation with literature value; all others assigned by analogy.

Reduction of α-Haloketones. The reduction of ketones to optically active secondary alcohols can potentially lead to a myriad of synthetic transformations. Recently, TarB-NO_2 was used in the conversion of α-haloketones to chiral styrene oxides, which are useful as pharmaceutical starting materials.[64] All but the 2′,2,4-trichloroacetophenone substrate showed high ee's. It was discovered that substitution at the ortho position with electron-withdrawing groups activated the carbonyl carbon, making it more susceptible to achiral reduction. Results from this study are summarized in Table 11.

Table 11. **Enantioselectivities of epoxides formed from the reduction of α-haloaryl ketones using TarB-NO_2**

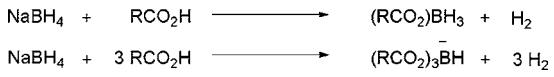


Entry	Ketone	$LiBH_4$	$NaBH_4$ (yield)[a]
1		84	93 (94)[b]
2		91	94 (80)[b]
3		89	86 (87)[c]
4		26	36 (95)[c]
5		90	95 (89)[c]
6		86	94 (84)[c]

[a] Isolated yield. [b] Products were of the (*S*) configuration as determined by chiroptical comparison. [c] Configuration assigned based on mechanistic model.

Mechanism of Asymmetric Reduction Promoted by TarB-NO_2. Discussion of the mechanism of TarB-NO_2-promoted reduction revolves around the formation of acyloxyborohydrides. Carboxylic acids are known to react with $NaBH_4$ to form a boronate complex. In the presence of three or more equivalents of carboxylic acid a less reactive triacyloxyborohydride complex is produced (Scheme 13).[57]

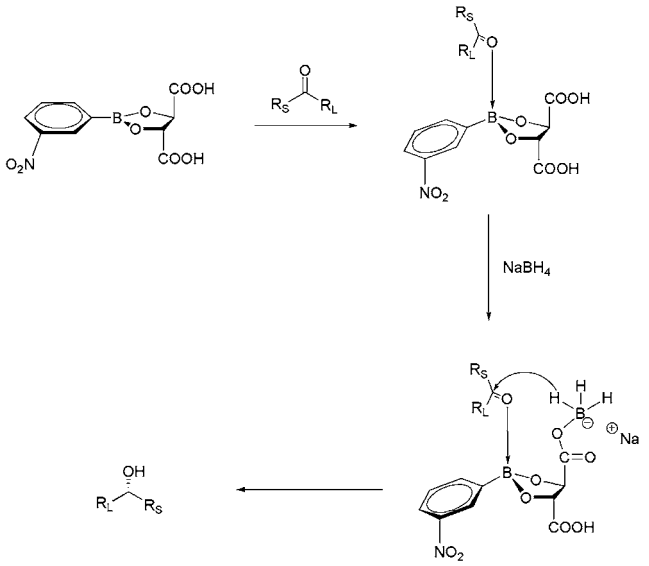
Scheme 13. **Formation of acyloxyborohydrides by sodium borohydride and carboxylic acids**



Conjugation of $NaBH_4$ to the tartaric acid enhances its solubility in THF and allows the hydride to be delivered nearly exclusively by the chiral borohydride complex. The ketone is coordinated to the Lewis acidic boron, generating tetrahedral geometry. While it would seem that the ketone could coordinate to boron from several directions, it is in fact controlled by a phenomenon known as the proximal effect. As the ketone approaches the boron atom, it stacks in a sideways fashion, holding the carbonyl oxygen and carbonyl carbon in the same plane. Computer models have determined that the carbonyl carbon is in its lowest-energy state when it is nearer (proximal) to the carboxylic acid. $NaBH_4$ binds to the carboxyl end of tartaric acid, liberating H_2 and creating the acyloxyborohydride.[65] Facial delivery of the hydride is determined by this intermediate (Scheme 14).

(56) According to catalogs of major suppliers, $LiBH_4$ is roughly 15 times as expensive as $NaBH_4$.
(57) Gribble, G. W. *Chem. Soc. Rev.* **1998**, *27*, 395−404.
(58) Hirao, A.; Itsuno, S.; Mochizuki, H.; Nakahara, S.; Yamazaki, N. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1424−1428.
(59) Yamada, K.; Takeda, M.; Iwakuma, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 265−270.
(60) Bianchi, G.; Achilli, F.; Gamba, A.; Vercesi, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 417−422.
(61) Yamada, K.; Takeda, M.; Iwakuma, T. *Tetrahedron Lett.* **1981**, *22*, 3869−3872.
(62) Brown, H. C.; Chandresekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539−1546.
(63) Kim, J.; Singaram, B. *Tetrahedron Lett.* **2006**. In Press.
(64) Cordes, D. B.; Kwong, T. J.; Morgan, K. A.; Singaram, B. *Tetrahedron Lett.* **2006**, *47*, 349−351.

Scheme 14. **Mechanism of TarB-NO_2 enantioselectivity**



Further examination of the mechanism was undertaken through computational modeling. The representative reaction of TarB-NO_2 with acetophenone was mimicked with 1,3,2-dioxoborolane-4-carboxylic acid and formaldehyde. As can be seen in Figure 3, the formaldehyde is lined up proximally to the carboxylic acid moiety, an intermediate that was determined to be 0.95 kcal/mol lower in energy than its distal counterpart and exothermic by up to 6.6 kcal/mol.

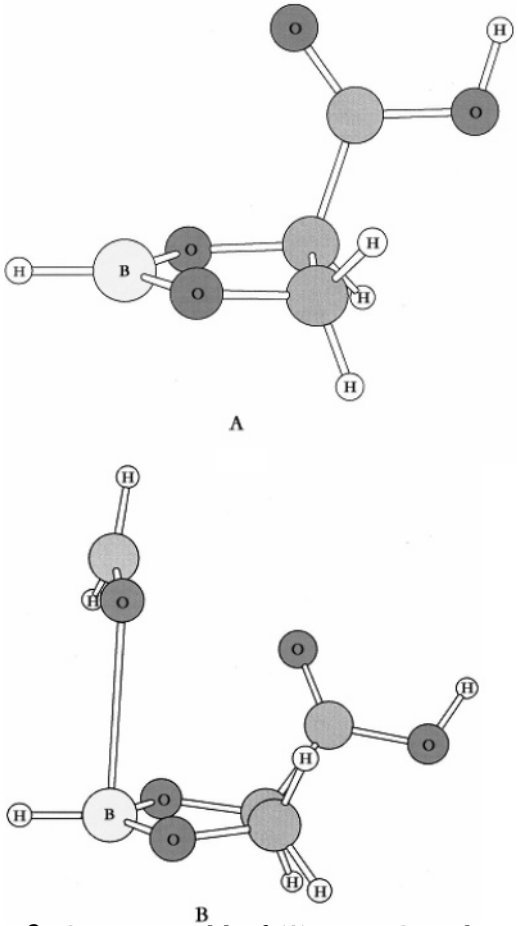


Figure 3. **Computer models of (A) TarB-NO_2 analogue 1,3,2-dioxoborolane-4-carboxylic acid and (B) the proximal formaldehyde complex. Unlabeled atoms represent carbon.**

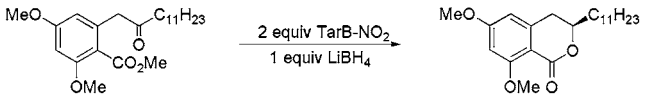
Table 12. **Comparison of substrates reduced by CBS, DIP-Cl, and TarB-NO_2**

		%ee		
Entry	Ketone	CBS Catalyst	DIP-Cl	TarB-NO_2
1		99	98	99
2		98	95	84
3		97	95	94
4		84	26	82
5		91	32	80

Introduction of $NaBH_4$ initiates release of hydrogen gas and formation of the acyloxyborohydride intermediate. The proximal acyloxyborohydride/formaldehyde complex has been calculated to be more stable than the distal complex by up to 2.1 kcal/mol. Three transition states (two proximal and one distal), corresponding to delivery of hydride from the boronate to the formaldehyde, were examined. One of the proximal transition states was over 18 kcal/mol lower in energy than the others. In this transition state the sodium ion has migrated away from BH_3 and towards the dioxoborolane boron. It is triply coordinated to the carbonyl oxygen of the carboxylic acid, a dioxoborolane oxygen, and the carbonyl oxygen of formaldehyde (Figure 4).

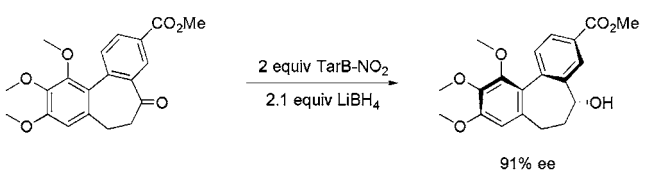
Applications. Recent reports have demonstrated the utility of TarB-NO_2 in comparison to other popular reducing reagents. The total synthesis of (3*R*)-3,4-dihydro-6,8-dimethoxy-3-undecyl-1*H*-[2]benzopyranone involves a critical reduction step of an α-ketoester intermediate. Diisocamphenyl borane, Alpine-borane, and even enzymes were unable to facilitate this key reduction step. TarB-NO_2 furnished the desired product in 80% ee (Scheme 15).[66]

Scheme 15. **Enantioselective reduction using TarB-NO_2 in the total synthesis of (3*R*)-3,4-dihydro-6,8-dimethoxy-3-undecyl-1*H*-[2]benzopyranone**



The enantioselective synthesis of (−)-7*S*-allocolchicine also requires asymmetric reduction. The stereochemistry of the alcohol is extremely important because it dictates the stereochemistry of the final product. In this reductive step, (*S*)-methyl-CBS catalyst provided the corresponding alcohol with a maximum 70% ee when used in equimolar amounts. Kinetic resolution of the racemic alcohol also proved to be ineffective. Addition of TarB-NO_2 to the prochiral ketone produced the desired alcohol in 91% ee (Scheme 16).[67]

Scheme 16. **Enantioselective reduction using TarB-NO_2 in the total synthesis of (−)-7*S*-allocolchicine**



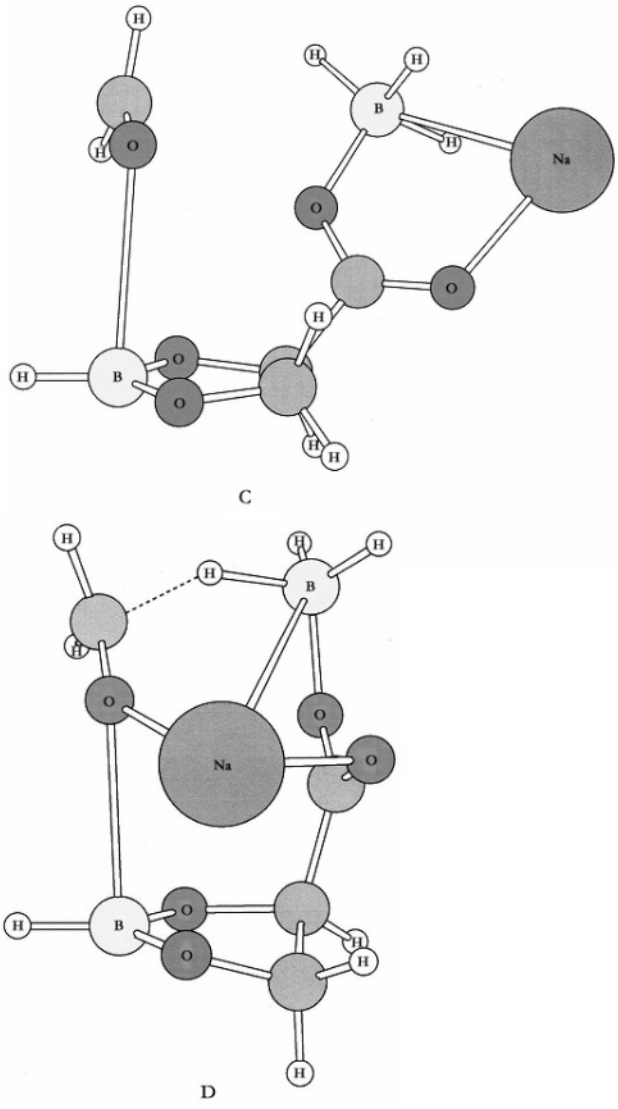


Figure 4. **Computer models of (C) the sodium complex and (D) the lowest-energy proximal transition state. Unlabeled atoms represent carbon.**

7. Conclusions

Nearly a century has passed since the first reports of asymmetric reductions. However, much of the thrust in the research on asymmetric reduction and development of efficient chiral reducing agents has occurred in the last two decades.[32] Most of the reagents available for chiral reductions are based on boron compounds. The objective of this review was to trace major developments in the area of asymmetric reduction involving borohydrides. Modification of $NaBH_4$ with readily available chiral auxiliaries has provided inexpensive reagents for organic chemists. In this review, particular emphasis has been given to the development of asymmetric reducing agent borohydride/TarB-NO_2. We have traced major developments, largely in our own research program, which led from the initial reduction system of $LiBH_4$/TarB-NO_2 to the present time where we can successfully reduce various ketones using $NaBH_4$/TarB-NO_2.

Our exploration of asymmetric arylalkyl ketone reductions led us to test the asymmetric induction on aliphatic substrates. Hindered ketones are good substrates for asymmetric reductions. Unbranched aliphatic ketones, such as methyl ketones, present a challenge because the groups flanking the carbonyl are similar and enantioselectivity declines quickly. Aromatic and hindered ketones have been reduced with excellent enantioselectivity using TarB-NO_2, and results from aliphatic substrates are promising. Pinacolone has given ee's as high as 94%, and isopropyl methyl ketone has given 83% ee after reduction. Even 2-octanone has been reduced to a scalemic mix of approximately 60% ee. Table 12 shows a comparison of substrates reduced by CBS catalyst, DIP-Cl, and TarB-NO_2.

TarB-NO_2 is among a new class of chiral Lewis acids that present a novel method to asymmetric reductions. The reduction appears to operate through an acyloxyborohydride intermediate, whose intermediate and transition states are supported by computational calculations. The concept of preparing chiral acyloxyborohydrides from borohydrides and chiral bifunctional reagents possessing both Lewis and carboxylic acids shows promise for a new asymmetric synthetic methodology. The ease of its synthesis and its low cost as well as its ability to selectively reduce select aliphatic substrates with reasonable enantioselectivity make TarB-NO_2 competitive with popular asymmetric reducing reagents.

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(65) The importance of the carboxylic acid functionality was verified using the methyl ester of tartaric acid. Reductions from this conjugate showed full conversion of ketone to alcohol, but only 7% ee in the reduction of acetophenone.

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