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Asymmetric Reduction of Ketones Under Mild Conditions Using $NaBH_4$ and TarB-NO_2: An Efficient and Unusual Chiral Acyloxyborohydride Reducing System

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Dedicated to the memory of Richter von Grunenfeld

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High enantioselectivities are obtained for the reduction of a series of ketones using the inexpensive and mild reducing agent $NaBH_4$ with TarB-NO_2 (**1**). This easily prepared tartaric acid-based reagent combines a Lewis acid with carboxylic acids in a single bifunctional reagent. When combined with $NaBH_4$, the resulting chiral acyloxyborohydride mediates the reduction of aromatic ketones to provide the product alcohols in enantiomeric excesses of 93–98%. Several aliphatic ketones were also reduced with moderate to excellent enantioselectivity. A unique mechanism is provided with supporting calculations for the proposed active species and transition state.

Introduction

Asymmetric reduction of prochiral ketones often provides the most efficient route to optically active secondary alcohols. A number of boron-based reagents have been developed for this transformation. These include both borane-modified catalysts, such as CBS catalyst[1] and numerous chirally modified borohydride reducing agents.[2] Among borohydride reagents, those obtained through modification of mild and inexpensive sodium borohydride ($NaBH_4$) are of particular interest.[3] Over the past few decades, chirally modified $NaBH_4$ has been used for the asymmetric reduction of ketones with varying degrees of success under a wide range of experimental conditions. Early work involved chiral modification of $NaBH_4$ with phase-transfer catalysts,[4] monosaccharide derivatives,[5,6,7] amino alcohols,[8,9,10] and amino acids.[11,12] Several researchers found that both reaction rate and chiral induction improved when Lewis acids, such as salts of zinc or zirconium, were included in the reaction mixture.[5,7,–10] These systems often provided low conversions with low to moderate enantioselectivities for the reduction of prochiral ketones. More recently, Mukaiyama has developed a catalytic system utilizing alcohol-modified $NaBH_4$ combined with a catalytic amount of a chiral β-ketoiminato cobalt(II) complex to provide high *ee* values for the reduction of a number of prochiral ketones and imines at reduced temperatures.[13–15] Interestingly, while the use of $NaBH_4$ with achiral carboxylic acids is well established as an efficient achiral reducing system, the application of chiral carboxylic acids with $NaBH_4$ for the asymetric reduction of ketones has not been thoroughly investigated.

Sodium borohydride has been used with carboxylic acids to carry out a wide range of reductions of nitrogen- and oxygen-based functionalities.[16,17] Borohydrides and carboxylic acids combine to form acyloxyborohydrides, a robust reducing species that is described in the following section. The particular combination of $NaBH_4$ and acetic acid, well-known as Gribble conditions, is commonly used to effect non-enantioselective reductions of ketones and imines. For the enantioselective reduction of ketones, Hirao[18,19] and Morrison[20] utilized $NaBH_4$ with achiral carboxylic acids and chiral sugar derivatives to obtain *ee* values as high as 64%. The use of $NaBH_4$ modified with optically active carboxylic acids was investigated by Nasipuri[21] and Bianchi[22] using mandelic and lactic acids, while Adams[23] and Yamazaki[24] utilized tartaric acid. Additional work by Yatagai[25,26] and Polyak[27] with tartaric acid-modified $NaBH_4$ gave moderate *ee* values for the reduction of some α- and β-substituted ketones, though enantioselectivities were lower for simple, unmodified ketones.

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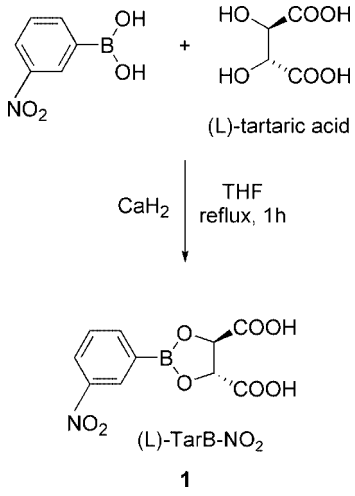
Previously, we reported the use of TarB-NO_2 (**1**), a tartaric acid-derived boronate ester, with lithium borohydride ($LiBH_4$) to provide high enantioselectivities for aryl ketone reduction.[28] Reagent **1** and other variously substituted tartaric acid-boronate esters are easily and quantitatively prepared by combining tartaric acid with the appropriately substituted arylboronic acid in refluxing THF in the presence of CaH_2 (Scheme 1). CaH_2 acts to remove water formed during esterification of the boronic acid and helps push the reaction to completion. A THF solution of the TarB-NO_2 reagent is obtained by filtering the reaction mixture to remove the calcium salts. Ketone reductions can then be caried out by using this TarB-NO_2 solution with lithium or sodium borohydride. Either enantiomer of the product alcohol can be obtained by appropriate choice of (L)- or (D)-tartaric acid for use in TarB-NO_2 preparation. Routine workup allows rapid separation of the product alcohol from TarB-NO_2 with an easy procedure for recovery of over 70% of the boronic acid. Other workers have since made use of the TarB-NO_2 reagent with $LiBH_4$ to complete difficult reduction steps.[29,30]



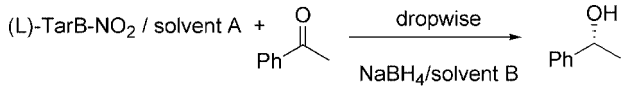
Scheme 1. Preparation of TarB-NO_2 reagent.

While $LiBH_4$ is quite effective when used with TarB-NO_2, it is considerably more expensive and difficult to handle than $NaBH_4$.[31] Here we report the successful extension of TarB-NO_2 chemistry to inexpensive $NaBH_4$ for the enantioselective reduction of aromatic and aliphatic ketones at room temperature through the intermediacy of a chiral sodium acyloxyborohydride active species. We describe solvent effects on enantioselectivity and conversion, and propose a mechanism with supporting calculations.

Results and Discussion

As part of our studies of TarB-NO_2-mediated reactions, we decided to investigate the use of $NaBH_4$ with reagent **1** for asymmetric reduction of ketones under both homo- and heterogeneous conditions. The reducing efficiency of modified and unmodified $NaBH_4$ is known to vary widely depending on the solvent and the degree to which the reducing agent is dissolved. Initially, we experimented with homogeneous reducing systems in which the unmodified $NaBH_4$ is entirely dissolved. Because TarB-NO_2 and its derivatives are sensitive to ester hydrolysis by polar hydroxylic solvents, our homogeneous reaction system was limited to less polar aprotic solvents. We investigated the use of the solvents *N*-methylpyrrolidone (NMP), diglyme (DG), and tetraglyme (TG) to prepare homogeneous $NaBH_4$ solutions that were added dropwise to the ketone/TarB-NO_2 mixture. Of these solvents, highest *ee* values were obtained using a $NaBH_4$/DG solution added dropwise to a premixed solution of the ketone substrate and reagent **1** in THF (Entry 3, Table 1).

Table 1. Effects of solvents on enantioselectivities in the reduction of acetophenone with (L)-TarB-NO_2 and $NaBH_4$ under homogeneous conditions.[a]



Entry	Solvent A	Solvent B	% *ee*[b]
1	NMP	NMP	0
2	THF	THF/NMP (3:1)	92
3	THF	Diglyme	97
4	Diglyme	Diglyme	88
5	Tetraglyme	Tetraglyme	78

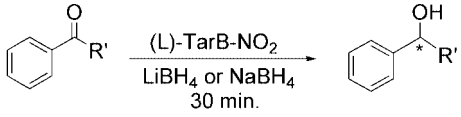
[a] Overall ratio of Solvent A to Solvent B was 1:1. Reactions carried out by dropwise addition of $NaBH_4$/solvent B solution to ketone/TarB-NO_2 solution in solvent A at room temperature. A ketone/TarB-NO_2/$NaBH_4$ ratio of 1:2:2 was used except for the reaction in tetraglyme where a 1:2:1 ratio was used. [b] Determined by GC analysis with a Supelco BetaDex 120 column. All reactions gave 100% conversion to according to the GC.

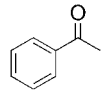
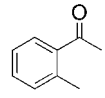
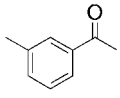
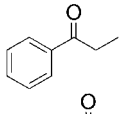
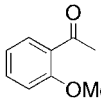
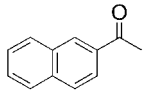
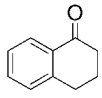
Attempts to use diglyme as the solvent for both the borohydride and ketone solutions resulted in lower *ee* (Entry 4). While NMP was useful for solubilizing $NaBH_4$, we observed complete conversion of the ketone to the racemic alcohol with some reduction of the pyrrolidone solvent to a pyrrolidine (Entry 1). ^{11}B NMR analysis of a mixture of $NaBH_4$, TarB-NO_2 and NMP showed formation of a BH_3:NMP adduct which we speculate to function as an achiral reducing species.[32] NMP was found to work smoothly, however, when used with 3 parts THF to prepare a homogeneous $NaBH_4$ solution that could then be added to the ketone substrate and TarB-NO_2 in THF (Entry 2). While affording good enantioselectivity, the use of both NMP and DG required lengthy extractions to separate the product alcohols from these high-boiling solvents.

Our survey of the literature found several indications that the use of $NaBH_4$ under heterogeneous conditions in solvents such as benzene, toluene, and THF could improve the enantioselectivities.[7,12,22,33] An explanation lies in the solubility of the active reducing species. In a homogeneous

system, both chirally modified and unmodified achiral sodium borohydride may compete for the ketone substrate. In solvents such as THF, however, only the chirally modified borohydride is soluble, thus limiting achiral reduction by unmodified borohydride. Based on this speculation, we used a heterogeneous suspension of $NaBH_4$/THF. In our optimized procedure, we added 2 equiv. of $NaBH_4$ in a single portion to a 1:2 ketone/TarB-NO_2 solution in THF under nitrogen at 25 °C. Addition of the $NaBH_4$ causes a rapid evolution of hydrogen gas which subsides after approximately fifteen minutes. The reaction is complete in less than 30 minutes and the product alcohol is obtained in very high enantiomeric excess and with 100% conversion. We found that this procedure is more convenient than using NMP or DG and compares very favorably with a homogeneous $LiBH_4$/THF system (Table 2).

Table 2. Enantioselectivities for reductions of aromatic ketones with (L)-TarB-NO_2. All products were of the (*R*) configuration as determined by optical rotation. All *ee* values were determined by GC analysis with a Chiral BetaDex 120 column. All reactions gave 100% conversion to the alcohol according to GC.

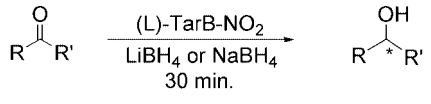


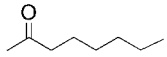
Ketone	$LiBH_4$-THF homogenous	$NaBH_4$-Diglyme homogenous	$NaBH_4$-THF heterogeneous (yield)[a]
	99	97	98 (90)
	96	95	97 (85)
	88	97	98 (79)
	85	90	93 (76)
	78	64	95 (65)
	99	96	98 (93)
	94	78	97 (84)

[a] Isolated yields.

We also experimented with the TarB-NO_2 system and aliphatic substrates. Aliphatic ketones, especially unhindered, straight-chain ketones such as 2-octanone, are notoriously difficult to reduce with high induction. Using the same conditions reported for our reductions of aromatic ketones, we were able to obtain good results for the asymmetric reduction of several aliphatic ketones. These results compare favorably with similar results reported by other groups for the asymmetric reduction of aliphatic ketones (Table 3).

Table 3. Enantioselectivities for reductions of aliphatic ketones with (L)-TarB-NO_2. All *ee* values and conversions were determined by GC analysis with a Chiral BetaDex 120 column.

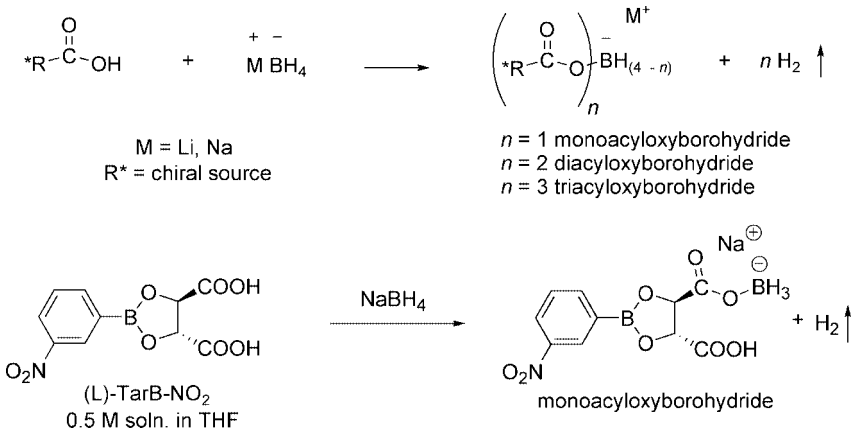


Ketone	$LiBH_4$-THF homogeneous (conversion)	$NaBH_4$-THF heterogeneous (conversion)
	87 (>99)	95 (>99)
	84 (98)	94 (98)
	60 (>99)	62 (>99)

The relatively hindered dimethylcyclopentanone and pinacolone substrates were both reduced with excellent enantioselectivity, while lower, though moderate optical induction was obtained for the reduction of unhindered 2-octanone. As with the aromatic substrates, we observed that the heterogeneous $NaBH_4$ system provided superior results to those obtained using a homogeneous $LiBH_4$ system.

Interestingly, the difference in solubility in THF between $NaBH_4$ and $LiBH_4$ may explain the superior results obtained with $NaBH_4$. Unmodified and achiral $LiBH_4$ is highly soluble in THF and may reduce the ketone achirally before it reacts with TarB-NO_2 to form the chiral acyloxyborohydride. On the other hand, unmodified and achiral $NaBH_4$ is essentially insoluble and, so, will not appreciably reduce the ketone until it is brought into solution through reaction with the TarB-NO_2 reagent to produce the soluble, chiral, and highly reactive acyloxyborohydride.

Based on ^{11}B NMR and hydrogen evolution experiments, the active reducing species responsible for the asymmetric reduction in our system appears to be a chiral acyloxyborohydride. We have also observed indications of acyloxyborohydride formation when using TarB-X reagents with $LiBH_4$.[34] Combination of borohydride reagents with carboxylic acids is known to provide variously substituted acyloxyborohydride species with concomitant production of hydrogen gas (Scheme 2).[16,17,34,35,36] The identity of the dominant acyloxyborohydride reducing species depends largely on the molar ratio between carboxylic acid and the borohydride, though exact determination of the dominant species is difficult.[16,17,37–39] Generally, triacyloxyborohydrides are the most easily prepared and characterized, though other stable mono-[37,38] and diacyloxyborohy-

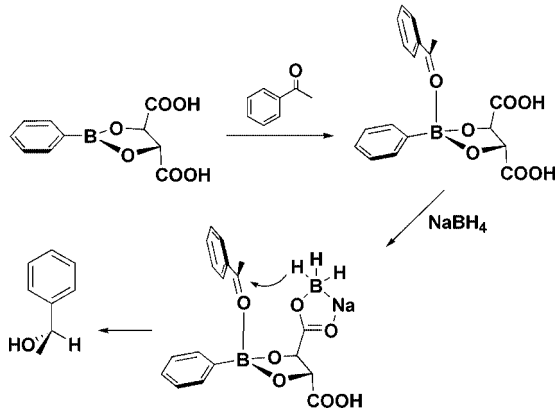


Scheme 2. Generation of a generic acyloxyborohydride and (L)-TarB-NO_2 monoacyloxyborohydride.

dride[39] species have been reported. In our procedure, TarB-NO_2 and $NaBH_4$ are used in equimolar amounts, which would tend to favor the formation of a single monoacyloxyborohydride moiety per TarB-NO_2 molecule (Scheme 2). The dominance of the monoacyloxyborohydride is consistent with both ^{11}B NMR spectroscopic data from $LiBH_4$ and $NaBH_4$ titration experiments, and with our observation that approximately 1 equiv. of H_2 gas is liberated in the first ten minutes after addition of equimolar amounts of TarB-NO_2 and $NaBH_4$.[34]

Most often prepared and used in situ, acyloxyborohydrides are known to facilitate numerous transformations of oxygen- and nitrogen-containing functionalities in high yield, though their deliberate employment in conjunction with Lewis acids for asymmetric synthesis has been limited. When used with borohydrides, TarB-NO_2 (**1**) and related reagents can combine the reducing efficiency of acyloxyborohydride species with the coordinating ability of chiral boron-Lewis acids to provide for the highly enantioselective reduction of ketones to secondary alcohols. We speculate that the carbonyl oxygen of the prochiral ketone substrate coordinates to the boron of the TarB-X reagent, thus preferentially presenting one face of the ketone for attack by an acyloxyborohydride moiety. Our proposed mechanism is given in Scheme 3.

The reduction of ketone substrates with borohydride reagents occurs much more rapidly in the presence of carboxylic acids such as TarB-NO_2 than without. In fact, while TarB-NO_2 mediated reduction of acetophenone is complete in less than thirty minutes, the same reduction using only $NaBH_4$ in THF is only 10% complete after a half-hour and even after a full day the conversion only reaches 45%. These differences indicate that there is a considerably lower activation energy for the TarB-NO_2 acyloxyborohydride-mediated reduction. To better understand the implications of the proposed mechanism and to investigate the differences in activation energy, a series of computational studies were carried out. As a computational model for the reaction of TarB-NO_2 with acetophenone, we examined the reaction of 1,3,2-dioxoborolane-4-carboxylic acid with formaldehyde (Figure 1).[40] With regard to initial complex formation, the proximal complex shown in Figure 1 in which the carbonyl carbon of formaldehyde is closer to the carboxyl group was calculated to be more stable than the distal complex (carbonyl carbon oriented away from carboxyl) by 0.95 kcal/mol (B3LYP/6-31G*//B3LYP/6-31G*). Formation of the more stable proximal formaldehyde complex with the TarB-NO_2 analog was calculated to be exothermic by 6.6 (HF/6-31G*//MP2/6-31G*) and 4.7 (HF/6-31G*//B3LYP/6-31G*) kcal/mol.



Scheme 3. Proposed mechanism for reduction of acetophenone by TarB-NO_2.

Addition of sodium borohydride results in loss of hydrogen and the formation of a sodium complex (see Figure 2). Here, the proximal acyloxyborohydride/formaldehyde is calculated to be more stable than distal by 2.1 kcal/mol (HF/6-31G*//MP2/6-31G*) and 1.4 kcal/mol (HF/6-31G*//B3LYP/6-31G*).

Three transition states (two proximal, one distal) corresponding to the delivery of hydrogen from boron to the carbonyl carbon were characterized. We found one transition state (proximal) to be lower in energy than the other two by more than 18 kcal/mol; its structure is shown in Figure 2. In this favored transition state, the sodium has migrated away from the BH_3 boron (4.07 Å), toward the dioxoborolane boron (3.12 Å), and is coordinated with the carbonyl oxygen (2.13 Å), a dioxoborolane oxygen (2.51 Å),

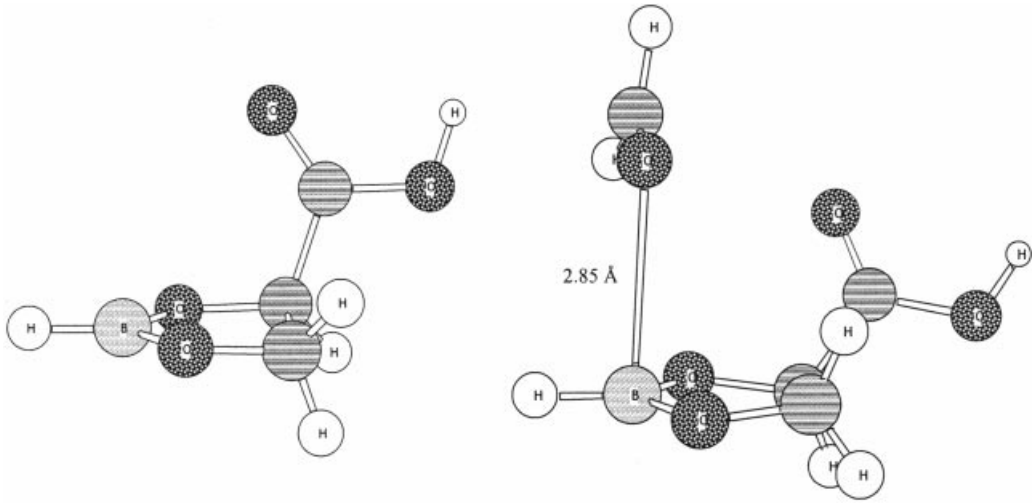


Figure 1. 1,3,2-Dioxoborolane-4-carboxylic acid and proximal formaldehyde complex (HF/6-31G*). Unlabelled atoms represent carbon.

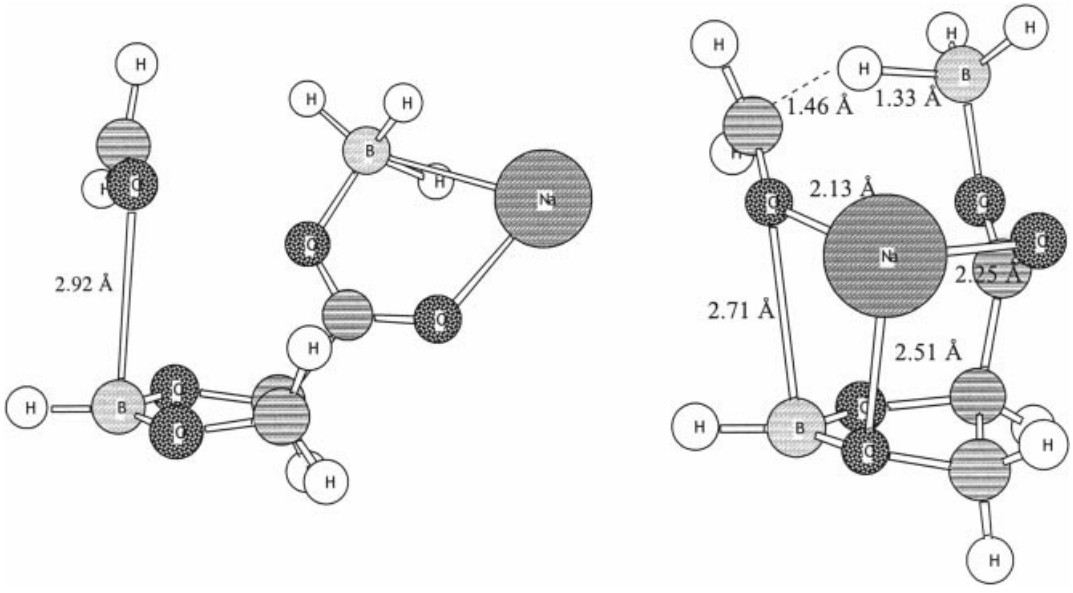


Figure 2. Sodium complex and the proximal transition state (HF/6-31G*). Unlabelled atoms represent carbon.

and a carboxylate oxygen (2.25 Å). By contrast, in the higher energy transition states the sodium is associated with the two carboxylate oxygen atoms and the BH_3 boron. Proximity of the sodium ion with three oxygen atoms appears to be the key feature in stabilization of the favored transition state. At the transition state, the forming C–H bond length is 1.46 Å, and the breaking B–H bond length is 1.33 Å, compared to a B–H length of 1.24 Å in the initial complex. The electron density surface shows that the B–H bond has greater electron density than the C–H bond, indicating that this is an early transition state.[41] The activation energy for this process is calculated at 5.7 kcal/mol (HF/6-31G*//MP2/6-31G*) and 1.7 kcal/mol (HF/6-31G*//B3LYP/6-31G*). For comparison, the corresponding value calculated for the reaction of formaldehyde with lithium aluminum hydride is 2.1 kcal/mol (B3LYP/6-31G**//B3LYP/6-31G**).[42] Normal mode vibration analysis for each of the transition states shows a vibration corresponding to the shortening of the C–H bond, and corresponding lengthening of the B–H bond, as would be expected for transfer of H from B to C.

It is interesting to compare the activation energies for the above reaction to the direct combination of formaldehyde and sodium borohydride in the absence of the TarB-NO_2 analog. For the direct combination of formaldehyde with $NaBH_4$ the transition state occurs much later on the reaction coordinate with C–H and B–H bond lengths of 1.1 Å and 2.2 Å respectively. The activation energy calculated at different levels of theory for this is 26.4 kcal/mol (HF/6-31G*//MP2/6-31G*), 24.8 kcal/mol (HF/6-31G*//B3LYP/6-31G*), and 25.0 kcal/mol (B3LYP/6-31G*//B3LYP/6-31G*). These values do not take into account the effect of solvent, which Eisenstein and co-workers have shown can dramatically lower the calculated activation energy.[43] For

comparison, the experimental activation energy for the reduction of acetone by sodium borohydride in water is 7.6 ± 0.5 kcal/mol.[44] We conclude from these calculations that TarB-NO_2 dramatically lowers the activation energy for reduction of ketones with borohydride reagents and provides a pathway for the hydride to be delivered in a stereoselective manner.

This reduction process appears to be analogous to reactions involving enzymes, in the sense that the TarB-NO_2 analog provides a complex with the substrate in which there is a lower energy reduction pathway than in the absence of the TarB-NO_2 analog. While our model formaldehyde substrate is not prochiral, it follows from the calculations and from observed data that the TarB-NO_2 molecule is capable of forming an analogous structure with prochiral substrates thus providing a pathway to deliver hydride enantioselectively. From the calculated data, it appears that both proximal and distal complexes can form rapidly and reversibly, but that only the proximal complex leads to the favored transition state. The special stabilization of this transition state comes from the ability of the sodium ion to coordinate with three oxygen atoms.

Conclusions

Aromatic ketones can be reduced quantitatively and with a high degree of enantioselectivity using TarB-NO_2 and borohydride reducing agents. Significantly, inexpensive $NaBH_4$ can be used to provide results that are often superior to those obtained using $LiBH_4$. The reduction appears to operate through an acyloxyborohydride intermediate and we were able to obtain computational support for both the intermediate and an analogous transition state structure. Studies are in progress to expand the scope of reactions promoted by this inexpensive, convenient, and easily prepared TarB-X reagent. The concept of preparing chiral acyloxyborohydrides from borohydrides and chiral bifunctional reagents possessing both Lewis and carboxylic acids may well provide a new approach to asymmetric synthetic methodology.

Experimental Section

General: All reactions and transfers conducted in oven- or flame-dried glassware under inert atmosphere using air-sensitive techniques. All ketones purchased from Aldrich and used without purification. 3-nitrophenylboronic acid, CaH_2, and tartaric acid purchased from Acros and used without purification. THF was distilled from Na benzophenone ketyl under nitrogen and stored in a sealed ampoule before use. ^{1}H NMR and ^{13}C NMR spectra were acquired with a Varian 500 spectrometer using [D_8]THF (internal reference at δ = 1.73 ppm for ^{1}H NMR and 25.4 for ^{13}C NMR). ^{11}B NMR spectra were acquired using a Bruker 250 spectrometer (BF_3–Et_2O external reference at 0 ppm). Configurations determined using a Jasco DIP-370 polarimeter at 25 °C. Gas chromatography analysis was performed with a Supelco Beta Dex 120 chiral column. Racemic products were prepared to verify retention times in the gas chromatographic determination of enantiomeric excesses. Identities of alcohol products were confirmed using ^{1}H NMR spectroscopy.

Preparation of (L)-TarB-NO_2: A 500-mL round-bottomed flask with sidearm and stir bar was oven-dried, cooled under nitrogen and charged with 3-nitrophenylboronic acid (20.04 g, 120 mmol), (L)-tartaric acid (18.00 g, 120 mmol) and CaH_2 (10.30 g, 24.5 mmol), sealed with a septum and fitted with a reflux condenser. Dry THF (240 mL) was added through the sidearm and the system was refluxed for 1 hour followed by cooling. The suspension was cannulated from the sealed reaction vessel to a sealed medium frit filter under inert atmosphere to remove calcium salts. The clear, yellow-brown solution was directly collected in an attached, dry flask then transferred via cannula to a dry ampoule as a 0.5 M solution in THF. ^{1}H NMR indicates that the yield is >98%. TarB-NO_2 solutions were stored in sealed ampoules at room temperature and kept away from light. These stock solutions are stable for as long as one year. (***Note:*** TarB-X reagents are moisture-sensitive. Air-sensitive techniques and dry glassware should be used in their preparation and application.)

Representative Isolation Scale Procedure: A 200-mL round-bottomed flask was flame-dried, cooled under N_2, then charged with acetophenone (1.16 mL, 10 mmol) and TarB-NO_2 (40 mL of a 0.5 M solution in THF, 20 mmol) and stirred for ten minutes. $NaBH_4$ (0.755 g, 20 mmol), was then added in a single portion to the ketone/TarB-NO_2 solution causing rapid gas evolution. The reaction was left to stir for 30 min and then slowly quenched with 3 M HCl until gas evolution was no longer observed. The mixture was brought to pH 12 with 3 M NaOH and extracted with diethyl ether (3 × 50 mL). The combined ether extracts were washed with DI H_2O (2 × 50 mL) and dried with $MgSO_4$. GC analysis with a Supelco Beta-Dex 120 column revealed 100% conversion and 98% *ee* of (*R*)-1-phenylethanol. After solvent removal, the crude alcohol product was distilled under reduced pressure (60 °C, ca. 5 Torr) to afford the pure product alcohol in 90% yield. The boronic acid was recovered by acidification of the aqueous layer with 12 M HCl followed by chilling the solution at 4 °C. The boronic acid precipitate was filtered and washed with pentane (2.40 g, 71% recovery).

Computational Methods: Geometries of reactants, complexes, and transition-state structures were optimized using ab initio molecular orbital theory employing the Hartree–Fock 6-31G* basis set. All transition states were characterized by having only one imaginary frequency. Calculations were carried out using the Spartan′02 electronic structure program. Electron correlation is accounted for by evaluating second-order Møller–Plesset and Becke 3LYP density functional energies[45] for the HF/6-31G* geometries.

Supporting Information Available (for details see footnote on the first page of this article): Synthetic preparation and ^{1}H, ^{13}C, and ^{11}B NMR spectra for (L)-TarB-NO_2. Analytical scale procedures. Procedure and ^{11}B NMR spectra from titrations of $NaBH_4$ with TarB-NO_2. ^{11}B NMR spectra from reaction in NMP solvent. Procedure for hydrogen evolution experiments. Details of computational experiments and Figure of transition state electron density surface.

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