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Asymmetric reductions using the chiral boronic ester TarB–H: a practical and inexpensive procedure for synthesizing chiral alcohols

Scott Eagon, Jinsoo Kim, Katie Yan, Dustin Haddenham and Bakthan Singaram*

Department of Chemistry and Biochemistry, University of California, Santa Cruz, 1156 High Street, Santa Cruz, CA 95064, USA

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Abstract—Chiral alcohols are prepared in high enantiomeric excesses using an inexpensive and easily synthesized tartaric acid derived boronic ester (TarB–H) with sodium borohydride. The phenylboronic acid could be recovered quantitatively using a simple extraction with sodium hydroxide and diethyl ether. The optimized TarB–H system was used to reduce aromatic and aliphatic ketones in an open flask to chiral alcohols with enantiomeric excesses up to 99%.

The reduction of ketones to optically active secondary alcohols is a powerful technique in the synthesis of optically pure compounds.[1] A number of boron-derived reducing agents and catalysts, such as CBS,[2] other oxazaborolidine reagents,[3–5] and DIP-Cl® have proven adept at reducing aromatic ketones. Both oxazaborolidine-based reagents and DIP-Cl®[6] use BH3:L, which in turn is prepared from $NaBH_4$. Consequently, asymmetric reductions involving the direct use of $NaBH_4$ are more desirable. Sodium borohydride has been used with various other mediators to reduce ketones to chiral alcohols. Modifications of $NaBH_4$ to chiral reducing reagents have been prepared using amino acids,[7,8] monosaccharides,[9–11] and phase transfer catalysts[12] for the reduction of aromatic and hindered ketones. Mukaiyama et al. developed a catalyst using alcohol-modified $NaBH_4$ and a chiral β-ketoiminato cobalt(II) complex to reduce ketones and imines with good enantiomeric excess.[13–15] Sodium borohydride modified carboxylic acid systems using chiral sugars and achiral carboxylic acids have enantioselectively reduced ketones to chiral alcohols with ee's up to 64%.[16–18] Chiral carboxylic acid systems have also been developed to reduce ketones with $NaBH_4$ using mandelic, lactic, and tartaric acid.[19–25]

We have recently reported that the tartaric acid-derived reagent TarB–X mediates the asymmetric reduction of various aliphatic and aromatic ketones using $LiBH_4$.[26,27] Since $LiBH_4$ is soluble in THF, the hydride could either complex with the TarB–X reagent and give chiral reduction, or react directly with the ketone to give achiral reduction. Initial screening during these reductions revealed that TarB–NO_2 was the best mediator for asymmetric induction when used in conjunction with $LiBH_4$. We later substituted $LiBH_4$ with $NaBH_4$ and found that it was able to give higher induction. This is due to the fact that only the acyloxyborohydride, which is formed by the complexing of carboxylic acid with $NaBH_4$, is soluble in THF and thus chiral reduction is favored.[28] TarB–NO_2 was able to reduce various ketones under mild conditions; however, *meta*-nitro phenylboronic acid is relatively more expensive than phenyl boronic acid and reductions using TarB–NO_2 require a dry and inert atmosphere to maintain high enantioselectivities.[29] We decided to investigate how different substituents on the phenylboronic acid would affect the asymmetric induction observed using $NaBH_4$ as our hydride source. In this paper we report our TarB–X optimization studies for the asymmetric reduction of ketones using $NaBH_4$ and the first examples of successful asymmetric reduction of ketones without the rigorous exclusion of air and moisture.

TarB–X (**1**) is easily prepared by combining the desired isomer of tartaric acid with the substituted phenylboronic acid in refluxing THF over CaH_2 for 1 h

Keywords: Asymmetric reduction; Sodium borohydride; Acyloxyborohydride; TarB–X.
* Corresponding author. Tel.: +1 831 459 3154; fax: +1 831 459 2935; e-mail: Singaram@chemistry.ucsc.edu

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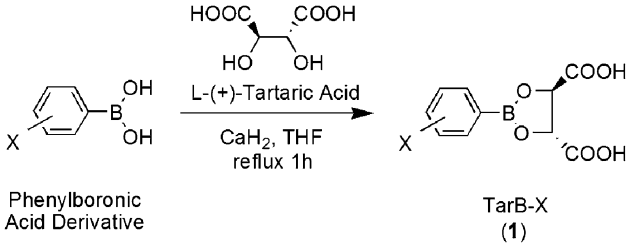


Scheme 1. Synthesis of (L)—TarB–X.

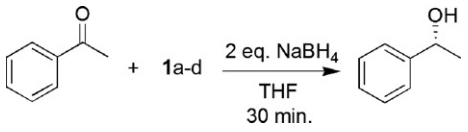
(Scheme 1). The solution is then filtered and stored as a molar solution in an ampoule.

Reduction is carried out by premixing 1 equiv of TarB–X with a ketone for 15 min, followed by addition of 2 equiv of $NaBH_4$, which is stirred for 1 h. Computer modeling supports prior ^{11}B NMR data that reduction proceeds via a chiral acyloxyborohydride intermediate species (**2**), which is formed when $NaBH_4$ reacts with the carboxylic acid moiety of TarB–X (Scheme 2).[30]

Initially we selected various substituted arylboronic acids, including the parent phenylboronic acid and L-(+)-tartaric acid, and synthesized several TarB–X derivatives. We then used these TarB–X compounds in the asymmetric reduction of acetophenone using $NaBH_4$ as our hydride source. For this study we used ketone/TarB–X/$NaBH_4$ in a 1:1:2 ratio. The reaction was carried out at 25 °C under argon and the enantiomeric excess of the product alcohol was determined by chiral GC analysis. The results are summarized in Table 1.

As anticipated, TarB–NO_2 mediated reduction gave superior results, with TarB–Cl also giving comparable induction. We decided to investigate whether TarB–NO_2 mediated reductions using $NaBH_4$ could maintain high enantioselectivity in air. Sodium borohydride is known to be very stable to hydrolysis and oxidation. However, it was not clear whether TarB–X reagents are resistant to hydrolysis. Most boron-derived reducing agents are extremely water sensitive and must be used under an inert and dry atmosphere. For example, when using the CBS catalyst Fu et al. reported that an increase in water concentration from as little as 0.02% to 0.3% led to a 25% decrease in enantioselection.[31] Similarly, DIP-Cl® is also highly susceptible to hydrolysis.[32] To investigate the possibility of using TarB–X without a

Table 1. Enantioselective reduction of acetophenone as a function of phenylboronic acid under inert atmosphere[a]



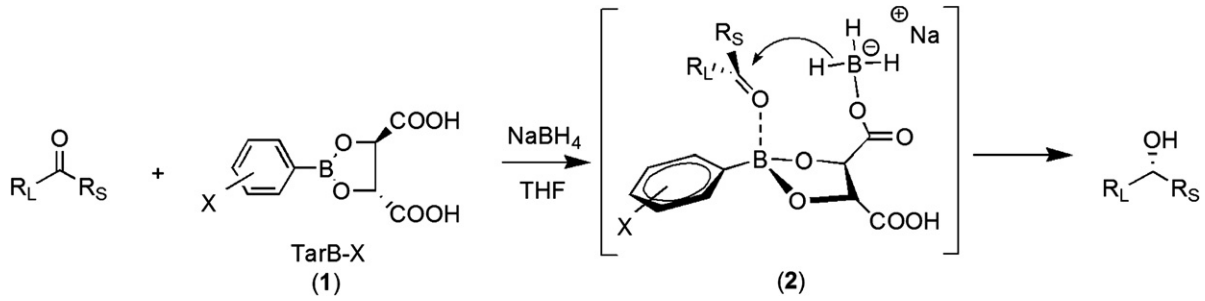
1	X	% conv.[b]	% ee[b,c]
a	3-NO_2	100	99
b	H	100	85
c	4-F	91	90
d	4-Cl	100	99

[a] See Supplementary data for experimental procedure.
[b] Determined by GC analysis of the acetylated alcohols on a chiral Supelco Beta-Dex 120 column.
[c] Products were of the (*R*) configuration as determined by optical rotation.

dry and inert atmosphere, we first examined the stoichiometry of TarB–NO_2 and found that 1 and 1.5 equiv of TarB–NO_2 gave lower induction under these conditions. We attribute this decrease in asymmetric induction to the hydrolysis of TarB–NO_2 by adventitious water. This is evidenced by the appearance of the methine proton of free tartaric acid in the ^1H NMR spectrum. This was circumvented by using 2 equiv of TarB–NO_2. To determine if other phenylboronic acids would be effective under these conditions, we conducted a second substituent study using the ketone/TarB–X/$NaBH_4$ in a 1:2:2 ratio and were pleased to find that TarB–H gave excellent asymmetric induction equal to those observed with TarB–NO_2 and TarB–Cl (Table 2).

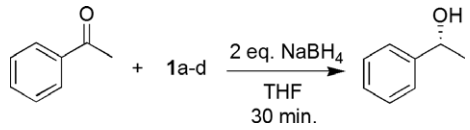
Since phenylboronic acid is significantly less expensive[33] than the substituted phenylboronic acids we decided to employ TarB–H, prepared from phenylboronic acid, in the reduction of representative aromatic ketones in air using $NaBH_4$ as the hydride source.[34] The results are summarized in Table 3.

The results were excellent with most substrates giving greater than 95% ee except in the case of *o*-bromoacetophenone and propiophenone. We then attempted the reduction of alpha-haloacetophenones using TarB–H in air. These substrates, after reduction and a basic workup, provided chiral styrene oxides. However, the enantiomeric excess of the product epoxide was only around 50–60%. We then found that 2 equiv of TarB–Cl (**1d**) in air gave good results comparable to our



Scheme 2. Asymmetric reduction of a prochiral ketone via the proposed acyloxyborohydride intermediate.

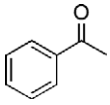
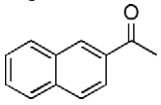
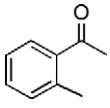
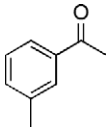
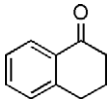
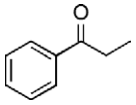
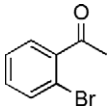
Table 2. Enantioselective reduction of acetophenone as a function of phenylboronic acid and amount of TarB–X[a]



1	X	equiv TarB–X	% conv.[b]	% ee[b,c]
a	3-NO_2	1	95	88
a	3-NO_2	1.5	100	90
a	3-NO_2	2	100	99
b	H	1	100	80
b	H	1.5	100	92
b	H	2	100	99
c	4-F	2	97	93
d	4-Cl	2	100	99

[a] Reactions carried out as described in Ref. 35.
[b] Determined by GC analysis of the acetylated alcohols on a chiral Supelco Beta-Dex 120 column.
[c] Products were of the (*R*) configuration as determined by optical rotation.

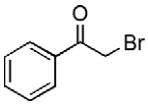
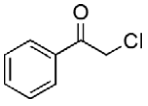
Table 3. Reduction of various aromatic ketones with TarB–H in air[a]

Ketone	Isolated yield[b] (%)	% ee[c]	Config.[d]
	83	99	(*R*)
	80	99	(*R*)
	90	96	(*R*)
	81	95	(*R*)
	97	95	(*R*)
	80	86	(*R*)
	86	64	(*R*)

[a] Reactions carried out as described in Ref. 35.
[b] All reactions gave 100% conversion to alcohol according to GC and NMR.
[c] Determined by GC analysis of the acetylated alcohols on a Supelco Beta-Dex 120 column.
[d] Determined by optical rotation in comparison to the literature values. See Supplementary data.

previous results obtained using TarB–NO_2 under dry and inert conditions (Table 4).[27]

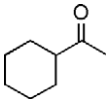
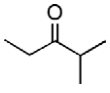
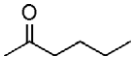
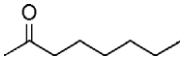
Table 4. Reduction of α-haloacetophenones in air with TarB–Cl[a]

Ketone	Isolated yield[b]	% ee[c]	Config.[d]
	98	86	(*S*)
	82	80	(*S*)

[a] Reactions carried out as described in Ref. 35.
[b] All reactions gave 100% conversion to alcohol according to GC and NMR.
[c] Determined by GC analysis of the epoxides on a Supelco Beta-Dex 120 column.
[d] Determined by optical rotation in comparison to the literature values. See Supplementary data.

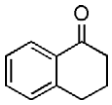
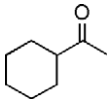
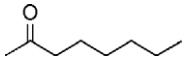
With our copasetic results from the reduction of aromatic ketones, we turned to the reduction of aliphatic ketones using TarB–H. The *tert*-alkyl ketones all gave excellent results, with good to moderate results for *sec*-alkyl and *n*-alkyl ketones (Table 5).

Table 5. Reduction of various aliphatic ketones in air with TarB–H[a]

Ketone	Isolated yield[b] (%)	% ee[c]	Config.[d]
	80	99	(*R*)
	89	96	(*R*)
	88	89	(*R*)
	92	88	(*R*)
	89	85	(*R*)
	68	67	(*R*)
	99	61	(*R*)
	85	61	(*R*)

[a] Reactions carried out as described in Ref. 35.
[b] All reactions gave 100% conversion to alcohol according to GC and NMR.
[c] Determined by GC analysis of the acetylated alcohols on a Supelco Beta-Dex 120 column.
[d] Determined by optical rotation in comparison to the literature values. See Supplementary data.

Table 6. Comparison of TarB–H with DIP-Cl® and CBS

Ketone	% ee		
	CBS[a]	DIP-Cl®[b]	TarB–H
	86	—	95
	98	95	96
	92	98	99
	91	32	89
	84	26	88
	—	6	61

[a] See Ref. 2.
[b] See Refs. 3 and 6.

In comparison to DIP-Cl® and the CBS catalyst, TarB–H performed very well. Table 6 compares the three reagents in the reduction of select ketones. TarB–H achieved parity with the other two reagents with *tert*-alkyl ketones and equal or better results with *sec*-alkyl and *n*-alkyl ketones. It should also be pointed out that only TarB–H mediated asymmetric reduction can be carried out in an inert atmosphere without the rigorous exclusion of water.

TarB–H provides good to excellent asymmetric reduction under mild conditions, making it very attractive for large scale synthesis. TarB–H mediated reductions proceed smoothly in air without the need for rigorous drying of the reagents or an inert atmosphere like DIP-Cl® or the CBS catalyst. It is easily prepared using either enantiomer tartaric acid, both of which are commercially available and inexpensive. TarB–H can also reduce ketones using $NaBH_4$ instead of more reactive BH_3:L species derived from $NaBH_4$. Additionally, phenylboronic acid can easily be recovered essentially quantitatively and recycled using a simple ethereal extraction. Its ease of preparation and mild reaction conditions make TarB–H/$NaBH_4$ an excellent asymmetric reducing system for both academic and industrial endeavors.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.075.

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33. Phenylboronic acid costs approximately \$430/mol, 4-fluorophenylboronic acid \$1400/mol, 4-chlorophenylboronic acid \$1,500/mol, and 3-nitrophenylboronic acid \$1600/mol.
34. On a small scale this reaction can be run in an open flask in a well-ventilated fume hood to prevent buildup of H_2 gas.
35. *General procedure for the reduction of ketones with TarB–H in air. The reduction of acetophenone is representative.* A 100 mL oven dried round-bottomed flask was equipped with a stir bar and a septum and allowed to cool to ambient temperature in air. A bubbler was connected to the flask, which was then subsequently charged with the acetophenone (0.58 mL, 5 mmol) and TarB–H (20 mL of a 0.5 M solution in THF, 10 mmol). The ketone and TarB–H were stirred for 15 min. after which $NaBH_4$ (0.38 g, 10 mmol) was added directly to the solution. The mixture was allowed to stir for 1 h. The solution was quenched dropwise with 1 M HCl. CAUTION: H_2 gas evolution. The mixture was brought to pH 12 with 3 M NaOH and stirred for 30 min. The solution was extracted with pentane (3×10 mL) and the combined organic layers were dried with $MgSO_4$. Evaporation under reduced pressure yielded the product alcohol. The enantiomeric excess of the acetylated alcohol was determined by GC on a Supelco β-cyclodextrin 120 column ($30\ m \times 0.25$ mm). For the α-haloacetophenone derivatives, the product epoxide was run without further modification through the GC.