Mild and Practical Reductions of Prochiral Ketones to Chiral Alcohols Using the Chiral Boronic Ester TarB-H

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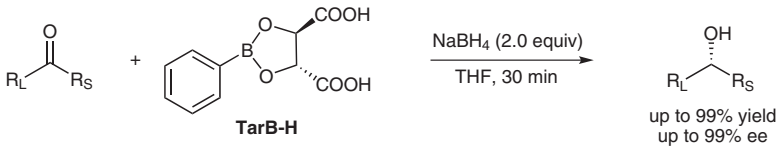
Abstract: Chiral alcohols are prepared under mild conditions in high enantiomeric excesses using the tartaric acid derived chiral boronic ester TarB-H. The phenylboronic acid was quantitatively recovered and recycled using a simple extraction with sodium hydroxide and diethyl ether. Aromatic and aliphatic secondary alcohols were prepared in up to 99% ee.

Key words: boron, reductions, asymmetric synthesis, chiral alcohols



Scheme 1 Reduction of prochiral ketones with TarB-H

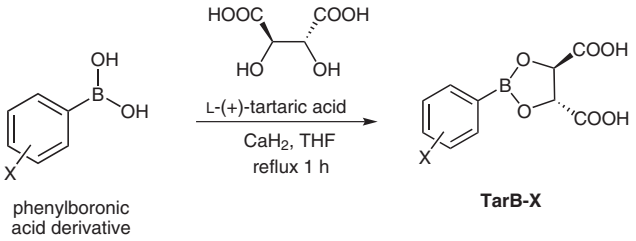
Chiral secondary alcohols are key intermediates in a large number of biologically active compounds.[1,2] A number of boron containing reducing agents such as CBS[3] and *B*-chlorodiisopinocampheylborane (DIP-Cl)[4] have been used to synthesize chiral alcohols in excellent yields and enantiomeric excesses. Both CBS and DIP-Cl use BH_3:L in stoichiometric amounts, which is in turn prepared from sodium borohydride. Consequently, direct reductions of ketones using sodium borohydride are more desirable.

We have reported that the tartaric acid derived reagent TarB-X mediates the asymmetric reduction of various ketones using lithium borohydride.[5] Since lithium borohydride is soluble in tetrahydrofuran , the hydride can give either achiral reduction in solution or complex with the TarB-X reagent and give chiral reduction. Initial screenings revealed that the *meta*-nitro derivative TarB-NO_2 gave the best results when used concomitantly with lithium borohydride. We later replaced lithium borohydride with sodium borohydride and found that it gave superior results. We concluded that this increase in induction was due to the fact that only the acyloxyborohydride, which is formed when sodium borohydride reacts with the carboxylic acid moiety of TarB-X, is soluble in tetrahydrofuran and thus direct reduction of the ketone in solution is minimized.[6,7] TarB-NO_2 proved adept in the reduction of various ketones at room temperature, but required a dry and inert atmosphere to maintain high enantioselectivities.

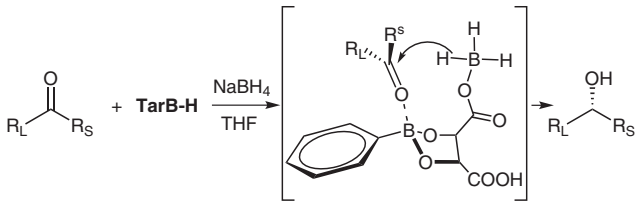
TarB-X is easily prepared by mixing the desired isomer of tartaric acid with the phenylboronic acid in refluxing tetrahydrofuran over calcium hydride for one hour (Scheme 2). The solution is filtered through a fritted filter and stored as a molar solution in an ampoule.

Computer modeling and ^{11}B NMR data supports our theory that reduction proceeds via a chiral acyloxyborohydride intermediate species, which is formed when the carboxylic acid group on TarB-X reacts with sodium borohydride (Scheme 3).[7]

Most boron-derived reducing agents, including CBS and DIP-Cl, are extremely susceptible to hydrolysis and thus



Scheme 2 Synthesis of TarB-X



Scheme 3 Asymmetric reduction of a prochiral ketone via the proposed acyloxyborohydride intermediate

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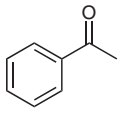
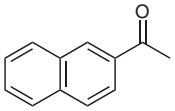
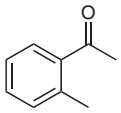
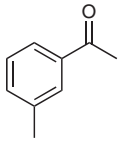
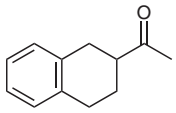
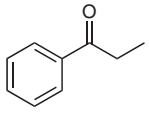
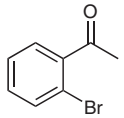
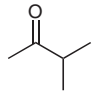
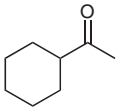
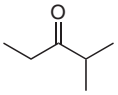
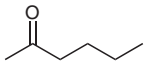
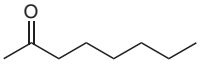
are usually used under an inert atmosphere.[8,9] In order to make the TarB-X system more amenable to large-scale synthesis, we conducted various experiments to find a derivative that could give the same results as TarB-NO_2 without the need for a dry and inert atmosphere.[10] Our results indicated that by using two equivalents of TarB-H we could achieve the same induction as TarB-NO_2 in a closed flask. Although we have to use a superstoichiometric amount of TarB-H, the parent phenylboronic acid can be easily recovered and recycled. Phenylboronic acid is also significantly less expensive than the 3-nitrophenylboronic acid used to synthesize TarB-NO_2.[11]

Using two equivalents of TarB-H and sodium borohyride in an open flask, we reduced a variety of aromatic and aliphatic ketones to chiral secondary alcohols at room temperature on a 5 mmol scale (Scheme 1, Table 1).[10]

Table 1 Reduction of Various Ketones with TarB-H in an Open Flask

Entry	Ketone	Yield[a] (%)	ee[b] (%)	Config[c]
1		83	99	*R*
2		80	99	*R*
3		90	96	*R*
4		81	95	*R*
5		97	95	*R*
6		80	86	*R*
7		86	64	*R*
8		80	99	*R*
9		89	96	*R*
10		88	89	*R*
11		92	88	*R*
12		89	85	*R*
13		68	67	*R*
14		99	61	*R*
15		85	61	*R*

[a] All reactions gave 100% conversion according to GC and NMR.
[b] Determined by GC analysis of the acetylated alcohols on a Supelco Beta-Dex 120 column.
[c] Determined by optical rotation values in comparison to the literature values.

Our results were excellent with aromatic ketones (entries 1–5), all of which we were able to reduce with greater than 95% ee excepting 2-bromoacetophenone and propiophenone (entries 6 and 7). Tertiary alkyl ketones all gave excellent results as well (entries 8 and 9), with good to moderate results for secondary and *n*-alkyl ketones (entries 10–15). In order to control the reactions at larger scales we cooled the reaction over ice water and entrained the evolving hydrogen gas through a bubbler to prevent buildup.

TarB-H is an extremely mild boron-based reducing agent that can be used to synthesize a variety of aromatic and aliphatic chiral secondary alcohols with exceptional enantiomeric excesses without the need for rigorous exclusion of water. TarB-H also used sodium borohydride as its hydride source instead of the more expensive and reactive BH_3:L species. Additionally, the phenylboronic acid used in the synthesis of TarB-H can be easily recovered and recycled for further use.

All alcohols obtained in Table 1 were characterized by GC, optical rotation, and ^1H and ^{13}C NMR.[10]

(*R*)-1-Phenylethanol; Gram-Scale Synthesis

A 500-mL oven dried round-bottom flask was equipped with a stirrer bar and allowed to cool to r.t. in air. The flask was charged with acetophenone (1.63 mL, 14 mmol) and 0.5 M TarB-H in THF (56 mL, 28 mmol) and subsequently cooled in an ice bath. The ketone and TarB-H were stirred for 15 min. after which $NaBH_4$ (1.06 g, 28 mmol) was added directly to the soln. The flask was then immedi-

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ately capped with a septa and a bubbler line to vent evolving H_2 gas. The mixture was allowed to stir for 2 h. The soln was quenched dropwise with 1 M HCl (50 mL), evolving H_2 gas. The mixture was made basic (pH 12) with solid NaOH (4.2 g) and stirred for 30 min. The solution was extracted with pentane (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$). Filtration and evaporation under reduced pressure yielded (*R*)-1-phenylethanol (1.502 g, 88%) as a colorless oil; 96% ee. The enantiomeric excess of the acetylated alcohol was determined by GC on a Supelco β-cyclodextrin 120 column (30 m × 0.25 mm). GC (T_{det} = 300 °C, T_{inj} = 220 °C, T_{column} = 120 °C, He carrier gas, 45 cm^3/min): t_R = 16.0 (minor), 16.6 min (major).

$[\alpha]_D^{25}$ +52.1 (*c* 0.79, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 5 H), 4.90 (dd, *J* = 7.0 Hz, 1 H), 2.01 (br, 1 H), 1.50 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 145.9, 128.6, 127.5, 125.5, 70.4, 25.1.

Recovery of the Boronic Acid

The basic aqueous layer was placed in a 250-mL flask and acidified with concd HCl to pH ≤1. The aqueous layer was then extracted with Et_2O (3 × 40 mL). The combined ether layers were dried ($MgSO_4$). Filtration and evaporation yielded the boronic acid as a white powder (2.88 g, 85%).

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(11) Phenylboronic acid costs approximately $430/mol and 3-nitrophenylboronic acid $1600/mol.

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