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Enantioselective reduction of aryl ketones using $LiBH_4$ and TarB-X: a chiral Lewis acid†

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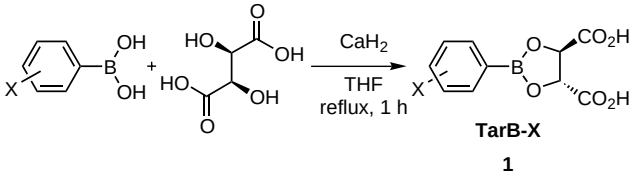
Abstract—High enantioselectivities are obtained using a tartaric acid-derived boronate ester in combination with lithium borohydride for asymmetric reduction of aryl ketones. The chiral Lewis acid, TarB-X, is easily prepared in 1 h, and the resulting alcohols are obtained in enantiomeric excesses of 88–99%.

Enantioselective reduction of prochiral ketones to their corresponding optically active alcohols is one of the most powerful methodologies utilized in asymmetric synthesis.[1] A number of systems have been reported to effect enantioselectivity, and a great majority involve boron reagents.[2] Borane (BH_3) and borohydride (BH_4^-) containing compounds are the two fundamental classes of boron-based reducing agents. Prior to use in asymmetric synthesis, they were known to be key reagents in the reduction of specific functionalities.[3] Once it was demonstrated that optically pure materials could be obtained via chiral borane and borohydride reagents, much attention was focused on finding the best chiral precursor. In 1981, Itsuno et al. reported the first promising result. Utilizing a mixture of chiral amino alcohols and BH_3:THF, the authors obtained enantiomeric excesses in the range of 10–73% ee.[4] Since then, numerous studies on the asymmetric reduction of prochiral ketones involving chiral borane reagents, have emerged.[2,5] For example, Corey's systematic study of oxazaborolidines led to the development of the CBS catalyst, which when used catalytically affords products in 99% ee.[6]



TarB-X

1

Scheme 1. Preparation of TarB-X.

Chiral borohydrides have also found utility in asymmetric synthesis. Most notable are the reagents prepared via modification of $NaBH_4$. Specific examples include sodium borohydride modified with monosaccharide derivatives,[7] amino alcohols,[8] β-oxoaldimine cobalt (II) complex,[9] mandelic acid,[10] amino acids,[11] and tartaric acid.[12]

In connection with our program on LABs,[13] we became interested in asymmetric reductions involving borohydrides. After a survey of the literature, a recent report caught our attention. Nozaki and co-workers reported the preparation of bisboronate esters from naturally occurring (L)-tartaric acid and demonstrated their effectiveness as chiral Lewis acids in the reduction of amino-substituted aryl ketones.[14] Employing a series of reducing agents, they found that the best results were obtained using a stoichiometric amount of $LiBH_4$. Although the procedure required stoichiometric amounts of all reagents, it utilized inexpensive chiral auxiliaries and reagents that could be recycled. Moreover, the previous success of tartaric acid-derived catalysts,[12,15] further demonstrated the potential of such a system, prompting us to pursue the generality of Nozaki's methodology.

Initially we attempted to repeat Nozaki's work. When 2 equiv. of phenylboronic acid were reacted with (L)-tar-

Keywords: enantioselective; asymmetric; chiral Lewis acid; tartaric acid; boronic acid; reduction.

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† This paper is cordially dedicated to Professor Herbert C. Brown on the occasion of his 90th birthday.

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taric acid in refluxing toluene/THF, decomposition of tartaric acid was apparent after 1 h, effectively turning the solution black. Because toluene was required to azeotropically remove water, high temperature reflux was necessary. This proved to be problematic since tartaric acid rapidly degrades above 100°C. As a result, we opted to develop a procedure using milder conditions. Surprisingly, we found that 2 equiv. of boronic acid were not necessary to produce an active reagent. Instead, only 1 equiv. of arylboronic acid was required to generate a compound that functioned as a highly selective chiral Lewis acid in the reduction of aryl ketones with lithium borohydride. Herein we report the preparation, characterization, and synthetic utility of this novel tartaric acid-derived Lewis acid: TarB-X **1**. A variety of boronate esters were prepared according to Scheme 1. In the presence of CaH_2, (L)-tartaric acid reacts readily with arylboronic acids generating, after 1 h in refluxing THF, the cyclic boronate esters **1** in nearly quantitative yield.[16,17] To ensure that these compounds were in fact novel,[18] and uniquely different from Nozaki's, they were carefully characterized using ^1H, ^{13}C, and ^{11}B NMR,[19] as well as FT-IR spectroscopy and active hydride estimation. As indicated in Fig. 1, (L)-tartaric acid contains two equivalent methine protons with a chemical shift of 4.3 ppm in THF-d_8 relative to TMS.

As indicated in Fig. 1, (L)-tartaric acid contains two equivalent methine of 3-nitrophenylboronic acid the methine protons shift to 5.0 ppm. However, the peak remains a singlet, indicating that the molecule is C_2 symmetric with respect to the appended boronic acid. The relative integration of aromatic protons to methine protons also matches the monoboronate adduct, giving a 2:1 ratio, respectively. The ^{13}C NMR spectrum, in analogy to Fig. 1, shows the expected peaks. Finally, the presence of free carboxylic acid groups in **1** was verified via active hydride estimation.[20] Upon addition of $LiBH_4$ to a solution of **1h** in THF, 2 equiv. of H_2(g) were generated. FT-IR validated the structure, giving a C=O stretch of 1736 cm^{-1} and an O–H stretch of 3427 cm^{-1}, which is typical of carboxylic acids.

The reduction of acetophenone with $LiBH_4$ was carried out utilizing **1a**–**h** as chiral Lewis acids (Table 1). Dropwise addition of $LiBH_4$ to a premixed solution of **1**:acetophenone (1:1) gave, after acid/base workup and purification, (*R*)-1-phenylethanol in high yield with enantiomeric excesses reaching 94% ee. The boronic acid was also efficiently recovered using 3 M NaOH.

To optimize the selectivity, different sets of conditions were explored using acetophenone as the model compound. At low and high temperatures, the asymmetric induction decreased in comparison to the ambient temperature reaction (Table 2). Tetrahydrofuran was the preferred solvent although similar ees were obtained in acetonitrile. Overall, the optimum results required 2 equiv. of TarB–NO_2 **1h**, 1 equiv. of $LiBH_4$, and 1 equiv. of acetophenone; under these conditions (*R*)-1-phenylethanol was obtained in 99% ee.

The generality of the asymmetric reducing system was determined via reduction of various aryl ketones with $LiBH_4$ and **1h** under the optimum conditions. As summarized in Table 3, excellent enantioselectivities were obtained for most substrates with the highest selectivity being achieved in the reduction of acetophenone, tetralone, indanone, and 2′-acetonaphthone.

To ensure that the unprotected carboxylic acid was a necessary component of TarB-X, a separate experiment was carried out. The protected tartrate boronate ester **2** (Fig. 2) was prepared from dimethyltartrate and 4-chlorophenylboronic acid. Reduction of acetophenone in the presence of **2** under standard conditions,[22] gave the corresponding alcohol in only 7% enantiomeric

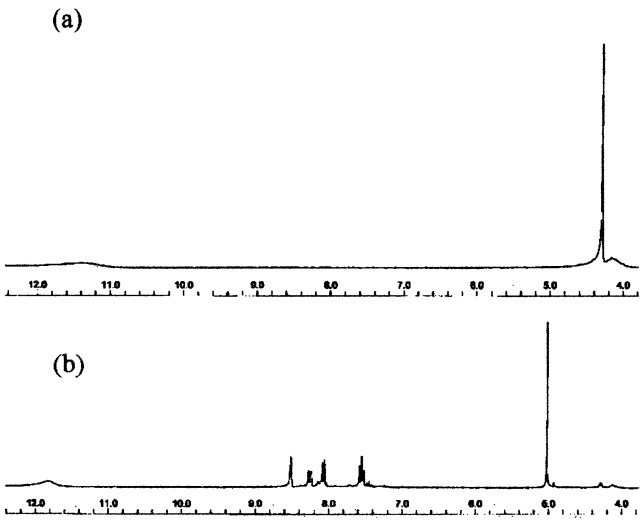
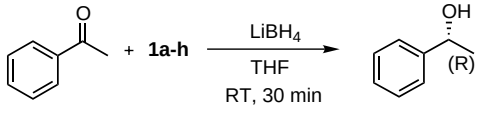


Figure 1. ^1H NMR of (a) (L)-tartaric acid and (b) TarB-NO_2·**1h** in THF-d_8.

Table 1. Enantioselective reduction of acetophenone as a function of arylboronic acid[a]



premix 30 min

1	X	% ee[b,c,d]
a	H	71
b	2-F	90
c	4-F	90
d	2,3,4,5,6-F	13
e	4-CF_3	91
f	3,5-CF_3	76
g	4-Cl	90
h	3-NO_2	94

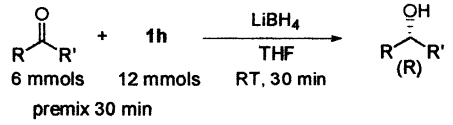
[a] Reactions carried out at room temperature according to Ref. 21, method A.
[b] Determined by GC analysis on a Supelco Beta-Dex 120 column.
[c] All products were of the (*R*) configuration as determined by chiroptical comparison.
[d] All reactions gave 100% conversion to the alcohol according to GC.

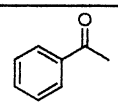
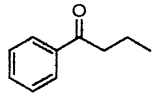
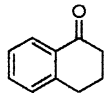
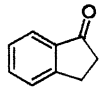
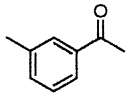
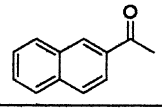
Table 2. Enantioselective reduction of acetophenone under different conditions with Lewis acid **1**[a]

1	**1** (mmol)	$LiBH_4$[b] (mmol)	Acetophenone (mmol)	Solvent	°C	% ee[c,d]
g	3	6	6	THF	23	50
g	6	3[e]	6	THF	23	88
g	6	6	6	Et_2O[f]	23	32
g	6	6	6	CH_3CN[g]	23	90
g	12	6	6	THF	23	99
h	6	6	6	THF	−15	74
h	6	6	6	THF	0	83
h	6	6	6	THF	40	85
h	12	6	6	THF	23	99

[a] Reactions carried out as described in Ref. 21, method A, unless otherwise noted.
[b] All reactions gave 100% conversion to the alcohol according to GC unless otherwise noted.
[c] Determined by GC analysis on a Supelco Beta-Dex 120 column.
[d] All products were of the (*R*) configuration as determined by chiroptical comparison.
[e] Only 50% conversion to the alcohol according to GC.
[f] **1g** was prepared in Et_2O as in Ref. 17, method A, and reduction performed in Et_2O as in Ref. 21, method A.
[g] **1g** was prepared in CH_3CN as in Ref. 17, method A, and reduction performed in CH_3CN as in Ref. 21, method A.

Table 3. Reduction of aryl ketones with $LiBH_4$ /**1h**[a]



ketone	mmols $LiBH_4$[b]	time h	% ee[c,d]
	6	0.5	99 (99)
	6	0.5	(90)[e]
	9	1	94 (94)
	12	1.5	99 (99)
	6	0.5	88
	6	0.5	99 (99)

[a] Reactions carried out as described in reference 21, method B.
[b] All reactions gave 100% conversion to the alcohol according to GC.
[c] Determined by GC analysis on a Supelco Beta-Dex 120 column.
[d] Values in parentheses were determined via optical rotation; all products were of the (*R*) configuration.
[e] Enantiomers did not separate on GC.

excess. Consequently, the free carboxylic acid is essential in order to achieve high asymmetric induction.

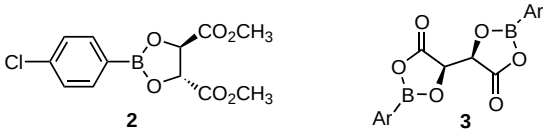


Figure 2. Protected (L)-tartaric acid derivatives.

To the best of our knowledge there have been no reports of simple boronate esters derived from unprotected (L)-tartaric acid. Most of the research involving boron appended to (L)-tartaric acid has focused on tartrate and tartramide modified boronates,[15] such as Nozaki's **3**.[14] Therefore, TarB-X, with its free carboxylic acid groups, represents a new type of chiral Lewis acid.[12c] In addition, because the reagent is easily prepared, induces high enantioselectivity, and can be essentially fully recovered, the implications for its use in both industry and academia appear to be quite promising.

References

1. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapters 2 and 3.
2. For a comprehensive review on asymmetric boron-catalyzed reactions, see: Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763.
3. Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567.
4. (a) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1981**, 315; (b) Itsuno, S.; Hirao, A.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1673.
5. (a) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1994**, *66*, 201; (b) Ramachandran, P. V.; Brown, H. C.; Pitre, S. *Org. Lett.* **2001**, *3*, 17.
6. For a comprehensive review on oxazaborolidines, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

7. (a) Hirao, A.; Mochizuki, H.; Nakahama, S.; Yamazaki, N. *J. Org. Chem.* **1979**, *44*, 1720; (b) Hirao, A.; Nakahama, S.; Mochizuii, D.; Itsuno, S.; Ohowa, M.; Yamazaki, N. *J. Chem. Soc. Jpn.* **1979**, 807; (c) Hirao, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1424; (d) Morrison, J. D. *J. Org. Chem.* **1980**, *45*, 4229; (e) Hirao, A. *J. Org. Chem.* **1980**, *45*, 4231; (f) 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.
8. Itsuno, S.; Sakurai, Y.; Shimuzu, K.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1548.
9. (a) Nagata, T.; Yorozu, K.; Yamada, T.; Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2147; (b) Sugi, K. D.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1997**, 493.
10. Nasipuri, D.; Sarkar, A.; Konar, S. K.; Ghosh, A. *Ind. J. Chem.* **1982**, *21B*, 212.
11. (a) Umino, N.; Iwakuma, T.; Itoh, N. *Chem. Pharm. Bull.* **1979**, *27*, 1479; (b) Yamada, K.; Takeda, M.; Iwakuma, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 265.
12. (a) Yatagai, M.; Ohnukim, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1826; (b) Polyak, F. D.; Solodin, I. V.; Dorofeeva, T. V. *Synth. Commun.* **1991**, *21*, 1137; (c) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. The authors reported a tartaric acid derivative with one free carboxylic acid group.
13. Lithum aminoborohydrides, see: (a) Thomas, S.; Collins, C. J.; Cuzeens, J. R.; Spiciarich, D.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **2001**, *66*, 1999; (b) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378.
14. Nozaki, K.; Kobori, K.; Uemura, T.; Tsutsumi, T.; Takaya, H.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1109.
15. Gawronski, J.; Gawronska, K. *Tartaric and Malic Acids in Synthesis: a Source Book of Building Blocks, Ligands, Auxiliaries, and Resolving Agents*; John Wiley & Sons: New York, 1999; Chapter 8.
16. Arylboronic acids are known to form boroxines upon dehydration; the borixine facilitates facile attack by tartaric acid to afford the boronate ester, see: Ishira, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920.
17. **Representative procedures** for the preparation of TarB-X **1**. Method A: An oven-dried 50 mL round bottom flask with a sidearm was equipped with a magnetic stirring bar and reflux condenser, and cooled to room temperature under argon. The flask was charged with arylboronic acid (6 mmol), (L)-tartaric acid (6 mmol), and CaH_2 (12 mmol), and subsequently purged with argon. Anhydrous THF, distilled from sodium–benzophenone ketyl (15 mL), was added via syringe, and the suspension heated to reflux for 1 h. The reaction mixture was cooled to room temperature, transferred to a fritted funnel using a double-ended needle, and carefully filtered under argon. The filtrate was collected into an oven-dried 50 mL round bottom flask, sealed with a septum, and used without further purification. Method B: Same as above except the solvent was removed in vacuo and the product isolated (typically isolated yields were >97%); a stock solution (0.3 M in THF) was prepared, stored in an ampoule at 4°C, and used in the reduction step.[21] The purity of **1a**–**h** was estimated by NMR to be >98% in all cases with the minor impurity being due to unreacted (L)-tartaric acid.
18. Nozaki et al.[14] reported that their preparation of bisboronate esters of tartaric acid contained no free carboxylic acid groups (Fig. 2, **3**).
19. In THF relative to BF_3:Et_2O as an external standard two peaks are observed: one broad peak at 30 ppm and another broad peak at 10 ppm.
20. H_2(g) was 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.
21. **Representative procedure** for the reduction of ketone. Method A: The filtrate containing TarB-NO_2 **1h** (15 mL of a 0.4 M soln in THF), isolated from the first reaction,[17 (method A)] was kept under a blanket of argon while acetophenone (6 mmol, 0.721 g) was added via syringe; the solution was stirred at the appropriate temperature for 30 min. $LiBH_4$ (3 mL of a 2 M solution in THF) was carefully added dropwise over 10 min and the reaction mixture was kept stirring for 30 min or until TLC (hexane:ethyl acetate, 2:1) showed no more starting material. The solution was quenched (CAUTION!, hydrogen evolution) with 5 mL of H_2O, 5 mL of 3 M HCl, and brought to pH 12 with 3 M NaOH solution. The aqueous layer was extracted with diethyl ether (4×30 mL) and re-acidified with 12 M HCl to recover the boronic acid, which was dried under vacuum and washed with pentane (4.9 mmol, 0.891 g, 80% recovery). The combined organic layers were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After removal of the solvents the crude yellow oil was distilled under reduced pressure, collected with diethyl ether and dried under high vacuum for 1 h to yield 1-phenylethanol (5.3 mmol, 89%), $[\alpha]_D^{20} = +42.3°$ (*c* 5, MeOH), which corresponds to 94% ee of (*R*)-1-phenylethanol; this was confirmed by GC analysis on a Supelco Beta-Dex 120 column. Method B: TarB–NO_2 **1h** (12 mmol, 40 mL of a prepared 0.3 M stock solution in THF) was kept under argon while substrate (6 mmol) was added via syringe. The mixture was stirred at room temperature for 30 min. $LiBH_4$ (3 mL of a 2 M solution in THF) was carefully added dropwise over 10 min and the reaction mixture was kept stirring for 30 min or until TLC (hexane:ethyl acetate, 2:1) showed no more starting material. The remaining workup was the same as above to yield the corresponding alcohol.
22. Compound **2** (6 mmol) was prepared according to Ref. 17, method A and used in the $LiBH_4$ (6 mmol) reduction of acetophenone (6 mmol) as in Ref. 21, method A. GC analysis of alcohol showed 100% conversion and 7% ee of the (*R*)-isomer.