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A Chiral Bimetallic Lewis Acid as a Reaction Template. Asymmetric Reduction of Unsymmetric Ketones with $LiBH_4$

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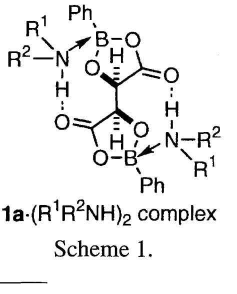
A new series of chiral bimetallic Lewis acids, 5,5′-bis[(*R*)-2-aryl-1,3,2-dioxaborolan-4-one], have been prepared from L-(+)-tartaric acid and arylboronic acids. In the presence of these Lewis acids, unsymmetric ketones were reduced quantitatively by $LiBH_4$, in moderate to good ee's (up to 99% ee). The counter cation of BH_4^- significantly affects the ee's of the products. The reaction is applicable to aryl alkyl ketones, dialkyl ketones, and diaryl ketones.

Asymmetric reduction of unsymmetric ketones using chiral borane or borohydride (tetrahydroborate) reagents is one of the most promising methods for the preparation of optically active secondary alcohols.[1] Since the discovery by Itsuno in 1981, the catalyst system of oxazaborolidine in combination with BH_3 has been considered as a powerful method for this purpose.[2] Later, the catalyst was fully identified and used on a wide variety of substrates by Corey.[3] The use of BH_3 in the presence of other chiral metal complexes is also reported for this purpose.[4] Besides these borane systems, the use of BH_4^- is another important topic. In 1981, Yamazaki reported that a mixture of $NaBH_4$ and a chiral acid or a chiral alcohol worked as an asymmetric reducing agent.[5] As was done with the BH_3 system, combination of $NaBH_4$ with other chiral metal complexes was also investigated.[6]

We recently communicated the synthesis of a chiral bimetallic Lewis acid **1a** and its binding property to Lewis bases (Scheme 1).[7] Formation of stable complexes was observed with primary and secondary amines, but not with tertiary ones. In the complexes, the two boron atoms of **1a** act as a Lewis acid, accepting the lone pair of the amines. Meanwhile, the carbonyl oxygens of **1a** work as a Lewis base, binding to amino protons. Chiral Lewis acid **1a** distinguished the enantiomers of (1*R**, 2*R**)-1,2-diphenylethane-1,2-diamine by providing a unique type of binding to each enantiomer. Considering the chiral-discrimination ability of **1a**, we came to investigate the use of **1a** in asymmetric synthesis. Here we report the asymmetric reduction of unsymmetric ketones using $LiBH_4$ in the presence of chiral bimetallic Lewis acids **1a**—**d**. Mechanistic aspects are discussed in relation to the interactions between substrates, reducing reagents, and Lewis acids **1**.



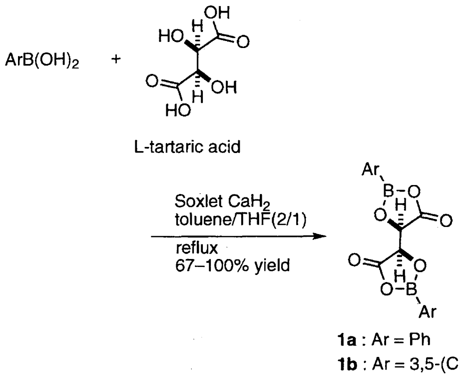
1a·$(R^1R^2NH)_2$ complex

Scheme 1.

Results and Discussion

1. Preparation of Lewis Acids 1a—d.

Lewis acids **1a**—**d** were prepared as shown in Eq. 1.[7] A toluene/THF solution of an arylboronic acid and L-tartaric acid was heated to reflux while water was removed by an azeotropic distillation. Evaporation of the solvents provided Lewis acids **1a**—**d** as highly moisture sensitive colorless to milky white solids. Lewis acids **1a**, **1c**, and **1d** exhibited no ^{1}H NMR peaks but the ones due to the desired compounds. As an exception, **1b** could not be obtained in its pure form and its purity was estimated to vary 25—73 wt% by ^{1}H NMR using acetophenone as an internal standard.[8] Obtained **1a**—**d** were directly used for the asymmetric reduction without any further treatments.



(1)

1a : Ar = Ph
1b : Ar = $3,5\text{-}(CF_3)_2C_6H_3$
1c : Ar = $3,5\text{-}(CH_3)_2C_6H_3$
1d : Ar = $4\text{-}CF_3C_6H_4$

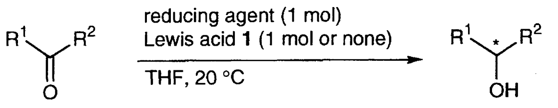
\# Deceased on October 4, 1995.

Table 1. Acceleration of $LiBH_4$-Reduction of Ketones **2** in the Presence of Lewis Acid **1a**[a)]

Run	Ketone	R^1	R^2	Lewis acid	Reaction time (min)	Conv. (%)
1	**2a**	C_6H_5	CH_3	1 mol	15	100
2	**2a**	C_6H_5	CH_3	None	15	77
3	**2b**	*o*-$H_2NC_6H_4$	CH_3	1 mol	30	100
4	**2b**	*o*-$H_2NC_6H_4$	CH_3	None	30	90
5	**2c**	*p*-$H_2NC_6H_4$	CH_3	1 mol	30	100
6	**2c**	*p*-$H_2NC_6H_4$	CH_3	None	30	3
7	**2i**	2-H_2N-5-ClC_6H_3	2,3-$(MeO)_2C_6H_3$	1 mol	30	100
8	**2i**	2-H_2N-5-ClC_6H_3	2,3-$(MeO)_2C_6H_3$	None	30	31

a) Substrate **2** (0.22 mmol) was added to a solution of Lewis acid **1a** (0.22 mmol) in THF (3 mL) at 20 °C. After stirring for 30 min, a THF solution of $LiBH_4$ (0.40 M, 0.55 mL, 0.22 mmol) was added dropwise at 20 °C. After stirring for 15 or 30 min, the conversions and chemical selectivities were determined by ^1H NMR of the crude mixture.

2. Asymmetric Reduction of Unsymmetric Ketones with Various Metal Hydrides in the Presence of Lewis Acids 1a—d. Acceleration by a Lewis Acid. Asymmetric reduction of unsymmetric ketones with metal hydrides was examined in the presence of Lewis acids **1a**—**d**. Because metal hydrides themselves are able to reduce ketones, the rate enhancement by a Lewis acid is essential in order to achieve the asymmetric reduction. Thus, unsymmetric ketones **2a**—**c** and **2i** were reduced with an excess amount of $LiBH_4$ in the presence or absence of Lewis acid **1a** (1 mol amount to the ketone). The results are shown in Eq. 2 and Table 1. The reduction was quenched after 15 or 30 min. In the presence of **1a**, the conversion to the alcohol was 100% for all of the substrates (Runs 1,3,5,7). Much lower conversions were observed in the absence of **1a** (Runs 2,4,6,8). Especially, a clear rate acceleration by **1a** was observed with a less reactive ketone, *para*-amino-substituted acetophenone **2c** (Runs 5 and 6).



2 (1 mol) **3** (2)

Effect of Substituents on Lewis acid 1. We next investigated the effect of the substituents on Lewis acid **1**. Lewis acids **1a**—**d** were compared, and the results are summarized in Table 2. The reduction of acetophenone (**2a**) afforded 1-phenylethanol (**3a**) of 84% ee in the presence of an equimolar amount of **1a** (Run 1). The use of Lewis acid **1b** improved the ee up to 95% (Run 2). It should be noted that the purity of Lewis acid **1b** affected neither reaction conversion nor %ee of the product, as will be discussed later in Table 4, Runs 7 and 8.

Effect of Metal Hydrides. The effect of reducing agents was examined (Table 3).[9)] As shown in Runs 1—3, the counter cation of the BH_4^- ion significantly affected the efficiency and the enantioselectivity of the reaction. In both respects, $LiBH_4$ was the reagent of choice and was used in the following studies.

Optimization of the Procedure. The effect of the mixing order was next examined as shown in Chart 1. When a THF solution of $LiBH_4$ was added to a premixed solution of *meta*-aminoacetophenone (**2d**) and Lewis acid (**1c**) in THF (Procedure I), the conversion to alcohol **3d** was 100% and the ee of **3d** was 61%. In Procedure II, a solution of **1c** and $LiBH_4$ was added to a THF solution of **2d**. The conversion dropped to 5% in the same reaction time, and the obtained product turned out to be racemic. The hydride probably reacted with **1c** before the addition of the substrate **2d**. When each solution of **1c** and $LiBH_4$ was simultaneously added dropwise to a solution of **2d** (Procedure III), the conversion was 100% to give **3d** of 30% ee. On the basis of the results, we conclude that premixing the substrate ketone with the

Table 2. Reduction of Acetophenone (**2a**) with $LiBH_4$ in the Presence of Lewis Acids **1a**—**d**[a)]

Run	Lewis acid	% ee[b,c)]
1	**1a**	84 (*R*)
2	**1b**[d)]	95 (*R*)
3	**1c**	70 (*R*)
4	**1d**	77 (*R*)

a) The reactions were carried out under the conditions stated in Table 1. b) Absolute configuration of the products is shown in parenthesis. c) Determined by HPLC analysis using a chiral column (Daicel, CHIRALCEL OD). d) Lewis acid **1b** of 73 wt% purity was used.

Table 3. Reduction of Acetophenone (**2a**) with Various Reducing Agents in the Presence of Lewis Acid **1a**[a)]

Run	Reducing agent	Conv. (%)[b)]	% ee[c,d)]
1	$LiBH_4$	100	84 (*R*)
2	Bu_4NBH_4	100	48 (*R*)
3	$Zn(BH_4)_2$[e)]	54	58 (*R*)
4	$LiAlH_4$	100	44 (*R*)

a) The reactions were carried out under the conditions stated in Table 1. b) Conversions and chemical selectivities were determined by ^1H NMR of the crude mixture unless otherwise stated. c) Absolute configuration of the products is shown in parenthesis. d) Determined by HPLC analysis using a chiral column (Daicel, CHIRALCEL OD). e) $Zn(BH_4)_2$ was used 0.5 mol amount to **2a**.

Table 4. Reduction of Ketones **2** with $LiBH_4$ in the Presence of Lewis Acids **1**[a]

Run	Substrate	R^1	R^2	Lewis acid	Product	%ee[b]
1	**2b**	*o*-$NH_2C_6H_4$	CH_3	**1b**[c]	**3b**	56(−)[d,e]
2	**2b**	*o*-$NH_2C_6H_4$	CH_3	**1c**	**3b**	35(−)[d,e]
3	**2c**	*p*-$NH_2C_6H_4$	CH_3	**1a**	**3c**	59(+)[e,f]
4	**2c**	*p*-$NH_2C_6H_4$	CH_3	**1b**[c]	**4c**	—
5	**2c**	*p*-$NH_2C_6H_4$	CH_3	**1c**	**3c**	46(−)[e,f]
6	**2d**	*m*-$NH_2C_6H_4$	CH_3	**1a**	**3d**	22(+)[e,f]
7	**2d**	*m*-$NH_2C_6H_4$	CH_3	**1b**[c]	**3d**	99(+)[e,f]
8	**2d**	*m*-$NH_2C_6H_4$	CH_3	**1b**[g]	**3d**	96(+)[e,f]
9	**2d**	*m*-$NH_2C_6H_4$	CH_3	**1b**[c,h]	**3d**	2(+)[e,f]
10	**2d**	*m*-$NH_2C_6H_4$	CH_3	**1c**	**3d**	61(+)[e,f]
11	**2e**	*p*-$BocNHC_6H_4$	CH_3	**1b**[c]	**3e**	90(+)[e,f]
12	**2f**	*cyclo*-Hex	CH_3	**1a**	**3f**	34(R)[i]
13	**2f**	*cyclo*-Hex	CH_3	**1b**[c]	**3f**	82(R)[i]
14	**2g**	C_6H_5	CF_3	**1a**	**3g**	11[d,j]
15	**2g**	C_6H_5	CF_3	**1b**[c]	**3g**	3[d,j]
16	**2h**	*n*-Hex	CF_3	**1a**	**3h**	5[i,j]
17	**2i**	2-H_2N-5-Cl-C_6H_3	2,3-$(MeO)_2$-C_6H_3	**1a**	**3i**	74(S)[d]
18	**2i**	2-H_2N-5-Cl-C_6H_3	2,3-$(MeO)_2$-C_6H_3	**1b**[c]	**3i**	85(S)[d]
19	**2i**	2-H_2N-5-Cl-C_6H_3	2,3-$(MeO)_2$-C_6H_3	**1c**	**3i**	80(S)[d]
20	**2j**	*p*-$NH_2C_6H_4$	C_6H_5	**1a**	**3j**	30(−)[e,f]
21	**2j**	*p*-$NH_2C_6H_4$	C_6H_5	**1b**[c]	**3j**+**4j** (3 : 7)	N.D.
22	**2j**	*p*-$NH_2C_6H_4$	C_6H_5	**1c**	**3j**	19(−)[e,f]
23	**2k**	*p*-$BocNHC_6H_4$	C_6H_5	**1b**[c]	**3k**	30(−)[e,f]

a) The reactions were carried out under the conditions stated in Table 1. b) Absolute configuration of each product is shown in parentheses. c) The purity of Lewis acid **1b** was 73 wt%. 1.0 mol amount of **1b** to substrate **2d** was used. d) Determined by HPLC analysis using a chiral column (Daicel, CHIRALCEL OJ). e) Absolute configuration of the product was not determined. Optical rotation sign is drawn in the parenthesis. f) Determined by HPLC analysis using a chiral column (Daicel, CHIRALCEL OD). g) Lewis acid **1b** whose purity was 25 wt%. h) Lewis acid **1b** (0.10 mol amount to substrate **2d**) was used. i) Determined by ^{19}F NMR of the corresponding (*R*)-MTPA ester. j) Neither absolute configuration nor the optical rotation sign of the product was not determined.

Lewis acid is essential to achieve high ee and conversion.

Asymmetric Reduction of Other Unsymmetric Ketones. Some other ketones were reduced by $LiBH_4$ in the presence of 1 mol amount of Lewis acids **1a**—**c** as shown in Eq. 3. The results are summarized in Table 4. The reaction proceeded in 100% conversion and no by-product was obtained unless otherwise stated. In the presence of **1b** and **1c**, *ortho*-aminoacetophenone **2b** was reduced to **3b** in moderate ee's, 56 and 35%, respectively (Runs 1 and 2). With **1a** or **1c**, *para*-aminoacetophenone (**2c**) gave **3c** (Runs 3 and 5), whereas *para*-amino(ethyl)benzene (**4c**) was obtained as a single product with **1b** (Run 4).[10] *Meta*-amino-substituted acetophenone **2d** was reduced to **3d** in up to 99% ee (Run 7). Using this substrate **2d**, we examined the effect of purity of **1b**. In Runs 7 and 8, reduction of **2d** was examined in the presence of **1b** whose purities were estimated to be 73 and 25 wt%, respectively. As pure **1b**, 1 mol amount to the substrate was used in each run. The comparable results suggest that the effects of the impurities are negligible and that the ee's are controlled by pure **1b**. By use of a catalytic amount of Lewis acid **1b** (0.1 mol amount to the substrate), almost racemic **3d** was obtained (Run 9). The over-reduction of *para*-amino-substituted **2c** was prevented by the protection of the amino group by Boc group and the corresponding alcohol **3e** was obtained in 90% ee (Run 11). A dialkyl ketone **2f** was reduced with good ee (Run 13) while trifluoromethyl

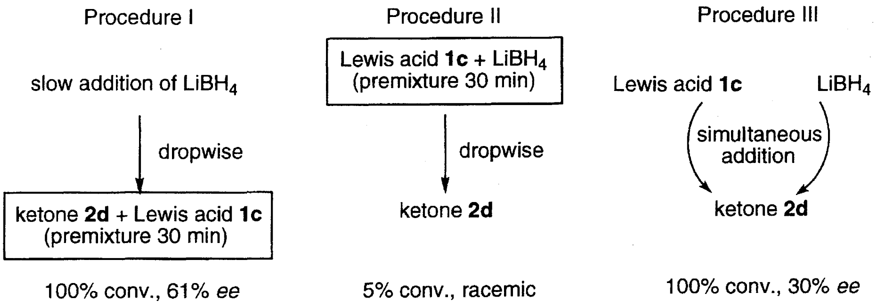
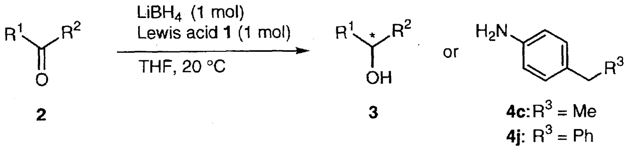


Chart 1.

ketones were reduced in much lower ee's (Runs 14, 15, and 16).

Asymmetric reduction of diaryl ketones[11] was also examined. *Ortho*-substituted benzophenone **2i** gave the corresponding alcohol **3i** in up to 85% ee (Runs 17, 18, and 19). The product **3i** is a synthetic intermediate for **5**, a potent hypotensive agent, TAK-355.[12] *Para*-aminobenzophenone (**2j**) was reduced in an enantioselective manner with **1a**—$LiBH_4$ and **1c**—$LiBH_4$, but the ee of **3j** was rather low (Runs 20 and 22). With a combination of the stronger Lewis acid **1b** and $LiBH_4$, **2j** gave a 3 : 7 mixture of **3j** and **4j** (Run 21). Protection of the amino group by a Boc group prevented the over-reduction but the ee of the corresponding alcohol **3k** was not satisfactory (Run 23).



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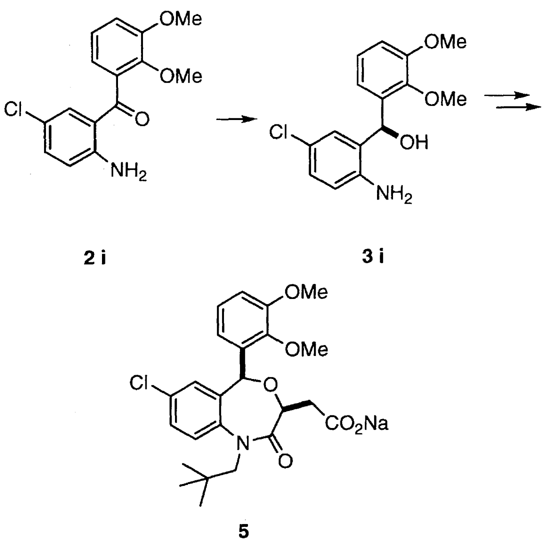
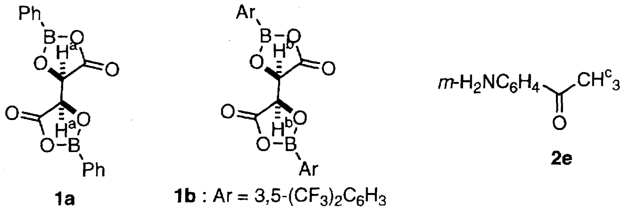


(4)

3. A Possible Role of the Lewis Acid in the Asymmetric Reduction. The interactions between Lewis acid **1** and $LiBH_4$ were investigated based on the ^1H NMR spectra at 20 °C. In a THF-d_8 solution of **1a** (52 mM) and $LiBH_4$ (52 mM), the methine protons (H^a) of **1a** and the protons of $LiBH_4$ appeared as broad peaks. Similar broadening was observed in a THF-d_8 solution of **1b** (34 mM) and $LiBH_4$ (34 mM). In addition, a remarkable up-field shift (5.0 ppm → 4.6 ppm) was detected for the methine protons (H^b) of **1b**. Next, the interactions between Lewis acid **1a** or **1b** and ketones **2a** or **2d** were similarly studied (Scheme 2). In a THF-d_8 solution of **1b** (13 mM) and **2a** (13 mM), **2a** showed no change over the whole signal pattern upon admixture with Lewis acid **1b**. In contrast, the peaks due to the methine protons (H^a) of **1a** and the methyl protons (H^c) of *meta*-amino-acetophenone (**2d**) became broadened in a $CDCl_3$ solution of **1a** (285 mM) and **2d** (95 mM). In addition, a significant up-field shift (2.6 ppm → 2.2 ppm) was observed for the methyl protons (H^c) of **2d**. Thus, Lewis acids **1** seem to have interactions both with $LiBH_4$ and with ketones **2**.



Scheme 2.

A possible model may be proposed for the present asymmetric reduction as follows. The carbonyl groups in **1**, Lewis basic sites, may capture the counter cation of the borohydride ion. This assumption matches well to the significant contribution of the counter cation to the enantioselectivity, and also agrees with the interaction between $LiBH_4$ and Lewis acid **1** observed by the NMR study. At the same time, the boron atoms in **1**, Lewis acidic sites, might interact with the carbonyl groups of ketones **2**. The fact that the premixture of **1** with **2** is essential to achieve the highest conversion and %ee seems to suggest some sort of complex formation between **1** and **2**. Thus, Lewis acid **1** may have made ketone **2** meet H^- under a chiral circumstance.

Conclusion. In the presence of a chiral bimetallic Lewis acid **1**, unsymmetric ketones **2** were reduced by $LiBH_4$, in moderate to good ee's (up to 99% ee). This procedure is a new and powerful method for the preparation of optically active secondary alcohols. Although an equimolar amount of the Lewis acid is necessary to achieve the highest ee's, we believe the present method is synthetically advantageous because: (i) the chiral source employed here is tartaric acid, which is cheap and easily available; and (ii) boronic acids can be recovered after aqueous work-up by simply extracting from acidified aqueous phase.

Experimental

General Method. All manipulations of oxygen- and moisture-sensitive materials were conducted under purified argon atmosphere (BASF-Catalyst R3-11) by the use of the standard Schlenk techniques. Silica-gel chromatography was performed using Wakogel C-200.

Apparatus. Nuclear magnetic resonance spectra were taken with JEOL EX-270 (^1H 270 MHz) spectrometer using tetramethylsilane as internal standards, and coupling constants were given in Hertz. HPLC analyses were performed with a Toso CO-8000 chromatograph using a Toso UV-8000 detector (column, Daicel CHIRALCEL OD, or, OJ, 25 cm ×0.46 cm i.d. detection, 254 nm light).

Chemicals. Most of reagents were obtained from Wako Pure Chemical Industries Ltd. or Nacalai Tesque Ltd. All of solvents used for the reactions and recrystallizations were distilled under argon after drying over an appropriate drying agent.

Preparation of Lewis Acid 1. L-(+)-Tartaric acid (0.441 g, 2.94 mmol) and arylboronic acid (2.94 mmol) were placed in a 300-mL three-neck flask equipped with a magnetic stir bar, a Soxhlet extractor filled with CaH_2, and a reflux condenser, and dissolved in toluene (100 mL) and THF (50 mL). The homogeneous solution was then heated at reflux for 12 h. The reaction mixture was cooled at room temperature. The solvents were removed in vacuo to give the corresponding Lewis acid **1**. **1a**: A colorless solid; ^{1}H NMR ($CDCl_3$) $\delta = 5.23$ (s, 1H), 7.35 (m, 2H), 7.54 (m, 1H), 7.81 (m, 2H); ^{13}C NMR ($CDCl_3$) $\delta = 74.95$, 128.3, 133.9, 135.5, 171.3; ^{11}B NMR ($CDCl_3$) $\delta = 48.5$; IR 1816 cm^{-1} (C=O). **1b**: A milky white powder (73 wt% purity); ^{1}H NMR ($CDCl_3$) $\delta = 5.27$ (s, 1H), 7.93 (s, 1H), 8.09 (s, 2H); Other peaks: ^{1}H NMR ($CDCl_3$) $\delta = 5.23$ (s, 1H), 8.02 (s, 1H), 8.31 (s, 2H), 8.15 (s, 1H), and 8.61 (s, 2H). The purity was estimated by the integration of the peak due to the methine proton of **1b** (at 5.23 ppm) in comparison with an internal standard, acetophenone. **1c**: A milky white powder; ^{1}H NMR ($CDCl_3$) $\delta = 2.10$ (s, 6H), 5.01 (s, 1H), 7.00 (s, 1H), 7.26 (s, 2H). **1d**: A milky white powder; ^{1}H NMR ($CDCl_3$) $\delta = 5.29$ (s, 1H), 7.64 (d, $J = 8.25$ Hz, 2H), 7.93 (d, $J = 8.25$ Hz, 2H).

General Procedure of Asymmetric Reduction of Ketones in the Presence of Lewis Acid 1. Ketone **2** (0.22 mmol) was added to a solution of Lewis acid **1** (0.22 mmol) in THF (3 mL) at 20 °C. After stirring for 30 min, a THF solution of a reducing agent (0.4 M, 0.55 mL, 0.22 mmol, 1 M = 1 mol dm^{-3}) was added dropwise at 20 °C. The reaction mixture was stirred for 30 min, and then aqueous work up was carried out with 1 M aqueous solution of NaOH. By employing diethyl ether for extraction, we could avoid the contamination of arylboronic acid in the organic phase. Arylboronic acids were recovered by acidification of the aqueous phase. After evaporation of the solvents, the crude product was purified by silica-gel column chromatography. No by-product was obtained and the conversions to the product are described in Tables 1, 2, 3, and 4. Methods employed for the ee-determination are also included in each table.

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