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Dihydroboronium derivatives of (*S*,*S*)-1,2-bis(*t*-butylmethylphosphino)ethane as convenient chiral ligand precursors

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Abstract—Dihydroboronium derivatives of (*S*,*S*)-1,2-bis(*t*-butylmethylphosphino)ethane (*t*-Bu-BisP*) were prepared and used as chiral diphosphine ligand precursors in Rh-catalyzed asymmetric hydrogenation of methyl (*Z*)-acetamidocinnamate to afford the hydrogenation product in up to 94% enantioselectivity.

Previously, we have reported the preparation of P-chiral trialkylphosphine ligands and their use in transition-metal-catalyzed asymmetric reactions.[1] The chirality at the donor atoms is expected to provide an asymmetric environment that is very close to the reaction center. This has led to the realization of high enantio-induction in some representative catalytic organic transformations.[2] However, as electron-rich phosphines are easily oxidized in air, they must be stored in a protected form, such as a phosphine–borane complex. This has compelled researchers to perform a complicated deprotection process prior to the use of these phosphines.[1,3,4] Therefore, the development of effective protecting groups for the electron-rich phosphines is one of the important subjects in the field of organophosphorus chemistry.[5]

We report herein the preparation of new P-chiral diphosphine ligand precursors for the transition-metal-catalyzed asymmetric transformation. In order to prepare a phosphine–borane complex that can be easily cleaved under mild conditions, catecholborane was chosen as the new candidate for the protecting group. Catecholborane exhibits weaker Lewis acidity than borane owing to the electronic feature of the catecholate moiety. Previously, it has been revealed that the reaction of trimethylphosphine with catecholborane resulted in the formation of [bis(trimethylphosphine)]boronium bis(catechol)borate rather than trimethylphosphine–catecholborane complex.[6] According to this fact, we tried to prepare new compounds **1** and/or **2** by the reaction of *t*-Bu-BisP* with catecholborane (see Fig. 1).

The reaction sequence is shown in Scheme 1.[7] Deboranation of phosphine–borane **3** was carried out by successive treatments with trifluoromethanesulfonic acid and aqueous sodium hydroxide. The obtained free diphosphine **4** was mixed with 2 equiv of catecholborane in THF at 50 °C. The reaction was completed within 12 h and the product was obtained as a white powder. ^{11}B NMR measurement revealed that there were two different signals at −58.0 and −4.9 ppm, implying the

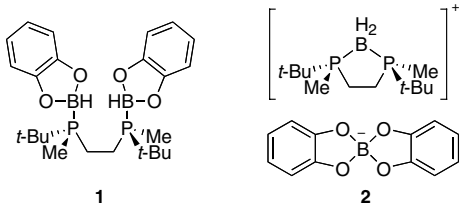

Figure 1. Two possible products obtained in the reaction of catecholborane and *t*-Bu-BisP*.

Keywords: (Diphosphine)boronium salts; P-chiral diphosphine; Catecholborane; Rh-catalyzed asymmetric hydrogenation.
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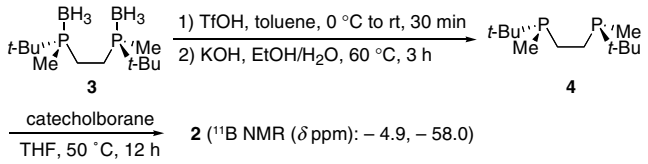


Scheme 1. Reaction of *t*-Bu-BisP* with catecholborane.

formation of dihydroboronium salt **2**. This cyclic structure was also supported by FAB-MS measurement that afforded a strong signal at $m/z = 247$, which was assigned to $[\text{BisP}^* + \text{BH}_2]^+$, and was unequivocally determined by single crystal X-ray analysis.

Figure 2 shows an ORTEP drawing of **2**.[8] It was revealed that one of the phosphorus–boron bonds (1.97 Å) was considerably longer than that of normal phosphine–borane complexes (1.90–1.93 Å). The expanded P–B bond is expected to be cleaved under mild conditions. This contrasts the fact that the P–B bond of the acyclic dihydro(diphosphine)boronium ion is shorter than that of the corresponding monophosphine–borane complex.[6,9] The five-membered ring structure may have affected the length of the P–B bond.

Dihydroboronium derivatives of *t*-Bu-BisP* with different counter anions were also prepared, as shown in Scheme 2. The reaction of BisP* with BH_2Br afforded the boronium salt possessing a bromide ion, which was then converted into other counter anions by treatment with the corresponding silver salts. It was observed that boronium salts **5**–**8** were sufficiently stable even when exposed to air or moisture.

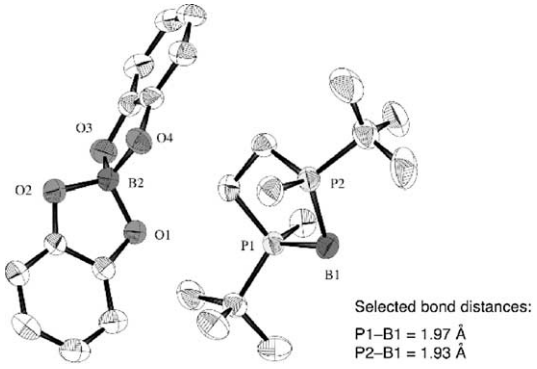
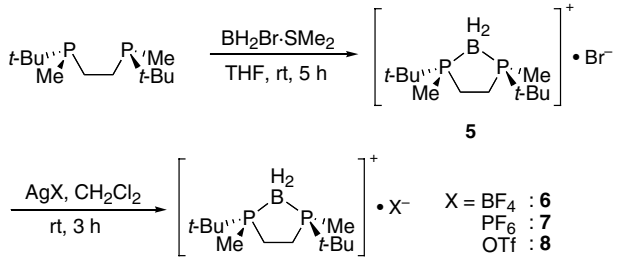
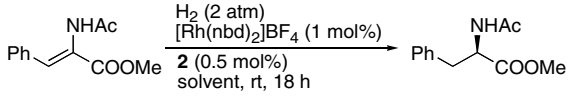


Figure 2. X-ray structure of **2**. All hydrogen atoms are omitted for clarity.



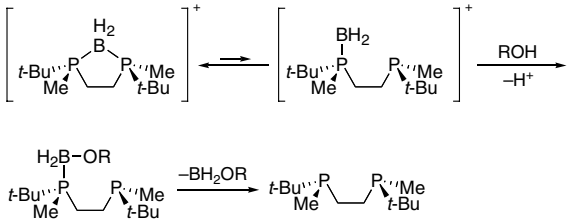
Scheme 2. Preparation of dihydroboronium salts **5**–**8**.

Table 1. Rh-catalyzed asymmetric hydrogenation of methyl acetamidocinnamate with P-chiral dihydroboronium salt **2**[a]



Entry	Solvent	Conv./%[b]	ee/%[c]
1	MeOH	98	90
2	EtOH	99	83
3	*i*-PrOH	>99	84
4	EtOAc	54	94
5	CH_2Cl_2	50	86
6	THF	14	94
7	MeCN	10	—
8	Toluene	Trace	—

[a] All reactions were carried out in methanol with 1 mol% of $[Rh(nbd)_2]BF_4$, 0.5 mol% of **2** under 2 atm of H_2 pressure at room temperature.
[b] Determined by ^1H NMR.
[c] Determined by chiral GC analysis.



Scheme 3. A proposed pathway of the in situ deprotection of dihydroboronium salts.

In order to investigate the applicability of the P-chiral boronium salt **2** as a convenient chiral phosphine ligand precursor, we used it in the Rh-catalyzed asymmetric hydrogenation of olefins.[10,11] First, the hydrogenation of methyl (*Z*)-acetamidocinnamate was carried out in various solvents, and the results are shown in Table 1. Previously, we reported that hydrogenation of the same substrate by the use of $[Rh(t\text{-Bu-BisP}^*)(nbd)]BF_4$ was completed within 1 h to give the product with 99.9% ee.[1a] Although the direct use of **2** afforded lower reactivity and enantioselectivity than the use of Rh–BisP* complex, more than 80% of enantioselectivity was observed in most cases. In alcohols, in particular, an almost quantitative yield of the hydrogenation product was obtained in 83% or higher enantioselectivity (entries 1–3). Ethyl acetate and dichloromethane also gave the hydrogenation product with high enantiomeric excess in moderate yields (entries 4 and 5). Tetrahydrofuran exhibited high enantioselectivity although the yield remained low (entry 6). On the other hand, acetonitrile and toluene were not effective for this system (entries 7 and 8). A protic solvent may promote the deboranation, according to the reaction depicted in Scheme 3 where the liberated *t*-Bu-BisP* rapidly coordinates to Rh and participates in the catalytic cycle.

Further investigation was carried out in the presence of additives, and the results are listed in Table 2. Enhanced

Table 2. Effect of additives on Rh-catalyzed asymmetric hydrogenation of methyl acetamidocinnamate with **2**[a]

Entry	Additive	Reaction time/h	Conv./%[b]	ee/%[c]
1	None	3	28	77
2	None	18	98	90
3[d]	AcOH	3	51	91
4[d]	Catecholborane	3	29	84
5	Et_3N	18	78	47

[a] All reactions were carried out in methanol with 1 mol% of $[Rh(nbd)_2]BF_4$, 1 mol% of **2** under 2 atm of H_2 pressure at room temperature.
[b] Determined by ^1H NMR.
[c] Determined by chiral GC analysis.
[d] $[Rh(nbd)_2]BF_4$ (0.4 mol%) and 0.5 mol% of **2** were used.

reactivity was observed in the presence of acetic acid whereas only a small change was induced by the addition of catecholborane (entries 3 and 4). This may indicate that the release of free ligand from the dihydroboronium ion is promoted by the presence of a Brønsted acid. On the other hand, the addition of triethylamine led to decrease in the chemical yield and the enantioselectivity (entry 5).

Finally, dihydroboronium salts **5**–**8** were employed in the hydrogenation reaction, and the results are summarized in Table 3. In each case, low conversion was observed in the absence of any additives. However, the reactivity was improved by the addition of catechol. Particularly in the case of the triflate salt, a 5-fold increase in the conversion was observed (entry 8). Similar increases in the chemical yield and the stereoselectivity were observed when sodium phenoxide was used as the additive (entry 9). The addition of catechol or phenoxide anion may have caused the release of free *t*-Bu-BisP* and the subsequent construction of a chiral Rh catalyst.

In conclusion, P-chiral dihydroboronium salt **2** was prepared from *t*-Bu-BisP* and catecholborane. The salt could be handled and stored in air, and directly applied to the Rh-catalyzed asymmetric hydrogenation of methyl (*Z*)-acetamidocinnamate as a chiral diphosphine ligand precursor. It was revealed that the boronium salt was in situ converted into the Rh-*t*-Bu-BisP* complex to catalyze the hydrogenation reaction in high enantioselectivity.

Table 3. Rh-catalyzed asymmetric hydrogenation of methyl acetamidocinnamate with dihydroboronium salts **5**–**8**[a]

Entry	Diphosphine–borane	Catechol[b]	Conv./%[c]	ee/%[d]
1	**5**	–	12	60
2	**5**	+	27	92
3	**6**	–	20	77
4	**6**	+	47	86
5	**7**	–	25	86
6	**7**	+	56	79
7	**8**	–	17	91
8	**8**	+	83	88
9	**8**	+[e]	95	89

[a] All reactions were carried out in methanol with 0.5 mol% of $[Rh(nbd)_2]BF_4$ and 0.6 mol% of **5**–**8** under 2 atm of H_2 pressure at room temperature for 18 h.
[b] 0.6 mol%.
[c] Determined by ^1H NMR.
[d] Determined by chiral GC analysis.
[e] Sodium phenoxide (0.6 mol%) was added instead of catechol.

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7. Preparation of dihydroboronium salt **2**: To a dry toluene solution (10 mL) of (*S*,*S*)-1,2-bis(boranato(*tert*-butyl)-methylphosphino)ethane (260 mg, 1.0 mmol) was added trifluoromethanesulfonic acid (880 μL, 10 mmol) dropwise at 0 °C under Ar atmosphere. After 30 min, the mixture was allowed to warm to ambient temperature and stirred, while monitoring the reaction by TLC, until the starting phosphine–borane disappeared. The volatiles were removed under reduced pressure, and a solution of KOH (1.2 g, 20 mmol) in degassed EtOH–H_2O (10:1, 12 mL) was slowly added to the residue with stirring. The mixture was stirred at 60 °C for 2 h then cooled to room temperature. Degassed Et_2O (10 mL) was added, and the mixture was dried over Na_2SO_4. The solution was passed through a column (2 cm diameter) of basic alumina (20 g) eluting with degassed Et_2O (ca. 20 mL). The filtrate was concentrated under reduced pressure and the residue was again dissolved in THF (4 mL). To the solution was added catecholborane (270 μL, 2.5 mmol) at room temperature and stirred at 50 °C for 12 h. The reaction was quenched by saturated $NaHCO_3$ aq. (10 mL) and extracted with CH_2Cl_2, and then dried over Na_2SO_4. After it was concentrated under reduced pressure, the residue was reprecipitated from CH_2Cl_2/Et_2O (2 mL/10 mL) to give dihydroboronium salt **2** as white powder (223 mg, 47% yield): mp 190–192 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 6.65–6.54 (m, 8H), 2.29 (m, 2H), 1.87 (m, 2H), 1.35 (d, $^2J_{HP}$ = 11.0 Hz, 6H), 1.18 (d, $^3J_{HP}$ = 16.2 Hz, 18H), 1.25–0.45 (br, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

151.9 (s), 117.8 (s), 108.6 (s), 27.8 (t, J_{CP} = 21.1 Hz), 24.9 (s), 18.0 (dd, J_{CP} = 20.1, 23.1 Hz), 4.7 (dd, J_{CP} = 18.1, 22.1 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 43.9 (br m, J_{BP} = 85.0 Hz); ^{11}B NMR (160 MHz, $CDCl_3$) δ −4.9, −58.0; IR (KBr) ν_{max} 2965, 2920, 2470, 2420, 1485, 1235, 1060, 915, 750 cm^{-1}: MS (FAB) *m/z* = 247 (M − (cat)$_2$B$^-$). Anal. Calcd for $C_{24}H_{38}B_2O_4P_2$: C, 60.79; H, 8.08. Found: C, 60.67; H, 8.08.

8. CCDC-250102 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
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10. General procedure for asymmetric hydrogenation: A 50 mL Fisher–Porter tube was charged with substrate (1 mmol), $[Rh(nbd)_2]BF_4$ (2–5 μmol), and dihydroboronium salt (2.5–5 μmol). The tube was connected to the hydrogen tank via stainless steel tubing. The vessel was evacuated and filled with hydrogen gas to a pressure of 2 atm. This operation was repeated and the upper cock of the bottle was opened to allow quick addition of anhydrous, degassed solvent (4–5 mL) and additives (20 μmol) using a syringe. After four vacuum/H_2 cycles, the tube was pressurized to an initial pressure of 2 atm. The tube was closed off and the mixture was stirred at ambient temperature. After stirring for 3–18 h, the mixture was passed through a silica gel column with eluting EtOAc, and the filtrate was concentrated under reduced pressure. The residue was subjected to HPLC analysis.
11. The conditions for the determination of the enantiomeric purities of methyl *N*-acetylphenylalanine with chiral stationary column: DAICEL CHIRALCEL OD-H; hexane/2-propanol = 9/1; flow rate = 0.5 mL/min.