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Article

Chiral Borated Esters in Asymmetric Synthesis: 1. The First Asymmetric Reaction Catalyzed by Chiral Spiroborated Esters with an O_3BN Framework

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The first asymmetric reaction catalyzed by chiral spiroborated esters with an O_3BN framework was reported. In the presence of 0.1 equivalent of (*R*,*S*)-**1** or (*S*,*S*)-**1**, acetophenone was reduced by 0.6 equivalent of borane in THF at 0—5 ℃ for 2 h to give (*R*)-1-phenylethanol of up to 76% *ee* and 73% isolated yield. Influence of reaction conditions on the stereoselectivity of the reduction was investigated and a possible catalytic mechanism of the chiral spiroborated esters toward the reduction was also suggested.

Keywords asymmetric catalysis, reduction, chiral spiroborated ester, acetophenone

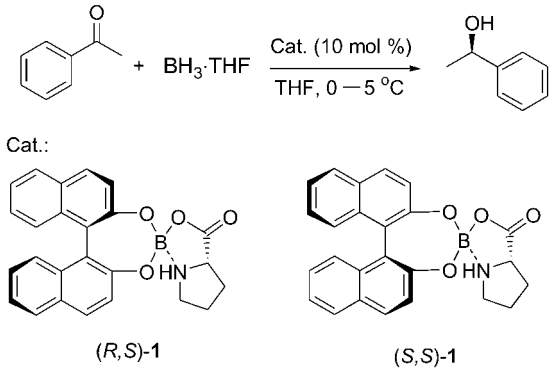
Introduction

Asymmetric reduction of prochiral carbonyl compounds is one of the most important ways to optically active alcohols. As far as the asymmetric reduction mediated by chiral boron compounds was concerned, tricoordinated chiral boranes[1] and chirally modified metal borohydrides[2] were early used as chiral reducing agents. However, all the reactions were stoichiometric. Only after Corey's chemzyme (a tricoordinated chiral oxazaborolidine)[3] was discovered in 1987, chiral boron chemistry started to enter a new stage of catalytic asymmetric syntheses.[4] However, asymmetric reactions catalyzed by tetracoordinated chiral boron compounds have seldom been investigated so far.[5] In 2002, Brown[6] published catalytic asymmetric reduction of prochiral ketones in the presence of chiral β-amino alcohol derivatives of 9-BBN with a C_2OBN framework. Just in the early 2002, we observed that chiral spiroborated esters with three B—O bonds and one N→B coordination bond (*i.e.* an O_3BN framework) showed asymmetric catalytic activity toward borane reductions of prochiral ketones, imines and oximes, and alkylation of aldehyde.[7] Here we wish to report the first asymmetric borane reductions catalyzed by chiral spiroborated esters with an O_3BN framework (Scheme 1).

Results and discussion

Asymmetric reactions catalyzed by chiral boron compounds with an O_3BN framework have never been reported. We previously synthesized (*S*)-proline derivatives[8] of 1,1'-bi-2-naphthoxylboric acid in the course of investigating preparative methodology of enantiomerically pure 1,1'-bi-2-naphthols and proved their spirocyclic structure by X-ray crystal structure analysis[8c] and ^{11}B NMR technique.[7] Their properties were examined and it was observed that they readily reacted with borane in THF to form a new reactive boron-containing species. When acetophenone was added to the reaction system, optically active (*R*)-1-phenylethanol was formed in good yield. This was the first example of asymmetric reactions catalyzed by a chiral spiroborated ester with an O_3BN framework. The influence of reaction conditions (reactant ratio, reaction temperature, reaction medium, *etc*.) on stereoselectivity of the reduction was also investigated. Under the most approriate conditions, (*R*)-1-phenylethanol was obtained in 76% *ee* and 73% isolated yield.

Scheme 1 Asymmetric borane reduction of acetophenone catalyzed by chiral spiroborated easter (*R*,*S*)-**1** or (*S*,*S*)-**1**



Influence of the amount of borane on stereoselectivity of the reduction

Reactant ratio is one of the most important factors

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influencing stereoselectivity for the reduction. In the presence of 0.1 equivelant of (*R*,*S*)-**1** or (*S*,*S*)-**1**, acetophenone was reduced with different amount of borane in THF, and the result was listed in Table 1. It was observed that acetophenone could not be completely reduced when the amount of borane was lower than 0.5 equivalent. On the other hand, stereoselectivy of the reduction was obviously decreased when the amount of borane was higher than 0.6 equivalent. This result perhaps was related to a non-catalytic competitive reaction (*i.e*. direct reaction of borane with acetophenone). It seems that 0.6 equivalent of borane is suitable for the reduction.

Influence of the used amount of the catalyst on stereoselectivity of the reduction

Relationship between the used amount of the chiral spiroborated esters and stereoselectivity of the reductions was also examined. The results of the reduction in the presence of 0.05—1.0 equivalent of the catalysts were showed in Table 2. It could be seen that the enantiomeric excess of the product was lowered in the cases of higher or lower than 0.1 equivalent of the catalyst. It looks as if attempt of upgrading enantiomeric purity of the product via increase of the used amount of the chiral catalysts was of no avail, in this asymmetric reduction.

Influence of reaction temperature on stereoselectivity of the reduction

Table 3 gave the results of asymmetric reduction of acetophenone in the presence of 0.1 equivalent of (*R*,*S*)-**1** or (*S*,*S*)-**1** at different temperature. It could be seen that the asymmetric reductions performed at 0—5 ℃ provided (*R*)-1-phenylethanol of higher enantiomeric purity (Entris 2 and 5). In the cases of higher or lower than 0—5 ℃, the reductions gave the product in lower *ee*. When the reduction performed at very low temperature (−78 ℃), *ee* of (*R*)-1-phenylethanol was decreased greatly, but the yield merely changed slightly (Entry 3). This fact meant that in the range of 0—78 ℃, the rate of the asymmetric catalytic reduction lowered

Table 1 Influence of the amount of borane on stereoselectivity of the reduction[a]

Entry	Cat.	Sub.∶BH_3∶cat. (molar ratio)	Temp./℃	Time/h	Yield/%	*ee*/%	Config.
1	(*S*,*S*)-**1**	1∶1.5∶0.1	0—5	2	79	42	*R*
2	(*S*,*S*)-**1**	1∶1.0∶0.1	0—5	2	74	56	*R*
3	(*S*,*S*)-**1**	1∶0.6∶0.1	0—5	2	73	68	*R*
4	(*R*,*S*)-**1**	1∶1.5∶0.1	0—5	2	81	48	*R*
5	(*R*,*S*)-**1**	1∶0.6∶0.1	0—5	2	73	76	*R*

[a] Cat., Config., *ee*., Sub. and Temp. are abbreviation of catalyst, configuration, enantiomeric excess, substrate and temperature, respectively. "Sub." represents acetophenone. All the reactions were carried out in THF and a 0.77—1.0 mol/L BH_3-THF solution was used. The yields were obtained after distillation under reduced pressure. *Ee* values were obtained by comparison with the maximum of specific rotation and determination of ^{1}H NMR spectra of diastereomeric phosphite esters formed using chlorophosphite derivative of (4*S*,5*S*)-*trans*-4,5-bis(hydroxymethyl)-2,2-dimethyl-l,3-dioxolane (BHMDMDO) as a chiral derivatizing agent.[7]

Table 2 Influence of the used amount of the catalyst on stereoselectivity of the reduction[a]

Entry	Cat.	Sub.∶BH_3∶Cat. (molar ratio)	Temp./℃	Time/h	Yield/%	*ee*/%	Config.
1	(*S*,*S*)-**1**	1∶0.6∶0.05	0—5	2	70	44	*R*
2	(*S*,*S*)-**1**	1∶0.6∶0.1	0—5	2	73	68	*R*
3	(*S*,*S*)-**1**	1∶0.6∶0.2	0—5	2	63	57	*R*
4	(*S*,*S*)-**1**	1∶2.0∶1.0	0—5	2	82	50	*R*
5	(*R*,*S*)-**1**	1∶0.6∶0.05	0—5	2	79	55	*R*
6	(*R*,*S*)-**1**	1∶0.6∶0.1	0—5	2	73	76	*R*

[a] Notes are the same as those in Table 1.

Table 3 Influence of reaction temperature on sterteoselectivity of the reduction[a]

Entry	Cat.	Sub.∶BH_3∶Cat. (molar ratio)	Temp./℃	Time/h	Yield/%	*ee*/%	Config.
1	(*S*,*S*)-**1**	1∶0.6∶0.1	ca. 28	2	72	62	*R*
2	(*S*,*S*)-**1**	1∶0.6∶0.1	0—5	2	73	68	*R*
3	(*S*,*S*)-**1**	1∶0.6∶0.1	−78	12	67	9	*R*
4	(*R*,*S*)-**1**	1∶0.6∶0.1	ca. 28	2	71	68	*R*
5	(*R*,*S*)-**1**	1∶0.6∶0.1	0—5	2	73	76	*R*

[a] Entries 1 and 4 were performed at ambient temperature of about 28 ℃. Other notes are the same as those in Table 1.

considerably with the fall of reaction temperature, while the rate of the non-catalytic reduction was not affected obviously.

Influence of the chirality of the ligands in the catalysts on stereoselectivity of the reduction

Stereoselectivity of the reduction was affected by the chirality of the diol ligand in the catalysts. It can be seen in the Table 3 (Entries 1, 4 and 2, 5) that the chelated chiral borated ester produced from (*R*)-1,1'-bi-2-naphthol shows higher chiral inductive ability than that from (*S*)-1,1'-bi-2-naphthol.

Influence of reaction system on stereoselectivity of the reduction

The composition of the reaction system influences considerably stereoselectivity of the asymmetric catalytic reduction, even occurrence of the reductive reaction (Table 4). In general, THF is an appropriate medium for the reduction. If the reduction occurred in a mixed solvent of THF and toluene (*V*/*V*=*ca.* 1∶1) at 0—5 ℃, the product with lower *ee* was obtained (Entry 2). However, under reflux, the system furnished the product in higher *ee* (Entry 3). It looks that higher reactive temperature is favourable for upgrading stereoselectivity of the reduction in the mixed system. When a strong Lewis acid, such as BF_3, was contained in a THF solution of borane,[9] stereoselectivity of the reduction was lowered. This result could be attributed to a competitive reaction between the Lewis acid and borane to the active boron-containing species. To avoid unfavourable influence of BF_3, borane used in the reduction was generated from the reaction of sodium borohydride and iodine in 1,2-dimethoxyethane.[10]

It was also observed that the reduction did not occur in a mixed system of THF and molecular sieves (4Å), meaning that borane was completely reacted by the molecular sieve before the reduction of the ketone occurred.

Mechanism of the reduction catalyzed by the chelated chiral borated esters

To understand catalysis of the chelated chiral borated esters to borane reduction of acetophenone, the reaction of (*R*,*S*)-**1** or (*S*,*S*)-**1** was examined with borane. To a THF solution of borane was added (*S*,*S*)-**1**. After the mixture was stirred for about 20 min, the inherently insoluble (*S*,*S*)-**1** in THF was dissolved completely, meaning that reaction occurred between borane and (*S*,*S*)-**1**. We determined ^{11}B NMR spectra of (*R*,*S*)-**1** and (*S*,*S*)-**1** (Figure 1) and observed that chemical shifts of (*R*,*S*)-**1** and (*S*,*S*)-**1** were at δ +8.33 and +8.25, respectively. After addition of a THF solution of borane, their spectra became complicated. Besides the original signals shifted by δ 0.2—0.1 upfield, there are four sets of signals, namely a quartet at δ −6.42±0.02, a quartet at δ −20.12±0.02, a triplet at δ −21.41 (partial band was overlapped with adjacent quartet) and a quintet at δ −35.53. But, no chemical shift of the boron compound with BO_3 framework was observed, which generally was at near δ +17. Chemical shifts at δ +8.13 and δ +8.14 meant that the boron atom in (*R*,*S*)-**1** and (*S*,*S*)-**1** could be in a new, relative strong shielded environment. On the other hand, quartet at near δ −20.12 indicated that a new compound with one $H_3B\leftarrow N$ framework was formed. It appeared that addition of a THF solution of borane made the original B←N bond of the chelated borated esters broken to form a borane-pyrrolidine complex, while the boron atom connected with three oxygen atoms was in a coordinated state to THF, because the boron atom in BO_3 framework was a harder acid and THF was a harder base than DMSO. Other signals can also be assigned. Quartet at δ −6.42 corresponds to DMSO→BH_3 produced via ligand exchange between THF and DMSO and is formed by coupling of the boron and three hydrogen atoms. This complex is able to dipolymerize to form unstable $B_2H_6(DMSO)_2$, which is further rearranged to form $BH_2^+(DMSO)_2BH_4^-$. This has been proved by a triplet at δ −21.41 and a quintet at δ −35.53. It appeared that there were the following reactions in this mixed system (Scheme 2). It is just (*R*,*S*)-**2** or (*S*,*S*)-**2** resulting from the reaction of borane with (*R*,*S*)-**1** or (*S*,*S*)-**1** that is a key intermediate in the catalytic reduction of acetophenone.

In a mixed system of (*R*,*S*)-**1** or (*S*,*S*)-**1**, borane, THF and acetophenone, due to the ketone being a harder base than THF, it would replace THF in (*R*,*S*)-**2** or (*S*,*S*)-**2** to form intermediate complex (*R*,*S*)-**3** or (*S*,*S*)-**3**, where C=O of acetophenone and B—H bond of BH_3 were

Table 4 Influence of reactive system on the stereoselectivity of the reduction[a]

Entry	Cat.	Reactive system	Temp./℃	Time/h	Yield/%	*ee*/%	Config.
1	(*S*,*S*)-**1**	THF	0—5	2	73	68	*R*
2	(*S*,*S*)-**1**	THF-toluene	0—5	2	82	43	*R*
3	(*S*,*S*)-**1**	THF-toluene	reflux	2	75	66	*R*
4	(*S*,*S*)-**1**	THF (trace BF_3)	0—5	2	72	60	*R*
5	(*S*,*S*)-**1**	THF/MS	0—5	2	—	—	—

[a] All the reactions were performed in a 1∶0.6∶0.1 molar ratio of acetophenone, borane and catalyst. MS is an abbreviation for molecular sieves. Other notes are the same as those in Table 1.

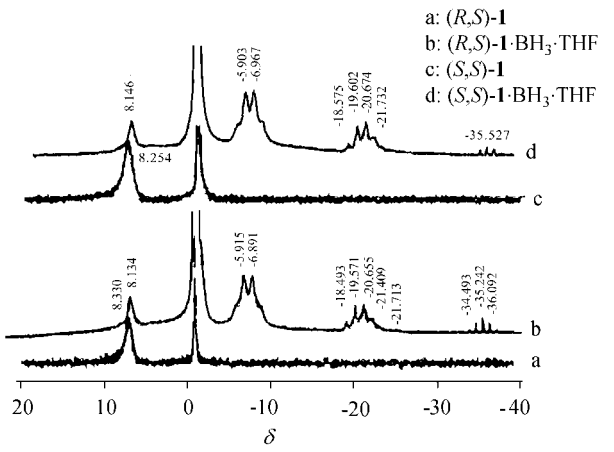
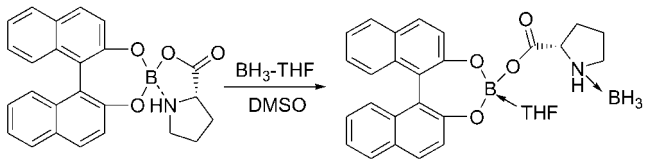


Figure 1 ^{11}B NMR spectra of (*R*,*S*)-**1** or (*S*,*S*)-**1** and their mixture with a THF solution of borane (DMSO-d_6, 300 MHz).

Scheme 2 Reactions in a mixed system of (*R*,*S*)-**1** or (*S*,*S*)-**1**, borane, THF and DMSO



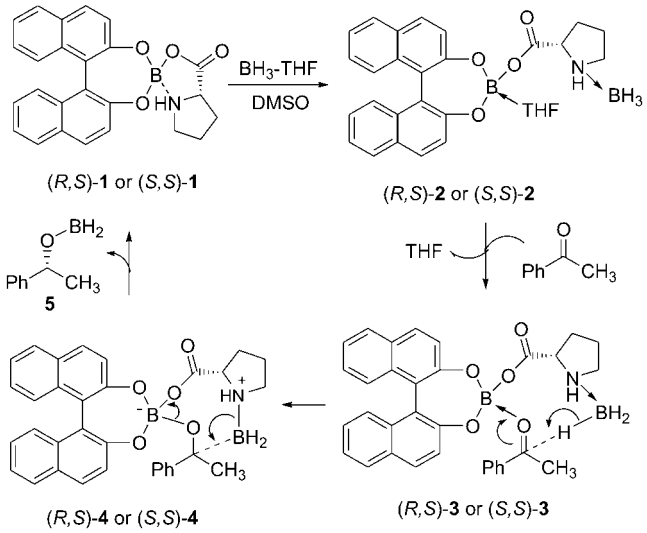
BH_3-THF + DMSO ⟶ BH_3-DMSO ⟶ $BH_2^+(DMSO)_2$ + BH_4^-

activated, which was followed by undergoing a hydrogen transfer reaction between the carbonyl group and BH_3 to form unstable **4**, and then further rearrangement to liberate 1-phenylethoxyborane **5**. Thus, a primary catalytic cycle was established (Scheme 3). **5** generated in the cycle could also coordinate to (*R*,*S*)-**1** or (*S*,*S*)-**1** as borane to form a new intermediate (*R*,*S*)-**2′** or (*S*,*S*)-**2′**, *i.e.* BH_3 of **2** was replaced by **5**. After the intermediate underwent successively coordination to acetophenone, hydrogen transfer and rearrangememt via a six-central transition state, bis(1-phenylethoxy)borane (**5′**) was formed. **5′** could no longer coordinate to (*R*,*S*)-**1** or (*S*,*S*)-**1**, because in the molecule, charge feedback of the two oxygen atoms to the boron resulted in relatively high charge density at the boron. To this, a full catalytic cycle was accomplished. This mechanism gave a satisfactory explanation for complete reduction of 1 equivalent of acetophenone by 0.6 equivalent of borane, in the catalytic reduction.

Conclusion

Asymmetrically catalytic activity of chiral spiroborated esters with an O_3BN framework toward borane reduction of prochiral ketones was observed for the first time. In the presence of 0.1 equivelant of (*R*,*S*)-**1** or (*S*,*S*)-**1**, acetophenone was reduced by borane in THF at 0—5℃ for 2 h to give (*R*)-1-phenylethanol of 76% *ee* and 73% isolated yield. In the asymmetrically catalytic

Scheme 3 A possible primary catalytic cycle of asymmetric borane reduction in the presence of (*R*,*S*)-**1** or (*S*,*S*)-**1**



reduction, a new tetracoordinated boron compound produced from the reaction of (*R*,*S*)-**1** or (*S*,*S*)-**1** and borane was a key intermediate.

Experimental

General

Spiroborated esters (*R*,*S*)-**1** or (*S*,*S*)-**1** were prepared according to the literature.[8] A THF solution of borane was obtained through leading gaseous diborane generated from the reaction[10] of sodium borohydride and iodine in 1,2-dimethoxyethane into dried THF. A borane-THF solution containing a trace of BF_3 was prepared by leading gaseous diborane generated from the reaction[9] of potassium borohydride and BF_3-OEt_2 into dried THF. Acetophenone was dried over CaH_2 and then distilled (90—94 ℃/4 kPa) and the distillate was stored over molecular sieves (4Å). Toluene used was of analytical grade.

IR spectra were recorded on a Testscan Shimadzu FTIR 8000 or a Nicolet 170 SX FT-IR spectrophotometer in KBr. ^{1}H NMR and ^{11}B NMR spectra were performed on a Varian Mercury VX 300 and all chemical shifts were reported as δ values relative to Me_4Si. Optical rotations were measured on a Perkin-Elmer 341 Mc polarimeter. Melting points were determined on a VEB Wagetechnik Rapio PHMK 05 instrument and not corrected. *E.e* values were obtained by comparison with the maximum of specific rotation and determination of ^{1}H NMR spectrum of diastereomeric phosphite esters formed using chlorophosphite derivative of (4*S*,5*S*)-*trans*-4,5-bis-(hydroxymethyl)-2,2-dimethyl-l,3-dioxolane (BHMDDO) as a chiral derivatizing agent.[7]

Catalytic reduction of acetophenone in the presence of (*R*,*S*)-1 or (*S*,*S*)-1

The reactions were run under Ar atmosphere. 0.245 g (0.6 mmol) of (*R*,*S*)-**1** was charged to a sufficiently dried 50 mL of two necked round bottomed flask

equipped with a reflux condenser and a rubber septum. 3.9 mL (3.6 mmol) of 0.92 mol/L solution of BH_3•THF was added via syringe at room temperature. After being stirred for 20 min, the mixture was cooled to 0—5 ℃, followed by adding acetophenone (6 mmol, 0.7 mL) via syringe, and the resultant mixture was stirred at the same temperature for 2 h. After evaporating THF, to the residue was added 2 mol/L HCl (20 mL) with stirring, and then extracted with ether (15 mL×3). The extracts were combined and alkalized with 2 mol/L NaOH to remove (*R*)-1,1'-bi-2-naphthol, which got into water phase as sodium 1,1'-bi-2-naphtholate. Enantiopure (*R*)-1,1'-bi-2-naphthol could be recovered via acidification of the water phase and recrystallization. The ethereal phase was separated and successively washed with saturated NH_4Cl solution, brine and H_2O, dried over anhydrous Na_2SO_4 and evaporated to give an oil, which upon distillation furnished (+)-1-phenylethanol (0.53 g in the yield of 72%, $[\alpha]_D^{34}$ +39.7 (*c* 2.52, CH_2Cl_2) {Lit:[11] $[\alpha]_D^{34}$ −52.5 (*c* 2.52, CH_2Cl_2)}, 76% *ee*. Determination of enantiomeric purity of (+)-1-phenylethanol using chlorophosphite derivative of BHMDMDO as a chiral derivatizing agent[7] gave a value of 74.6% *ee*. This product was characterized by IR and ^{1}H NMR spectra.

In the above reduction, if (*S*,*S*)-**1** was used as chiral catalyst, (+)-1-phenylethanol was obtained in 73% yield, $[\alpha]_D^{34}$ +35.5 (*c* 2.52, CH_2Cl_2), 68% *ee*.

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