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Highly enantioselective carbonyl reduction with borane catalyzed by chiral spiroborate esters derived from chiral 1,2-aminoalcohols

Viatcheslav Stepanenko, Margarita Ortiz-Marciales,* Wildeliz Correa, Melvin De Jesús, Sandraliz Espinosa and Lymaris Ortiz

Department of Chemistry, University of Puerto Rico-Humacao, CUH Station, Humacao, PR 00791, USA

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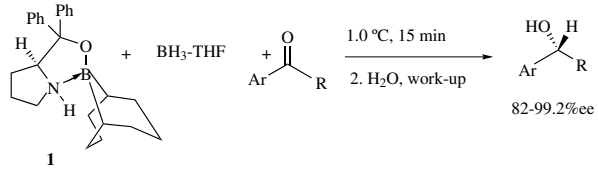
Abstract—Novel spiroborate esters derived from nonracemic 1,2-amino alcohols were examined as chiral catalysts in the borane reduction of acetophenone and other aromatic ketones at room temperature. The optically active alcohols were obtained in excellent chemical yields and enantioselectivities up to 99% ee with 10% of catalyst.

1. Introduction

Asymmetric reduction of prochiral ketones to obtain enantiomerically pure alcohols is one of the most important transformations in organic synthesis. Over the last 25 years, a large variety of asymmetric catalysts have been prepared from alumino- or borohydrides and chiral diols or amino alcohols, which are highly useful for the enantioselective reduction of carbonyl compounds.[1,2] In particular, the 1,3,2-oxazaborolidines derived from chiral amino alcohols have been recognized as exceptional catalysts in the reduction of aromatic ketones and in other enantioselective reactions.[3–5] The *B-H* oxazaborolidine–borane complexes are frequently reported as catalysts for carbonyl reductions since they are conveniently prepared from the corresponding amino alcohol and either borane–THF or borane dimethyl sulfide (DMS) complexes. However, the extreme sensitivity of these reagents to atmospheric moisture makes them difficult to isolate and purify. Consequently, they are prepared in situ prior to the use in asymmetric reductions. Moreover, *B-H* oxazaborolidines can form dimers and other species which can alter the nature of the catalyst.[6–8] Impurities present in the catalysts may lead to diminished selectivity and lead to irreproducible results.[9,10] On the other hand, B-substituted oxazaborolidines[5] show excellent enantioselectivity and synthetic utility but require careful purification steps to eliminate traces of boronic acid and their esters. Therefore, the commercially available reagents are very expensive.

Masui and Shioiri[11] obtained excellent enantioselectivities in the borane–DMS reduction of acetophenone and nitrogen containing prochiral ketones using a mixture of diphenylprolinol and trimethylborate as catalyst. They postulated the in situ formation of a very reactive *B*-methoxy oxazaborolidine.

Recently, Brown et al.[12] reported a new enantioselective reducing reagent system, in which the chiral catalyst is a tight amino-borane complex **1** and borane is the external hydride donor to reduce hindered and substituted aryl alkyl ketones, with good to high enantioselectivities, as shown in Scheme 1.



Scheme 1.

Boronic and borate esters form stable complexes with amino groups[13,14] and intramolecular coordination is also well documented.[15,16] Thormeier et al.[14] reduced acetophenone at 0 °C in THF in good yield and with

* Corresponding author. Tel.: +1 787 852 3222; fax: +1 787 850 9422; e-mail: mr_ortiz@webmail.uprh.edu

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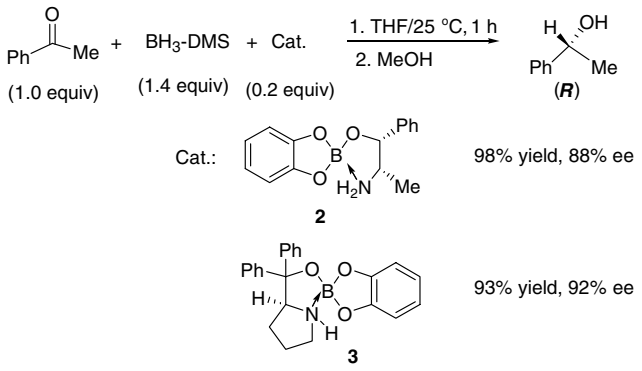
low to moderate enantioselectivity using 2 equiv of an in situ prepared chiral biarylhydroborate–aniline complex and in the presence of boron trifluoride–ethylether. More recently, Shan et al.[17,18] developed a new class of catalyst for the borane reduction of prochiral aliphatic and aromatic ketones based on spiroborate esters derived from chiral 1,1′-bi-2-naphthyl borate esters and chiral 1,2-amino alcohols or 2-amino acids. These gave modest to high enantioselectivities with 0.1 equiv of catalyst. The stereochemistry of the chiral diol-derived part of the catalyst did not influence the alcohol configuration. Our interest in new reagents for catalytic asymmetric synthesis led us to develop a new chiral spiroborate ester system, which offers great potential for the borane-based catalytic asymmetric synthesis of enantiopure alcohols.[19,20]

2. Results and discussion

Initially, we investigated the synthesis and properties of borate **2** (Scheme 2). This was prepared by the addition of (1*R*,2*S*)-(−)-norephedrine to catecholborane in ether at 0 °C for 1 h.[15] The white crystalline solid was washed with ether and isolated in 83% yield. By ^{11}B NMR, the characteristic signal for the central boron atom was observed at δ 11.6 ppm.[15] Other signals at δ 14.2 and 7.9 ppm, were also observed due to by-products, presumably belonging to the complexed spiro dicatecholborate and its borate amino complex,[17] respectively, which were estimated at ~20% by ^{1}H and ^{13}C NMR. Unfortunately, all attempts to remove these impurities by recrystallization of the sample did not improve the purity of the compound. Similar results were obtained when the reaction was carried out at a lower temperature (−40 °C). At −78 °C, the reaction did not take place. The synthesis of **2** in THF and dichloromethane gave lower chemical yields of 42% and 46%, respectively, again in low purity. An alternative method for the preparation of **2** from catechol, triisopropyl borate, and (1*R*,2*S*)-(−)-norephedrine also afforded a product with low purity.



Scheme 2.

The borane reduction of acetophenone was carried out in the presence of 20% of **2** (prepared in ether), obtaining the (*R*)-1-phenyl ethanol in quantitative yield and with 88% ee, as indicated in Scheme 2. Based on these results, other aromatic ketones were reduced enantioselectively in different solvents and the results are presented in Table 1. Modest to high enantioselectivities were achieved for all the substrates in THF. The selectivity decreases to 60% ee for the reduction of acetophenone in dichloromethane (entry 2), but is comparable in dioxane (86% ee, entry 3). Reduction of other substrates gave similar results to that of acetophenone (entries 4–6).

Table 1. Enantioselective reduction of aromatic ketones with spiroborate **2** (0.2 equiv)[a]

Entry	Ketone	Solvent	Yield[b] (%)	ee%[c]
1	Acetophenone	THF	98	88
2	Acetophenone	CH_2Cl_2	79[d]	60
3	Acetophenone	Dioxane	72[d]	86
4	4-Chloro-acetophenone	THF	74	87
5	4-Methoxy-1-tetralone	THF	70	85
6	3-Acetylpyridine	THF	90	82[e]

[a] 1 equiv of ketone:1.4 equiv of borane:0.2 equiv of cat. at rt, 1 h.
[b] Purified by Kugelrohr distillation.
[c] Determined by GC on a chiral column (CP-Chiralsil-DexCB).
[d] Crude product.
[e] 2 equiv of borane and a 24 h workup with methanol.

Next, we were interested in studying borate ester **3** (Scheme 2) with a diphenylprolinol-derived fragment, analogous to the CBS reagent and Brown's complex **1**. This compound was prepared from catecholborane and diphenylprolinol in 75% yield and about 80% purity by ^{1}H and ^{13}C NMR. By ^{11}B NMR, the characteristic signal for the central boron atom was observed at δ 11.7 ppm. The reduction of acetophenone with borane and 20% catalyst **3** afforded (*R*)-1-phenylethanol in 93% yield and 92% ee. Change of the amino alcohol moiety in the catalyst increased the enantioselectivity slightly.

Further modification of the catalytic system was envisaged through a change in the structure of the chiral spiroborate ester by employing a less strained diol ring system. We felt that this would make the compounds more stable. A series of new reagents **4**–**12**, shown in Figure 1, were conveniently prepared from ethylene glycol, triisopropyl borate, and readily available enantiopure amino alcohols according to the method reported by Huskens and Reetz.[16] The borate esters were obtained in essentially quantitative yields with only minor amounts (<10%) of impurities, as assessed by ^{11}B, ^{1}H, and ^{13}C NMR. No further purification was attempted. Their characteristic mp, specific rotation, and ^{11}B NMR signals are presented in Table 2. The white crystalline borate amino complexes were easy to handle under nitrogen, and exhibit little decomposition over prolonged storage (4–6 months) at rt. However, **10** did show some susceptibility to light.

To assess the enantioselectivity obtained by employing these chiral spiroborate esters **4**–**12** in the catalytic reduction of aromatic ketones, acetophenone was used as a model compound. The reduction was carried out with 1 M equiv of borane–DMS complex and 2.5–20% of the different catalysts at room temperature in THF.

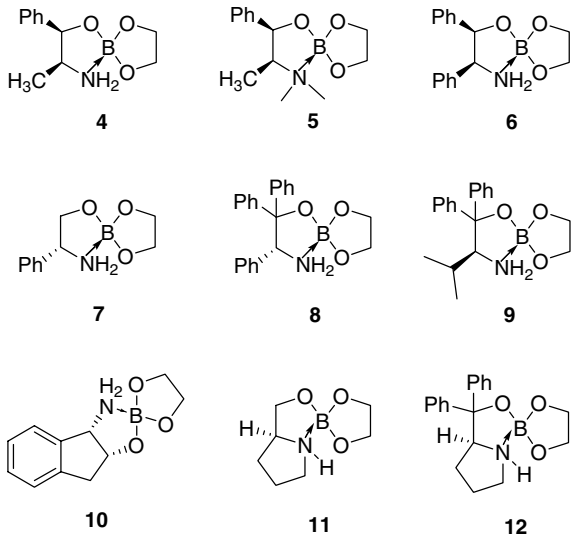


Figure 1. Spiroborate esters derived from chiral amino alcohols.

Table 2. Representative properties of spiroborates **4**–**12**

Cat.	Mp (°C)	$[\alpha]_D^{20}$	^{11}B NMR δ (ppm)
4	176–179	−37.5 (*c* 0.056, DMSO)	10.0 (s) (DMSO-d_6)
5	70–75	−5.0 (*c* 0.024, $CHCl_3$)	10.9 (s) ($CDCl_3$)
6	183 (dec)	+5.0 (*c* 0.029, DMSO)	10.5 (s) (DMSO-d_6)
7	161 (dec)	−38.7 (*c* 0.062, $CHCl_3$)	10.3 (s) (DMSO-d_6)
8	207–209	+98.0 (*c* 0.05, $CHCl_3$)	9.6 (s) ($CDCl_3$)
9	194 (dec)	+43.0 (*c* 0.023, DMSO)	10.5 (s) (DMSO-d_6)
10	151 (dec)	+28.6 (*c* 0.018, $CHCl_3$)	10.3 (s) ($CDCl_3$)
11	115–116	+13.0 (*c* 0.049, $CHCl_3$)	9.9 (s) ($CDCl_3$)
12	274 (dec)	−110.0 (*c* 0.03, DMSO)	10.3 (s) (DMSO-d_6)

Table 3 summarizes these results. Catalyst **4** showed higher enantioselectivity (Table 3, entry 1) than borate ester **2**. To establish the correlation between the amount of catalyst and enantioselectivity, systematic studies were carried out using borate ester **4** prepared from an inexpensive aminoalcohol. Decreasing the catalyst from 20 to 5 mol % slightly decreased the ee of the alcohol (Table 3, entries 1–3), and with 2.5 mol % the enantioselectivity was substantially lower (Table 3, entry 4). In almost all studies, the reactions were very fast. The reduction of acetophenone using 5% of catalysts **4** and **12** was complete within 15 min after the substrate was added, as shown by GC analysis. With the exception of the less reactive **5**, moderate to excellent enantioselectivities were achieved. In particular, catalysts **8**, **9**, and **12** were highly effective. In all cases, the reactions took place with excellent reproducibility. In addition, the amino alcohols could be recovered.

3. Conclusion

With the exception of **5**, spiroborate esters **2**–**12** are particularly stable and exhibit comparable enantioselectivities to those observed for the corresponding B-substituted oxazaborolidines (CBS reagent). These catalysts offer an excellent alternative for asymmetric reduction. Further studies are currently in progress to elucidate the reaction mechanism of asymmetric induction and applications of the catalytic system in the reduction of a variety of ketones and their imino analogues.

Table 3. Enantioselective borane reduction of acetophenone with spiroborate esters **4**–**12** as catalysts[a]

Entry	Cat.	mol %	Yield[b] (%)	ee%[c]	Conf.
1	**4**	20	92	92	*R*
2	**4**	10	75[d]	90	*R*
3	**4**	5	84	88	*R*
4	**4**	2.5	85	75	*R*
5	**5**	10	85[d,e]	0	—
6	**6**	10	87	90	*R*
7	**7**	10	94	82	*S*
8	**8**	20	75	98	*R*
9	**8**	10	99	96	*R*
10	**9**	10	89	98	*S*
11	**9**	5	97	98	*S*
12	**10**	10	75	95	*S*
13	**10**	5	96	94	*S*
14	**11**	10	93	83	*R*
15	**12**	10	98	99	*R*
16	**12**	5	95	98	*R*

[a] 1 equiv of ketone:1 equiv of borane at rt, 1 h.
[b] Purified by Kugelrohr distillation.
[c] Determined by GC on a chiral column (CP-Chiralsil-DexCB).
[d] Crude product.
[e] Traces of ketone was left after 3 h.

4. Experimental

4.1. Optimized procedure for the borane reduction of acetophenone using catalyst 12

Borane–DMS complex (10 M, 1.0 mL, 10.0 mmol) was added to a solution of catalyst **12** (0.323 g, 1.00 mmol) in dry THF (30 mL) and stirred at rt, under nitrogen for 15 min. A solution of acetophenone (1.2 g, 10.0 mmol) in THF (10 mL) was added to the reaction mixture for 1 h using an infusion pump. After 15 min, the reaction was monitored by GC, indicating that acetophenone was consumed. The solution was stirred at rt over 1 h, then cooled to 0 °C and quenched with methanol (10 mL). After stirring for 1 h at rt the solvents were removed under vacuum. The residue was dissolved in DCM (40 mL), washed with a saturated solution of ammonium chloride (25 mL), water (25 mL), and dried with sodium sulfate. The solvents were removed under vacuum and the residue was distilled in Kugelrohr apparatus under vacuum (59 °C/0.25 mmHg) to give the final product as a colorless oil (1.20 g, 98%), $[\alpha]_D^{20} = +43.8$ (*c* 0.039, MeOH). Chiral GC indicates ratio of enantiomers as 99.53:0.47, 99% ee.

Acknowledgements

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