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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5799–5802

Enantioselective reduction of prochiral ketones using spiroborate esters as catalysts

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Received 19 May 2007; revised 11 June 2007; accepted 15 June 2007
Available online 22 June 2007

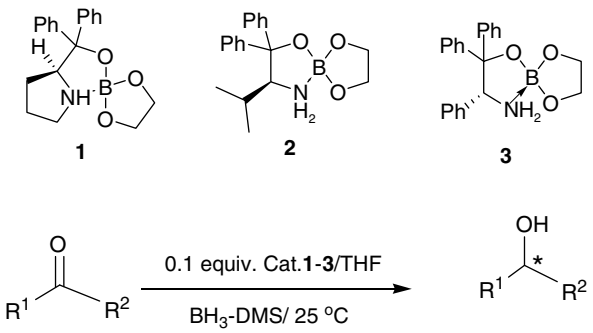
Abstract—Novel spiroborate esters derived nonracemic 1,2-aminoalcohols and ethylene glycol are reported as highly effective catalysts for the asymmetric borane reduction of a variety of prochiral ketones with borane–dimethyl sulfide complex at room temperature. Optically active alcohols were obtained in excellent chemical yields using 0.1–10 mol % of catalysts with up to 99% ee.

The asymmetric synthesis of secondary enantiopure alcohols from prochiral ketones is a key step in the preparation of a variety of pharmaceutical products.[1,2] To accomplish this transformation with high enantioselectivity, new methods, such as, asymmetric transfer hydrogenation,[3] metal catalyzed hydrogenations,[4] enzymatic reactions[5] and novel metal hydride reagents,[6–9] are continuously being developed as valuable synthetic tools. Chiral boron reagents, in particular oxazaborolidines[7] derived from nonracemic 1,2-aminoalcohols, are well known catalysts for the synthesis of highly enantiopure secondary alcohols. Other oxazaborolidine-like compounds have been applied for the borane reduction of prochiral ketones with good to excellent enantioselectivities.[8,9]

Borates and boronates have been previously established as effective chirality transfer reagents.[10] Borates accessed from nonracemic 1,1′-bi-2-naphtyldiol and complexed to anilines reduce acetophenone with up to 64% ee.[11] Spiroborate esters prepared from nonracemic 1,1′-bi-2-naphtylborate esters and enantiopure 1,2-aminoalcohols (or 2-aminoacids) have been found to catalytically reduce prochiral aromatic and aliphatic ketones with modest to high enantioselectivities.[8b,c]

We recently reported the synthesis of a new class of crystalline, air- and moisture stable spiroborate esters that were examined for the reduction of acetophenone as a model substrate to obtain nonracemic 1-phenylethanol.[12] Catalysts **1**–**3** (Scheme 1) proved to be the most valuable due to their outstanding enantioselectivity, facile synthesis, purity and convenience of handling. We present here the X-ray crystal structure of catalyst **1**, a correlation study of the catalytic load of **1** with the enantio-purity of alcohol, and the asymmetric borane reduction of representative ketones using **1**–**3** as catalyst.

Spiroborate esters **1** and **2** are readily prepared from commercially available diphenyl valinol and diphenyl-



Scheme 1.

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doi:10.1016/j.tetlet.2007.06.086

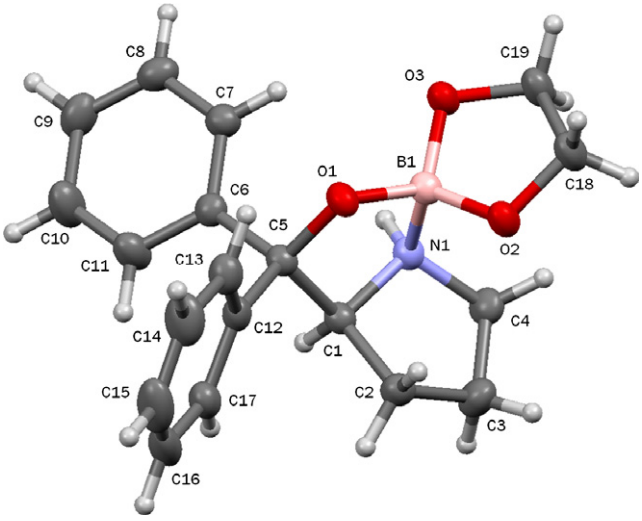


Figure 1. Crystal structure of spiroborate **1**.

prolinol, respectively, according to the reported procedure.[13] 1,1,2-Triphenyl ethanolamine was synthesized by established methods.[14] The white crystalline spiroborate complex **1** was found to be particularly stable after being exposed to moist air for 24 h at 25 °C, as evidenced by its unchanged ^{11}B, ^{1}H and ^{13}C NMR spectra. The X-ray diffraction analysis of **1** presented in Figure 1 clearly shows the structure of the amino spiroborate complex.[15] The observed B1–N1 bond distance at 1.665 (2) Å is comparable to the bonds of similar boron nitrogen coordinated complexes.[16]

To establish the optimal catalytic load required to achieve high enantioselectivity, the reduction of acetophenone was studied using different molar equivalents of catalyst **1** with 0.7 M equiv of BH_3·DMS complex in THF at room temperature. As indicated in Figure 2, 10 mol % of catalyst **1** afforded (*R*)-1-phenylethanol with 99% ee. Moreover, higher enantioselectivities (98% ee) were achieved with as low as 0.5 M % of catalytic load, and even with 0.1 M % of catalyst **1**, the enantiomeric excess was high (89%).

Spiroborates **2** and **3** were also investigated for the reduction of acetophenone obtaining (*R*)-1-phenylethanol with excellent chemical yield and 98% and 96% ee,

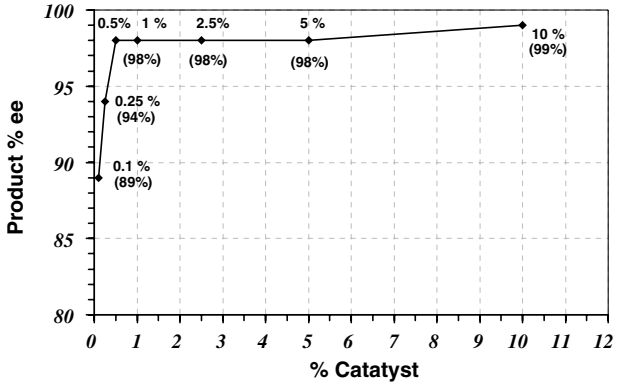
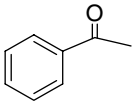
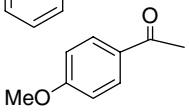
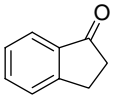
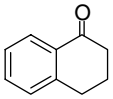
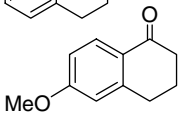
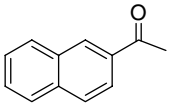
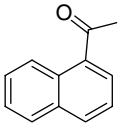
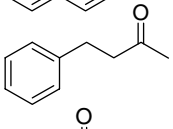
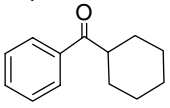
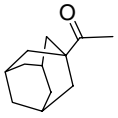


Figure 2. Asymmetric reduction of acetophenone in the presence of catalyst **1**.

respectively. In addition, catalyst **2** showed excellent enantioselectivity even with 5 mol % loading (98% ee). The reduction of representative arylalkyl and aliphatic ketones was also investigated and the results are shown in Table 1.[17] In general, the optical active alcohols were obtained in excellent chemical yields and outstanding enantio-purity for ketones with bulky group differentiation.

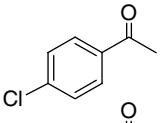
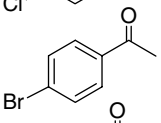
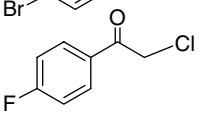
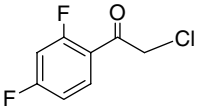
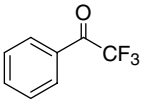
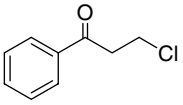
It was of interest to study the effect of electronic and steric factors in the reduction of halogenated acetophenones. Moreover, their enantiopure alcohols are very important intermediaries in organic synthesis.

Table 1. Electronic and steric effects on asymmetric reduction of aromatic and aliphatic ketones using spiroborates

Entry	Substrate	Cat.[a]	Yield[b] (%)	ee[c] (%)
1		**1**	98	99[d] (*R*)
2		**2**	97	98[d] (*R*)
3		**3**		96[d] (*R*)
4		**1**	90	92[e] (*R*)
5		**2**	94	97 (*R*)
6		**1**	96	96 (*R*)
7		**1**	99	>99 (*R*)
8		**1**	81	98[e] (*R*)
9		**1**	84	99[f] (*R*)
10		**1**	94	87
11		**1**	90	72 (*R*)
12		**1**	83	61 (*R*)
13		**1**	98	99 (*R*)

[a] 1 equiv ketone, 0.7 equiv BH_3·DMS and 0.1 equiv catalyst in THF at rt.
[b] Purified by flash chromatography column or Kugelrohr distillation.
[c] Determined by ^{31}P NMR of derivate with phosphonate (CDA).
[d] Determined by GC of alcohol on Chiral Column (CP-Chirasil-DexCB).
[e] Determined by GC of acetyl derivative on Chiral Column.
[f] Determined by HPLC of acetyl derivative on Chiral Column (Chiralpack ID).

Table 2. Reduction of representative halogenated aromatic ketones with spiroborate with 0.1 equiv of catalyst **1**

Entry	Substrate[a]	Yield[b] (%)	ee[c] (%)
1		98	99[d] (*R*)
2		84	98[e] (*R*)
3		83	95[e] (*S*)
4		88	98 (*S*)
5		97	82 (*S*)
6		86	94 (*R*)

[a] 1 equiv ketone, 0.7 equiv BH_3·DMS and 0.1 equiv catalyst in THF at rt.
[b] Purified by flash chromatography column or Kugelrohr distillation.
[c] Determined by ^{31}P NMR of derivate with phosphonate (CDA).
[d] Determined by GC of alcohol on Chiral Column (CP-Chirasil-DexCB).
[e] Determined by GC of acetyl derivative on Chiral Column.

Several halogenated ketones were reduced with borane–DMS in the presence of 10 mol % of catalyst **1** providing their corresponding alcohols with high enantiopurity (94–99% ee), except for the highly reactive 2,2,2,-trifluoroacetophenone (82% ee, entry 5), as illustrated in Table 2.

In conclusion, a facile and efficient method for the reduction of aralkyl-, aliphatic- and halogenated aromatic ketones in the presence of up to 0.5 mol % catalysts **1** with outstanding enantioselectivities has been established. Catalyst **1** offer an excellent alternative for asymmetric reduction of ketones similar in enantioselectivity to those reported for *B*-methyl oxazaborolidine (CBS reagent).[7]

Acknowledgements

Financial support by the National Institute of Health through their MBRS (GM 08216), IMBRE (NC P20 RR-016470) and NSF-ADVANCE (SBE-0123645) Grants is greatly appreciated. The NIH-IMBRE and NIH-RISE, NIH-MARC, NSF-AMP undergraduate student's support are also gratefully acknowledged.

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15. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 639750. Formula: $C_{19}H_{22}B_1N_1O_3$. Unit cell parameters: *a* 8.0330(4), *b* 9.9264(4), *c* 20.4313(9), space group *P*212121.
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17. *Representative procedure. R*-(−)-1-indanol (Table 1, entry 5): To a 100 mL round flask equipped with a septa and nitrogen flow, 10% of EG-Val borate **1** (0.325 g, 1.0 mmol) was added. Then, dry THF (30 mL) and BDS complex (1.0 mL 10 M, 10 mmol) were added to the reaction flask and the solution was stirred for about 15 min. A solution of 1-indanone (1.322 g, 10.0 mmol) in dry THF (10 mL) was added to the reaction mixture for 1 h. The reaction progress was followed by GC analysis. When the reaction was complete, the reaction mixture was cooled at 0 °C, MeOH (20 mL) was added and the mixture was heated in the rotoevaporator while removing the solvents. The concentrated mixture was treated with saturated NH_4Cl solution (25 mL) followed by extractions with dichloromethane (4 × 20 mL), dried with sodium sulfate and

concentrated. After vacuum distillation in a Kugelrohr oven (136 °C/0.6 mmHg), the white solid of 1-indanol was obtained in a 94% yield (1.264 g). Derivatization by Alexakis method[18] and analysis by ^{31}P NMR indicated 97.4% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87 (m, 1H, C8-H); 22.05 (s, 1H, OH); 0.41 (m, 1H, C8-H); 2.75 (m, 1H, C9-H); 2.99 (m, 1H, C9-H); 5.16 (t, $J = 6.2$ Hz, 1 H, C1-H); 7.15–7.19 (m, Ar, 3H); 7.35 (d, $J = 5.6$ Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7; 35.8; 76.3; 124.1; 124.8; 126.6; 128.2; 143.2; 144.9; (Mass, 70 eV, EI): 134.1 (M^+, 46.83%); 133.1 (100%), 117.2 (75.55%); 105.1 (10.08%); $[\alpha]_D^{20}$ −29.4 (*c* 0.033, $CHCl_3$); mp: 68–69 °C.

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