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Novel dimethoxy(aminoalkoxy)borate derived from (*S*)-diphenylprolinol as highly efficient catalyst for the enantioselective boron-mediated reduction of prochiral ketones

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ABSTRACT

The novel dimethoxyl(aminoalkoxy)borate **1** was isolated as a white crystalline dimer joined by H-bonding as evidenced by X-ray analysis, and demonstrated to be a highly effective catalyst for the asymmetric reduction of representative prochiral ketones with borane–DMS. Optically pure alcohols were obtained using only 1 mol % of catalyst **1** in up to 99% ee.

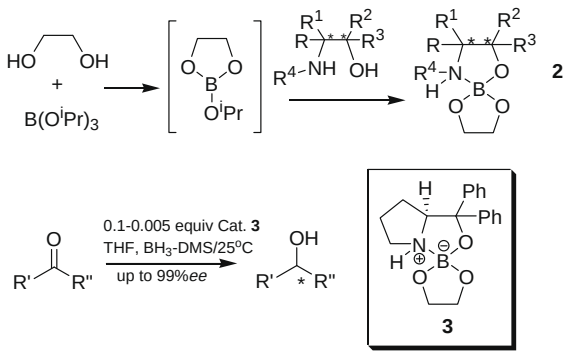
Asymmetric reduction of prochiral ketones is one of the most efficient methods to introduce chirality when synthesizing non-racemic biologically active compounds.[1] Chiral 1,3,2-oxazaborolidines have been intensely applied as highly effective catalysts for the asymmetric borane reduction of ketones.[2,3] Recently, the design of more stable and reliable borane catalysts and methods to improve the enantioselective process for a variety of substrates have been areas of great interest.[4]

Previously, we have shown that the spiroaminoborate esters **2** (Scheme 1), derived from chiral amino alcohols and ethylene glycol, are valuable catalysts for the asymmetric reduction of prochiral ketones to obtain non-racemic alcohols in high purity.[5] Furthermore, spiroborate **3** derived from (*S*)-diphenylprolinol achieved the best enantioselectivity for a wide variety ketones.[5c,d] As part of our new efforts to obtain non-spiro analogues of borate **3**, we describe here the synthesis, isolation and characterization of novel aminoborate esters **1** and **5**, (Scheme 2). Additionally, the enantioselectivity of these borates in the reduction of representative ketones was studied.

Masui and Shiori[6a] initially attempted to isolate a *B*-methoxy-1,3,2-oxazaborolidine from the reaction of (1*S*,2*S*,3*R*,5*S*)-3-amino-2-hydroxypinane and trimethyl borate. However, they were not successful, and they suggested as a reason, the oxazaborolidine instability. As a result, they used the in situ formation of the postulated *B*-methoxy-oxazaborolidine as a simpler and effective protocol for the borane reduction of acetophenone and α-oxoketoxime ethers.[6c] Also, Masui[6a] and other groups.[7,8a,b] studied the reduction of alkyl arylketones using as catalyst, the in situ generated oxazaborolidine **4**, derived from (*S*)-diphenylprolinol and trimethyl borate. Moreover, other related *B*-alkoxy-oxazaborolidines have been suggested as active catalytic species in the reduction of ketones,[6b,9] and in the reaction of addition to aldehydes.[8c] To our knowledge, these oxazaborolidines have not been isolated and/or characterized. Interestingly, when we carried out the reaction of (*S*)-diphenylprolinol with trimethyl borate in dry diisopropyl ether at room temperature, the aminoborate complex **1** was obtained as a crystalline compound in 68% yield. The product was characterized by ^{1}H, ^{13}C, ^{11}B NMRs and IR spectroscopic analysis.[10]

The structure of **1** was conclusively proved by X-ray analysis (Fig. 1).[11] Intriguingly, two molecules in a single unit are packed together by hydrogen bonding between the N–H and the O–CH_3 groups forming a dimeric structure, as illustrated in Figure 1.

The dimethoxyborate **5** (Scheme 2) derived from norephedrine was also obtained and characterized[12] but, unfortunately, the sample did not provide a good crystal for X-ray analysis.



Scheme 1. Synthesis of spiroaminoborate esters for the reduction of ketones.

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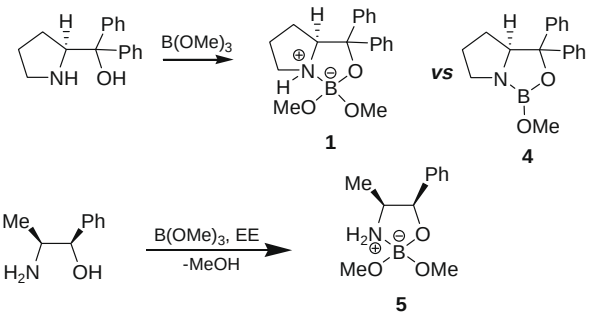
The theoretical parameters of borate esters **1** and **5**, and their dimmers by DFT B3LYP/6-31G(d) calculations showed that **1** and **5** are thermally favored, with a dimerization free energy (ΔG_{dim}) of −36.4 kcal/mol and −10.7 kcal/mol, respectively ($\Delta G_{dim} = \Delta G_{f/dim} - 2\Delta G_{f/monomer}$) (Table 1). Although they are both thermally favored, possibly, only compound **1** can dimerize because: (a) The different substituents (CH_3 and Ph) for **5** (Fig. 2, above) make the orientation of the N–H bonds relative to the O–CH_3 group unsymmetrical inducing extra strain energy. (b) The extra H-atom in **5** introduces a steric hindrance for its dimer to form, that is, the monomers never reached the 2.00 Å, the required distance to form the H-bonds, while in **1**, this distance was optimal, as confirmed by the X-ray experimental values of 1.963 Å.[11] (c) The enthalpy for dimer **1** is, at least, three times more exothermic than for **5**. (d) The charge distribution in **5** is not as high as in **1**. Moreover, the electrostatic potentials in Figure 2, shows that the arrangement of the most stable dimer **1** induces a larger electrostatic potential between the NH and the O groups, which, in turn, generates a higher Coulomb-type interaction between the atom-point charges.

We then examined the aminoborate esters **1** and **5**, as preformed catalysts, in the borane-mediated reduction of acetophenone. The results of the reaction employing different amount of catalyst **1** are presented in Table 2. Using 10–1 mol % of aminoborate ester **1**, the enantioselectivity was 99% (entries 1–4), and decreased slightly when 0.5 mol % of catalyst was loaded (entry 5). Noteworthy, even with 0.25 mol % load of catalyst the selectivity was still high, 97% ee (entry 6). From the practical point of view, the optimal amount of catalyst was 1 mol % (entry 4). The efficiency and enantioselectivity of catalyst **1** for the reduction of acetophenone was considerably higher compared with the suggested *B*-methoxy-1,3,2-oxazaborolidine **4** formed in situ.[6–9]

The reduction of acetophenone with 10 mol % of complex **5** under similar reaction conditions provided the 1-phenylethanol in only 85% ee.

Based on the high reactivity and excellent selectivity of aminoborate complex **1** in the reduction of acetophenone, we decided to apply the methodology for the reduction of representative ketones. The results are summarized in Table 3. The enantioselectivity in most cases was very high (up to 99% ee) and comparable with previous results obtained with the spiroborate ester **3**.[5] Moreover, in contrast to the low efficiency of the in situ prepared *B*-methoxy oxazaborolidine **4** reported by Xu et al.[7] for electron-deficient ketones, the enantioselectivity of **1** was not affected (4–6), obtaining more than 98% ee with only 1 mol % catalyst.[13] Although it seems



Scheme 2. Formation of aminoborate esters **1** and **5**.

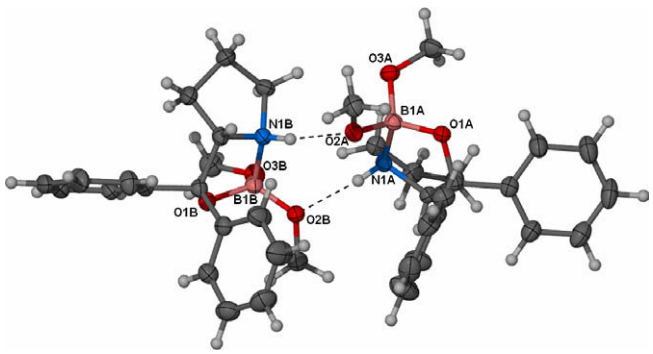


Figure 1. X-ray structure of the aminoborate ester dimer **1**.

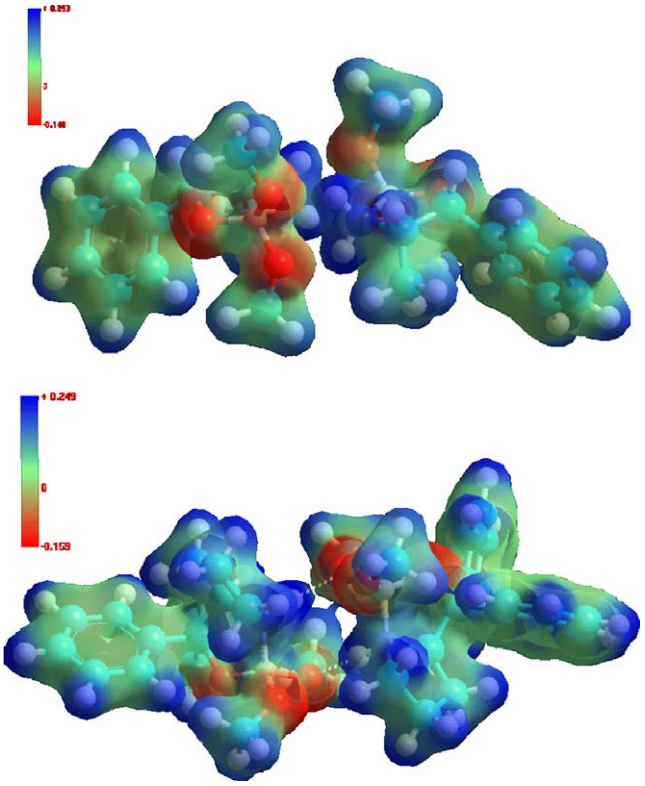


Figure 2. Optimized DFT structures of borate esters dimer **1** (below) and **5** (above). Contours give the electrostatic potentials of each species.

Table 1
Theoretical parameters of **1** and **5** and their corresponding dimers

Structures	ΔG_f (kcal/mol)	Torsion angle HNBO (degrees)	Atomic charge	
			O	N–H
1	−86,150.3	46.1	−0.331	0.051
5	−62,189.5	0.53; 7.32[a]	−0.383	0.036
Dimer-1	−172,337.0	−8.8	−0.363	0.122
Dimer-5	−124,389.7	6.30; 6.96[a]	−0.374	0.096

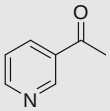
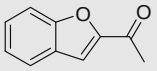
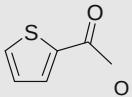
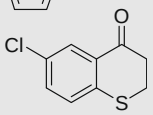
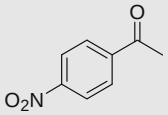
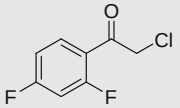
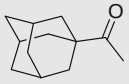
[a] The different angles are due to the unsymmetrical dimer.

Table 2
Reduction of acetophenone using different amount of borate **1**

Entry	Amount of **1** (%)	Yield[a,b] (%)	Ee[c] (%)
1	10	83	99
2	5	90	99
3	2.5	93	99
4	1	91	99
5	0.5	92	98
6	0.25	93	97

[a] The reduction was carried out with 0.7 equiv of borane–DMS in THF at 25 °C (rt).
[b] Isolated yield after distillation on Kugelrohr apparatus.
[c] Determined by GC of acetate on chiral column.

Table 3
Reduction of representative chiral ketones using 1 mol % of aminoborate ester **1**[a]

Entry	Substrate	Yield[b] (%)	ee[c] (%)	Configuration[d,14]
1[e]		93	95	(*R*)
2		91	96	(*R*)
3		90	96	(*R*)
4		92	99	(*R*)
5		95	99	(*R*)
6		88	98	(*S*)
7		94	99	(*R*)

[a] The reduction was carried out using 0.7 equiv of borane–DMS in THF at room temperature.
[b] Isolated yield after distillation in a Kugelrohr apparatus.
[c] Determined by GC of acetate on chiral column.
[d] Absolute configuration was determined by comparison of optical rotations with literature values. The configuration of new optical active compounds was assigned by analogy.
[e] The reduction was carried out using 1.7 equiv of borane–DMS.

that the in situ prepared oxazaborolidine methods are more convenient, these methods have been reported to provide less reproducible results,[8a] probably due to impurities present in the reaction mixture and, therefore, require larger amounts of expensive catalysts. Our process is more economical since it uses less diphenylprolinol. Moreover, the less catalytic load permits an easier purification process that is well suited to large scale syntheses.

In summary, we have prepared new dimethoxy(aminoalkoxy)borate catalysts, which were isolated and characterized. Aminoborate ester **1** was used for the highly enantioselective and efficient borane reduction of variety aromatic ketones with only 1 mol % of catalytic loading. Moreover, the versatility of the method was studied using a variety of heterocyclic and aliphatic ketones obtaining excellent yields of high enantiomerically enriched secondary alcohols, which are important in the synthesis of biologically active compounds.

Acknowledgements

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10. *Preparation of (−)-(3aS)-1,1-dimethoxy-3,3-diphenyl-hexahydro-1H-pyrrolo[1,2-c][1,3,2]oxazaborol-7-ium-1-uide* (1): To a solution of (*S*)-diphenyl(pyrrolidin-2-yl)methanol (2.53 g, 10.0 mmol) in dry isopropyl ether (25 mL) a freshly redistilled neat dimethyl borate (3 mL, 28.9 mmol) was added drop wise at room temperature under nitrogen atmosphere. The resulting mixture was left without stirring over 24 h (after 2 h white crystals started to grow). The precipitate was filtered, washed with isopropyl ether (4 × 10 mL) under nitrogen atmosphere and dried under vacuum at 60 °C over 12 h to give the final product as a white solid (2.21 g, 68 % yield). Mp 132–136 °C. IR (ν, cm^{-1}): 3300 (NH), 3059, 2964, 1598, 1390, 1103, 1022; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.42–1.66 (m, 4H, $(CH_2)_2$), 2.03–3.23 (m, 8H, B(O*Me*)$_2$ and NCH_2), 4.26–4.31 (m, 1H, NCH), 6.37 (br d, J = 6.0 Hz, 1H, NH), 7.11–7.28 (m, 6H, CH_{Ar}), 7.46–7.50 (m, 4H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 24.8, 29.0, 46.7, 49.6 (br, 2MeO), 81.4, 126.1, 126.2, 126.3, 126.5, 127.7, 127.8, 146.2, 147.8; ^{11}B NMR (128 MHz, $CDCl_3$): δ 6.7 (s); $[\alpha]_D^{23}$ −130 (*c* 1.3, $CHCl_3$).
11. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC CCDC 704941. Formula: C19 H24 B N O3; Crystal size 0.55 × 0.35 × 0.30 mm. Crystal system, space group monoclinic, *P* 21. Unit cell dimensions: a = 9.9641(5) Å alpha = 90 deg; b = 18.7001(9) Å beta = 107.8240(10)deg; c = 10.1265(5) Å gamma = 90 deg. Table hydrogen bonds with H···A < r(A) + 3.200 Å and ⟨DHA⟨110 deg:

D–H	d(D–H)	d(H···A)	<DHA	d(D···A)	A
N1A–H1NA	0.882	1.953	163.93	2.810	O2B
N1B–H1NB	0.911	1.963	167.05	2.858	O2A

12. *Preparation of* (it 4S,5R)-*2,2-dimethoxy-4-methyl-5-phenyl-1,3,2-oxazaborolidin-3-ium-2-uide* (*5*): To a solution of (1*R*,2*S*)-norephedrine (1.51 g, 10.00 mmol) in dry diethyl ether (25 mL), a freshly redistilled neat methyl borate (3 mL, 28.88 mmol) was added drop wise over 1 min at 25 °C under a nitrogen atmosphere. During the addition a white precipitate was formed. The resulting mixture was stirred over 12 h at 25 °C. The precipitate was filtered, washed with diethyl ether (5 × 10 mL) under nitrogen atmosphere and dried under vacuum to give final product as a white crystalline solid (1.70 g, 76% yield). Mp: 127–130 °C. IR (ν, cm^{-1}): 3225, 3083, 1607, 1449, 1337, 1196, 1119, 1067; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.66 (d, J = 6.8 Hz, 3H, CH*Me*), 3.21 (s, 6H, 2 OMe), 3.44–3.51 (m, 1H, NCH), 4.90 (d, J = 5.3 Hz, 1H, OCH), 5.46 (br s, 2H, NH_2), 7.18–7.39 (m, 5H, Ph); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.3, 48.6, 51.8, 126.0, 126.3, 127.7, 141.5; ^{11}B-NMR (128 MHz, DMSO-d_6): δ (ppm) 6.5 (s); $[\alpha]_D^{23}$ = −33° (*c* 4.3, DMSO). HRMS *m*/*z*: 222.12766 found (calculated for $C_{11}H_{17}O_3N_1{}^{11}B_1$, $(M-H)^+$ requires 222.12960).
13. *Reduction of 4′-nitroacetophenone using 1 mol % of borate ester 1. Preparation of (+)-(R)-1-(4-nitrophenyl) ethanol*: Borane–SMe_2 complex (10 M, 0.7 mL, 7.0 mmol) was added to a solution of catalyst **1** (32.5 mg, 0.10 mmol) in dry THF (5 mL) at 25 °C and the mixture was stirred for 1 h. A solution of 4′-nitroacetophenone (1.65 g, 10.0 mmol) in THF (5 mL) was added for 1 h using an infusion pump. The reaction mixture was stirred at rt over 1 h, then cooled at 0 °C and quenched with methanol (3 mL). The reaction mixture was concentrated, washed with water (50 mL) and the product was extracted with dichoromethane (3 × 20 mL). The extract was dried over Na_2SO_4 and concentrated; the residue was distilled in a Kugelrohr apparatus under vacuum to give the final product as a yellow oil (1.59 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.51 (d, J = 6.8 Hz, 3H, Me), 2.44 (br s, 1H, OH), 5.01 (q, J = 6.5 Hz, *CH*Me), 7.52–7.55 (m, 2H, CH_{Ar}), 8.16–8.19 (m, 2H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 25.5, 69.5, 123.7, 126.2, 147.2, 153.2. The enantiomeric excees

was determined by GC analysis of *O*-acetyl derivative on a CP-Chirasil-DexCB chiral column as 99% ee (R_t 63.3 min). $[\alpha]_D^{23}$ = +33° (*c* 2.2, $CHCl_3$).[7a]

14. *Optical rotation of (R)-1-(3-pyridyl)ethanol*: $[\alpha]_D^{20}$ = +39° (*c* 2.7, $CHCl_3$), ee 95%; Lit[15] $[\alpha]_D$ = +26.7° (*c* 2, $CHCl_3$), ee 90%; (*R*)-1-benzofuran-2-yl-ethanol: $[\alpha]_D^{20}$ = +18° (*c* 3, $CHCl_3$), ee 96%; (*R*)-1-(2-thienyl)ethanol: $[\alpha]_D^{20}$ = +27° (*c* 2.5, $CHCl_3$), ee 96%; Lit[15]: $[\alpha]_D$ = +24.2° (*c* 5, $CHCl_3$), ee 100%; (*R*)-6-chloro-thiochroman-4-ol: $[\alpha]_D^{20}$ = +79° (*c* 2.2, $CHCl_3$), ee 99%; (*S*)-2-chloro-1-(2,4-difluorophenyl)ethanol: $[\alpha]_D^{20}$ = +43° (*c* 5, $CHCl_3$), ee 98%; (*R*)-1-(1-adamantyl)ethanol: $[\alpha]_D^{20}$ = +1.5° (*c* 1.6, $CHCl_3$), ee 99%; Lit[16]: $[\alpha]_D^{23}$ = +1.6° (*c* 0.4, $CHCl_3$), ee >98%.
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