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Chiral terpene auxiliaries. Part 1: Highly enantioselective reduction of ketones with borane catalyzed by an oxazaborolidine derived from (−)-β-pinene

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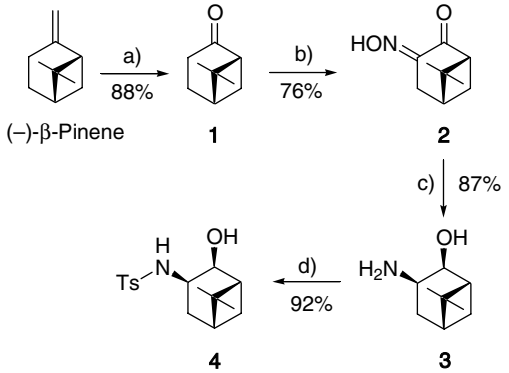
Abstract—(1*R*,2*S*,3*R*,5*R*)-3-Amino-6,6-dimethyl-2-hydroxybicyclo[3.1.1]heptane was synthesized in three steps from (−)-β-pinene. It was used for the in situ generation of a *B*-methoxy-oxazaborolidine catalyst for the asymmetric reduction of alkyl–aryl ketones with borane-dimethyl sulfide complex. In the presence of 3 mol % of the catalyst, the product alcohols were obtained in high yields and with enantiomeric excesses in the range of 93–98%.

Boron reagents and catalysts derived from chiral terpenes, especially α-pinene have proved to be very valuable in asymmetric synthesis.[1] Versatile pinane-based reagents were developed and successfully applied to many chiral transformations, for example, asymmetric reduction,[2a] hydroboration,[2a] allylboration,[2b] homologation,[2c] ring opening of epoxides,[2d] and others.[2e] Among these processes, the enantioselective reduction of prochiral ketones with stoichiometric reagents (DIP-Chloride™, Alpine-Borane®)[2a,f] or catalyzed by oxazaborolidines,[3] are widely used methods.

Over the past two decades, oxazaborolidines derived from amino acids, for example, 1,1-diphenylprolinol and 1,1-diphenylvalinol, have been extensively studied.[3] In contrast to the numerous stoichiometric applications of terpene-based organoboranes in asymmetric synthesis, very little is known on the utilization of terpene-derived oxazaborolidines as catalysts for the reduction of ketones with borane.[4] Masui and Shioiri used 2-hydroxy-3-aminopinane, obtained from α-pinene,[4a] for the preparation of oxazaborolidines, and simplified the reduction protocol by the in situ generation of *B*-methoxy-oxazaborolidines.[4b] Ponzo and Kaufmann extended the methodology to other *B*-alkoxy-oxazaborolidines, and obtained their best results with the catalyst generated from 1,1-diphenylprolinol and trioctylborate.[5] Consequently, we decided to synthesize a new terpene-derived aminoalcohol starting from the readily available optically pure (−)-β-pinene as shown in Scheme 1.

(+)-Nopinone[6] (**1**), obtained by ozonolysis of (−)-β-pinene, was transformed into ketoxime **2**.[7] Reduction of **2** with lithium tetrahydridoaluminate produced (1*R*,2*S*,3*R*,5*R*)-3-amino-6,6-dimethyl-2-hydroxy-bicyclo-[3.1.1]heptane (**3**) in 87% yield.[8] Its structure was confirmed by X-ray analysis of its *p*-tolunesulfonamide derivative **4**[9,10] (Fig. 1).



Scheme 1. Reagents and conditions: (a) (1) O_3, −78 °C, (2) $S(CH_3)_2$; (b) (1) *t*-BuOK, *n*-BuONO, (2) HCl(aq); (c) (1) $LiAlH_4$, THF, reflux, (2) 10% NaOH(aq), H_2O; (d) *p*-TsCl, Et_3N, CH_2Cl_2.

Keywords: Asymmetric reduction; 1,2-Aminoalcohols; Chiral oxazaborolidines; Terpenes.
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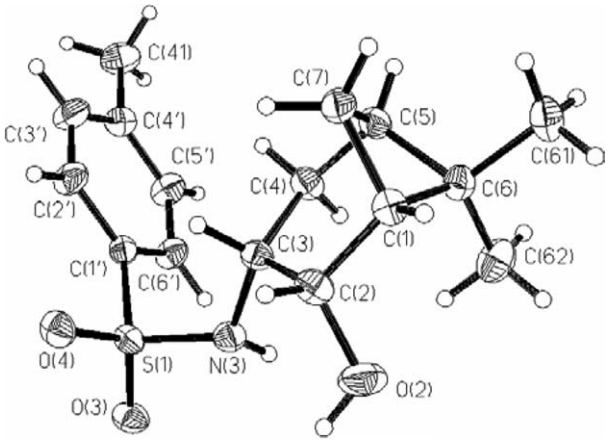
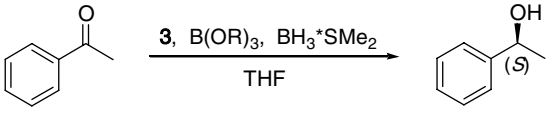


Figure 1. X-ray structure of **4**.[10]

We used commercially available trialkyl borates for the in situ generation of the active catalyst. Aminoalcohol **3** was treated with trimethyl, triisopropyl and tri-*n*-butyl borates and the corresponding *B*-alkoxy-oxazaborolidines were used without isolation from the reaction mixture to catalyze the reduction with borane at room temperature and at 0 °C. Initial studies were focused on the asymmetric reduction of acetophenone with borane in the presence of the catalyst (Table 1). Experiments with 10 mol % of **3** and 11 mol % of $B(OMe)_3$ proceeded smoothly to give (*S*)-1-phenylethanol of 97% ee in 99% yield (Table 1, entries 1 and 2). An increase in the steric bulk on boron using triisopropyl borate led to a lower enantiomeric excess probably due to an uncatalyzed side reduction reaction, especially at 0 °C (entries 3 and 4). Tri-*n*-butyl borate gave similar result to $B(OMe)_3$ (entry 5). Lower catalyst loadings (5 and 3 mol %) did not decrease the enantiomeric purity of the product alcohol. Even 1 mol % of **3** efficiently catalyzed the reduction producing 1-phenylethanol with 92% ee (entry 8).

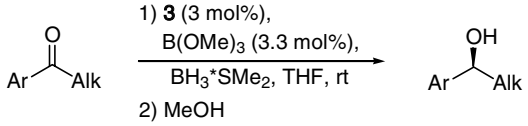
Table 1. Asymmetric reduction of acetophenone with BMS[a] catalyzed by oxazaborolidines generated from **3** and $B(OR)_3$[b]

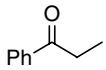
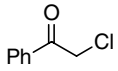
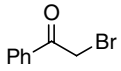
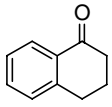
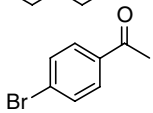
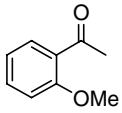
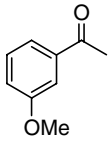
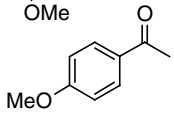
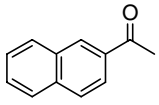
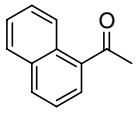


Entry	**3** (mol %)	R	Temp (°C)	Product[c]	
				Yield (%)[d]	ee (%)[e]
1	10	Me	0	98	96
2	10	Me	20	99	97
3	10	*i*-Pr	0	98	84
4	10	*i*-Pr	20	97	94
5	10	*n*-Bu	20	99	98
6	5	Me	20	97	97
7	3	Me	20	98	98
8	1	Me	20	96	92

[a] Borane–dimethyl sulfide complex (BH_3*$S(CH_3)_2$).
[b] For the typical procedure see Ref. 11.
[c] Configuration was established by comparing the sign of rotation with an authentic sample (Aldrich).
[d] Isolated yields after flash chromatography.
[e] Enantiomeric excess was established by GC analysis of the product alcohol on a Supelco β-dex 325™ column.

Table 2. Asymmetric reduction of selected ketones



Entry	Ketone	Product	
		Yield[a] (%)	ee[b] (%), (conf.)[c]
1		98	98 (*S*)
2		99	93 (*S*)
3		96	96 (*R*)
4		92	97[d] (*R*)
5		97	96 (*S*)
6		94	95 (*S*)
7		95	95 (*S*)
8		96	97 (*S*)
9		97	97 (*S*)
10		99	98 (*S*)
11		98	93 (*S*)

[a] Isolated yields after flash chromatography.
[b] Enantiomeric excess was established by GC analysis of the product alcohol on a Supelco β-dex 325™ column.
[c] Configurations were established by comparing signs of rotation with literature reports: entries 1, 2, 6, 8 see Ref. 12a, entry 3 see Ref. 12b, entry 4 see Ref. 12c, entries 5, 9 see Ref. 12d, entry 7 see Ref. 12e, entry 10 see Ref. 12f, entry 11 see Ref. 12g.
[d] $B(OBu)_3$ was used instead of $B(OMe)_3$, which gave 86% ee.

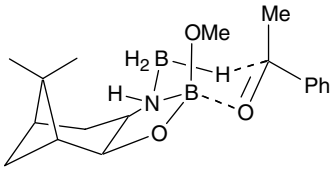


Figure 2. The chair-like transition state.

The optimal reaction conditions, 3 mol % of **3** and $B(OMe)_3$ at room temperature, which gave the highest yield for acetophenone and an excellent ee value (Table 1, entry 7), were applied for the reduction of other alkyl–aryl ketones (Table 2). As the results in Table 2 indicate, all the ketones were reduced with high enantioselectivities regardless of the substitution pattern or substituent.

In the generally accepted mechanism of the oxazaborolidine catalyzed reduction of ketones with borane, a cyclic transition state for the hydride transfer is proposed.[3a,13] In the case of the *B*-methoxy-oxazaborolidine prepared from **3** and $B(OMe)_3$, the stereochemistry of the reduced product can be explained by the transition state model depicted in Figure 2.

In conclusion, aminoalcohol **3** is conveniently prepared from (−)-β-pinene in three steps, and in a good yield. *B*-Methoxy-oxazaborolidine generated in situ from **3** is a superior catalyst for the asymmetric reduction of alkyl aryl ketones with borane. The optical purities of the product alcohols are as high as those obtained in reductions catalyzed by oxazaborolidines prepared from 1,1-diphenylprolinol, and are higher than those in the reported reactions catalyzed by other terpene-derived oxazaborolidines.

Acknowledgements

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8. (1*R*,2*S*,3*R*,5*R*)-(−)-3-Amino-6,6-dimethyl-2-hydroxy-bicyclo1[3.1.1]heptane (**3**): A three-necked flask, equipped with a reflux condenser, a dropping funnel and magnetic stirring bar, was charged with THF (250 ml) and $LiAlH_4$ (11.40 g, 0.3 mol). A solution of (+)-isonitrosonopinone (**2**) (16.70 g, 0.1 mol) in THF (100 ml) was then added and stirred at room temperature under a nitrogen atmosphere. The mixture was stirred under reflux for 24 h. The solution was cooled in an ice bath and ethyl acetate (11.4 ml), 10% NaOH(aq) (11.4 ml) and water (34.3 ml) were added carefully. After stirring the mixture at room temperature for 4 h, it was filtered under reduced pressure through a small pad of Celite. The filtrate was dried with anhydrous magnesium sulfate. Removal of the solvent provided a crude product, which was crystallized from diethyl ether to afford **3** (13.5 g, 87%), mp 77–78 °C, $[\alpha]_D^{22}$ −13.9 (*c* 2.4, $CHCl_3$). ^1H, $^1H \times {}^1H$ COSY NMR (300 MHz, $CDCl_3$) δ (subscript *c* or *t* means, that the proton is *cis* or *trans* to the dimethyl bridge) 0.99 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.19 (d, $J = 10.2$ Hz, 1H, H_{7c}), 1.51 (ddt, $J_1 = 13.2$ Hz, $J_2 = 7.8$ Hz, $J_3 = 1.5$ Hz, 1H, H_{4c}), 1.89 (q, $J = 5.5$ Hz, 1H, H_{5t}), 2.13 (dt, $J_1 = 10.2$ Hz, $J_2 = 6.0$ Hz, 1H, H_{7t}), 2.28 (m, 1H, H_{1t}), 2.34 (ddd, $J_1 = 13.4$ Hz, $J_2 = 9.6$ Hz, $J_3 = 5.0$ Hz, 1H, H_{4t}), 2.50 (br s, 3H, OH, NH_2, exchangeable with D_2O), 3.50 (dt, $J_1 = 9.6$ Hz, $J_2 = 7.9$ Hz, 1H, H_{3t}), 4.08 (dd, $J_1 = 7.8$ Hz, $J_2 = 4.8$ Hz, 1H, H_{2t}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.45, 25.09, 27.35, 36.42, 38.29 (*C*–$(CH_3)_2$), 40.97, 43.52, 46.31, 71.79. HETCOR $^1H \times {}^{13}C$ NMR cross peaks: 0.99 (s)–22.45 (CH_3); 1.19 (d), 2.13 (dt)–25.09 (CH_2); 1.19 (s)–27.35 (CH_3); 1.51 (ddt), 2.34 (ddd)–36.42 (CH_2); 1.89 (q)–40.97 (CH); 3.50 (dt)–43.52 ($CHNH_2$); 2.28 (m)–46.31 (CH); 4.08 (dd)–71.79 (CHOH). Anal. Calcd for $C_9H_{17}NO$ (155.24): C, 69.63; H, 11.04. Found: C, 69.59; H, 11.21.
9. (+)-*p*-Toluenesulfonamide **4**: *p*-TsCl (210 mg, 1.1 mmol) was added in one portion to a stirred solution of (−)-**3** (155 mg, 1 mmol) and Et_3N (0.28 ml, 2 mmol) in CH_2Cl_2 (10 ml) at 0 °C under an argon atmosphere. After 24 h, water was added, and stirring was continued for 15 min. The layers were separated and the organic layer was washed with 5% aqueous $NaHCO_3$ (5 ml), brine (5 ml) and then dried over magnesium sulfate. Evaporation of the solvent provided a crude product, which was crystallized from cyclohexane/toluene to afford **4** (255 mg, 92%), mp 131–132 °C, $[\alpha]_D^{20}$ +16.1 (*c* 5.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ (subscript *c* or *t* means, that the proton is *cis* or *trans* to the dimethyl bridge) 0.99 (s, 3H, CH_3), 1.14 (d, $J = 10.2$ Hz, 1H, H_{7c}), 1.17 (s, 3H, CH_3), 1.69 (ddt, $J_1 = 13.8$ Hz, $J_2 = 8.4$ Hz, $J_3 = 1.5$ Hz, 1H, H_{4c}), 1.86 (q, $J = 5.4$ Hz, 1H, H_{5t}), 1.97 (br s, 1H, OH), 2.08–2.14 (m, 3H), 2.43 (s, 3H, CH_3), 3.77 (dt, $J_1 = 9.3$ Hz, $J_2 = 8.4$ Hz, 1H, H_{3t}), 4.12 (dd, $J_1 = 7.8$ Hz, $J_2 = 4.8$ Hz, 1H, H_{2t}), 5.25 (br s, 1H, NH), 7.31 (d, $J = 7.8$ Hz, 2H, 2×CH), 7.80 (d, $J = 8.4$ Hz, 2H, 2×CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.48 (CH_3), 22.60 (CH_3), 24.82

(CH_2), 27.02 (CH_3), 36.57 (CH_2), 38.14 ($C(CH_3)_2$), 40.36 (CH), 46.34 (CH), 47.04 (CH), 71.79 (CHOH), 127.11 (2×CH), 129.68 (2×CH), 137.49 (C), 143.44 (C). Anal. Calcd for $C_{16}H_{23}NO_3S$ (309.43): C, 62.11; H, 7.52. Found: C, 62.11; H, 7.57.

10. Crystallographic data for the structure in this letter has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 279066. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Crystal data: Compound **4**: The diffraction data was collected at 293 K, single crystal $0.58 \times 0.32 \times 0.31$ mm, Oxford Diffraction KM4 CCD diffractometer, MoKα radiation $\lambda = 0.71073$ Å. Structure refined with SHELX97 package (Sheldrick, G. M.; Schneider, T. M. *Methods Enzymol.* **1997**, *277B*, 319). $C_{16}H_{23}N_1O_3S_1$, crystal system monoclinic, space group, *C*2; $a = 18.453(2)$, $b = 9.638(1)$, $c = 8.752(1)$ Å, $\beta = 93.64(1)°$, $V = 640.50(9)$ Å^3; $Z = 4$; $F(000) = 664$; $\mu = 0.218$ mm^{-1}; $R1 = 0.0432$, $wR2 = 0.1175$; $S = 1.092$. The relative positions of the tosyl and pinene ring systems is described by the torsion angle values: O2–C2–C3–C4 −101.6(2); C2–C3–N3–S1 −136.17(14); C3–N3–S1–C1′ 61.26(15); N3–S1–C1′–C2′ −107.23(16); the hydrogen bond N3···O4 [−x−1/2, y−1/2, −z−1] distance is 3.096 Å.
11. Typical procedure for the reduction: A round bottom flask, dried at 120 °C and cooled in a stream of argon, was charged with (−)-**3** (23 mg, 0.15 mmol), THF (1 ml), and $B(OMe)_3$ (18.5 μl, 0.165 mmol). This mixture was stirred for 1 h at room temp. Next, THF (4 ml) and BMS (10 M, 0.5 ml, 5 mmol) were added via syringe, followed by slow addition of acetophenone (0.60 g, 5 mmol) in THF (5 ml) using a syringe pump. The reaction mixture was then stirred for 0.5 h. Methanol (4 ml) was cautiously added, and after 3 h, volatiles were removed under vacuum on a rotary evaporator. The residue was flash chromatographed through a small pad of silica gel using petroleum ether–ethyl acetate (9:1) as solvent. 1-Phenylethanol (0.60 g, 98%) was isolated, and was analyzed by GC on a Supelco β-dex 325™ column 98% ee, $[\alpha]_D^{22}$ −53.2 (*c* 1.2, $CHCl_3$). Lit.[12a]: $[\alpha]_D^{25}$ −55.1 (*c* 1.63, $CHCl_3$) for >99% ee.
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