β-Hydroxyamide-Based Ligands and Their Use in the Enantioselective Borane Reduction of Prochiral Ketones

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ABSTRACT Hydroxyamide-based ligands have occupied a considerable place in asymmetric synthesis. Here we report the synthesis of seven β-hydroxyamide-based ligands from the reaction of 2-hydroxynicotinic acid with chiral amino alcohols and test their effect on the enantioselective reduction of aromatic prochiral ketones with borane in tetrahydofuran (THF). They produce the corresponding secondary alcohols with up to 76% enantiomeric excess (*ee*) and good to excellent yields (86-99%). *Chirality 26:21–26, 2013.* © 2013 Wiley Periodicals, Inc.

KEY WORDS: hydroxyamide; prochiral ketones; asymmetric borane reduction

INTRODUCTION

The synthesis of optically active compounds has become an important area of research for pharmaceutical industries and research academic institutions, as it is frequently observed that individual enantiomers of a chiral drug molecule display contrasting biological activities.[1,2] This has forced organic chemists to develop efficient and highly selective catalysts for the synthesis of single enantiomers through asymmetric reactions. Among the variety of asymmetric reactions leading to enantiomerically pure alcohols, the enantioselective reduction of prochiral ketones with borane in the presence of a chiral ligand has received considerable attention.[3] Optically active secondary alcohols are widely used in the preparation of chiral liquid crystal materials and other chiral optical materials.[4,5]

Apart from transition metal complexes, many researchers started working with hydride donors like aluminum and boron complexes. Among them, oxazaborolidine synthesized by Itsuno *et al.*[3,6] from L-valine gave high enantioselectivity for prochiral ketone reduction. This method was further developed by Corey *et al.*[7–11] which is generally known as the CBS method.

In addition to the CBS system, other catalysts such as hydroxyl-amides,[12–16] sulphonamides,[17–19] and phosphinamides,[20–23] prolinol-squaramide[24] have also been developed as efficient catalysts for the asymmetric reduction of ketones. As important intermediates in the preparation of chiral oxazoline ligands,[25] thiazoline ligands[26,27] and imidazoline ligands,[28,29] many chiral β-hydroxyamides have been synthesized from carboxylic acids and amino alcohols. In addition to developing versatile chiral catalysts, Liu and colleagues reported the synthesis of prolinol-based C_2-symmetric amino alcohols with multicoordination groups and their application in the catalytic borane-mediated reduction of prochiral ketones.[30]

Considering the potential coordination and H-bond donation ability of β-hydroxyamides, some of them have been applied to asymmetric catalysis as ligands or catalysts.[15] There is a continuing interest in the development of new tridentates chiral ligands to be tested in the borane enantioselective reduction of prochiral ketones. In order to obtain tridentate chiral ligands, we synthesized β-hydroxyamide ligands **1–7** from 2-hydroxynicotinic acid and commercially available amino alcohols and tested their catalytic activity for the enantioselective borane reduction of prochiral ketones.

EXPERIMENTAL SECTION

General Methods

All glassware was oven-dried for several hours at 120°C, assembled while hot, and cooled in a stream of dry nitrogen gas. All chemicals were reagent grade unless otherwise specified. Solvents were dried according to established procedures by distillation under argon atmosphere from the appropriate drying agent. Silica gel 60 (Merck, Darmstadt, Germany; 0.040–0.063 mm) and silica gel / thin-layer chromatography (TLC)-cards (F254) were used for flash column chromatography and TLC. Melting points were determined with a Gallenkamp Model apparatus with open capillaries. Infrared spectra were recorded on a Mattson 1000 FTIR model spectrometer. Elemental analyses were performed with a Carlo-Erba 1108 model apparatus. Optical rotations were taken on a Perkin Elmer (Boston, MA) 341 model polarimeter. ^{1}H (400 MHz) and ^{13}C (100 MHz) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker (Billerica, MA) AV400 High Performance Digital FT-NMR Spectrometer. The chemical shifts (δ) and coupling constants (J) are expressed in parts per million and Hertz, respectively.

The enantiomeric excess (*ee*) value determination was carried out using chiral high-performance liquid chromatography (HPLC) on a Daicel Chiralcel OD-H and Chiralcel AS-3 column on aBioRad (Hercules, CA) model 2800 pump and BioRad UV-detector. The absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation.

Preparation of the β-Hydroxyamide-Based Ligands 1–7

2-Hydroxy-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]pyridine-3-carboxamide 1. 2-Hydroxynicotinic acid (958 mg, 6.9 mmol) was dissolved in dry dimethylformamide (DMF). The mixture was cooled to −15°C. Then *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDCl) (1321 mg, 6.9 mmol) and HOBt (1056 mg, 6.9 mmol) were added to this solution at the same temperature. The solution of (2*S*)-2-amino-2-phenylethanol (904 mg, 6.6 mmol) in dry DMF (15 mL) was introduced into the solution dropwise over a period of 0.5 h under an argon atmosphere at the same temperature. After the addition was completed, the mixture was allowed to the warm to room temperature and stirred for an appropriate time (monitored by TLC). When the reaction was completed, the DMF was

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removed under reduced pressure. Water (10 mL) was then added to quench the reaction. The mixture was extracted with $CHCl_3$ (2 x 10 mL) and dried over anhydrous Na_2SO_4. Afterwards the organic phase was evaporated under reduced pressure to give the crude product, which was purified by column chromatography through silica gel, eluted with 10:1 ethyl acetate/methanol solvent mixture (TLC R_f=0.37), to give the pure yield **1** as a white solid in 90% (1540 mg) yield. M.p: 131.6-134°C,$[\alpha]_D^{20} = -107.4$ (*c* 1, tetrahydofuran, THF). IR (KBr): 3232, 3178, 3029, 2920, 2853, 1684, 1613, 1548, 1470, 1322, 1235, 1073, 1034, 912, 778, 701, 570 cm^{-1}. 1H NMR (DMSO-d_6): δ (ppm) 3.68 (s, 2H, CH_2), 5.06 (q, *J*=5.4 Hz, 2H, O*H* and Ph*CH*), 6.48 (t, *J*=6.6 Hz, 1H, Ar-*H*), 7.23-7.33 (m, 5H, Ar-*H*), 7.72 (d, *J*=5.5 Hz, 1H, Ar-*H*), 8.32 (d, *J*=7.0 Hz, 1H, Ar-*H*), 10.42 (d, *J*=8.0 Hz, 1H, N*H*), 12.51 (s, 1H, Ar-O*H*). ^{13}C NMR (DMSO-d_6): δ(ppm) 55.23 (Ph*CH*), 65.19 (*C*H_2OH), 106.71 (Ar- *C*), 120.9 (Ar-*C*), 127.28 (Ar-2*C*, overlapped, from HETCOR,), 128.64 (Ar-*C*), 139.9 (Ar-*C*), 141.64 (Ar-*C*), 144.46 (Ar-*C*), 162.80 (Ar-*C*-OH), 163.32 (C=0). Anal. Calcd. for $C_{14}H_{14}N_2O_3$ (mw:258 g/mol): C, 65.12; H, 5.4; N, 10.85. Found: C, 65.20; H, 5.5; N, 10.90.

2-Hydroxy-*N*-[(2*S*)-1-hydroxy-3-phenylpropan-2-yl]pyridine-3-carboxamide 2. This compound was prepared as described above for **1** starting from 2-hydroxynicotinic acid (958 mg, 6.9 mmol), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDCl) (1321 mg, 6.9 mmol), HOBt (1056 mg, 6.9 mmol), and (2*S*)-2-amino-3-phenyl-1-propanol (996.6 mg, 6.6 mmol). The crude product was purified by recrystallizing from methanol to give **2** (1060 mg, 58%) as a yellow solid. M. p.: 166.4-168.1°C,$[\alpha]_D^{20} = -114.4^o$ (*c* 1, THF). IR (KBr): 3397, 3226, 3108, 3070, 2999, 2928, 1673, 1587, 1549, 1470, 1326, 1233, 896, 752, 692, 572 cm^{-1} .1H NMR (DMSO-d_6): A part of AB spin system: δ (ppm) 2.78 (dd, *J*=7.4 and 13.6 Hz, 1H, PhCH_2), B part of AB spin system: 2.92 (dd, *J*=6.2 and 13.2 Hz, 1H, PhCH_2), 3.45 (m, 2H, CH_2OH), 4.15 (d, *J*=5.8 Hz, 1H, *CH*-NH), 4.95 (s, 1H, O*H*), 6.45 (t, *J*=6.6 Hz, Ar-*H*), 7.17-7.26 (m, 5H, Ar-*H*), 7.68 (d, *J*=5.7 Hz, 1H, Ar-*H*), 8.30 (d, *J*=7.0 Hz, 1H, Ar-*H*), 9.92 (d, *J*=8.0 Hz, 1H, N*H*), 12.44 (s, 1H, Ar-O*H*). ^{13}C NMR (DMSO-d_6): δ(ppm) 37.40 (Ph*C*H_2), 52.71 (Bn*C*H), 62.37 (*C*H_2OH), 106.61 (Ar-*C*), 120.88 (Ar-*C*), 126.51 (Ar-*C*), 128.64 (Ar-*C*), 129.65 (Ar-*C*), 139.27 (Ar-*C*), 139.72 (Ar-*C*), 144.30 (Ar-*C*), 162.69 (Ar-*C*-OH), 163.31 (C=0). Anal. Calcd. for $C_{15}H_{16}N_2O_3$ (mw:272 g/mol) C, 66.18; H, 5.88; N, 10.29. Found: C, 66.20; H, 5.94; N, 10.30.

2-Hydroxy-*N*-[(2*S*)-1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl]pyridine-3-carboxamide 3. This compound was prepared as described above for **1** starting from 2-hydroxynicotinic acid (584.2 mg, 4.2 mmol), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDCl) (804.3 mg, 4.2 mmol), HOBt (642.6 mg, 4.2 mmol), and (2*S*)-(−)-2-amino-3-methyl-1,1-diphenyl-1-butanol (1000 mg, 3.9 mmol). The crude product was purified by recrystallizing from ethyl acetate to give **3** (1100 mg, 75%) as a white solid. M.p: 242.1-243.6°C,$[\alpha]_D^{20} = -72.9$ (*c* 1, THF), IR (KBr): 3391, 3285, 3119, 3067, 2956, 2926, 2853, 1663, 1626, 1546, 1480, 1324, 1240, 1060, 776, 699, 558 cm^{-1} ,^{1}H NMR (DMSO-d_6): δ (ppm) 0.76 (d, *J*=6.8 Hz, 3H, -CH_3), 0.86 (d, *J*=6.7 Hz, 3H, -CH_3), 1.76-1.82 (m, 1H, *CH*(CH_3)$_2$), 5.03 (d, *J*=10.0 Hz, 1H, *CH*-NH), 5.97 (s, 1H, O*H*), 6.41 (t, *J*=6.6 Hz, Ar-*H*), 7.04-8.29 (m, 12H, Ar-*H*), 10.07 (d, *J*=10 Hz, 1H, N*H*), 12.31 (s, 1H, Ar-*OH*). ^{13}C NMR (DMSO-d_6): δ(ppm) 18.45 (*C*H_3), 23.50 (*C*H_3), 29.17 (−*C*H(CH_3)$_2$), 58.25 (*C*H-NH), 81.59 (alph.C), 106.38 (Ar- *C*), 121.04 (Ar-*C*), 126.18 (Ar-*C*), 126.52 (Ar-*C*), 126.56 (Ar-*C*), 126.66 (Ar-*C*), 127.85 (Ar-*C*), 128.40 (Ar-*C*), 139.53 (Ar-*C*), 144.38 (Ar-*C*), 147.37 (Ar-*C*), 147.51 (Ar-*C*), 162.51 (Ar-*C*-OH), 163.66 (C=0). Anal. Calcd. for $C_{23}H_{24}N_2O_3$ (mw: 376 g/mol): C, 73.40; H, 6.38; N, 7.45. Found: C, 73.43; H, 6.40; N, 7.48.

2-Hydroxy-*N*-[(1*S*)-2-hydroxy-1,2,2-triphenylethyl)pyridine-3-carboxamide 4. This compound was prepared as described above for **1** starting from 2-hydroxynicotinic acid (487 mg, 3.5 mmol), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDCl) (670 mg, 3.5 mmol), HOBt (535.5 mg, 3.5 mmol), and (*S*)-(−)-2-amino-1,1,2-triphenylethanol (950 mg, 3.3 mmol). The crude product was purified by recrystallizing from ethyl acetate to give **4** (1120 mg, 75%) as a white solid. M.p: 250.2-252.1 °C, $[\alpha]_D^{20} = -295.6$ (*c* 1, THF). IR (KBr): 3433, 3235, , 3060, 3026, 2969, 1659, 1604, 1551, 1483, 1323, 1237, 1149, 1059, 774, 698 cm^{-1} ,^{1}H NMR (DMSO-d_6): δ (ppm) 6.02 (d, *J*=9.3 Hz, 1H, C*H*-NH), 6.24 (s, 1H, O*H*), 6.40 (t, *J*=6.7 Hz, Ar-*H*), 7.04-7.65 (m, 16H, Ar-*H*), 8.23-8.26 (m, 1H, Ar-*H*), 10.81 (d, *J*=9.3 Hz, 1H, N*H*), 12.35 (s, 1H, Ar-O*H*). ^{13}C NMR (DMSO-d_6): δ(ppm) 59.15 (*C*H), 80.69 (alph.*C*), 106.49 (Ar- *C*), 120.77 (Ar-*C*), 126.70 (Ar-*C*), 126.80 (Ar-*C*), 126.92 (Ar-*C*), 126.93 (Ar-*C*), 127.06 (Ar-*C*), 127.33 (Ar-*C*), 127.77 (Ar-*C*), 128.04 (Ar-*C*), 129.79 (Ar-*C*), 139.86 (Ar-*C*), 140.49 (Ar-*C*), 144.40 (Ar-*C*), 146.18 (Ar-*C*), 146.50 (Ar-*C*), 162.53 (Ar-*C*-OH), 162.66 (C=0). Anal. Calcd. for $C_{26}H_{22}N_2O_3$ (mw: 410 g/mol): C, 76.10; H, 5.36; N, 6.83. Found: C, 76.13; H, 5.40; N, 6.80.

2-Hydroxy-*N*-[(2*S*)-1-hydroxy-1,1,3-triphenylpropan-2-yl]pyridine-3-carboxamide 5. This compound was prepared as described above for **1** starting from 2-hydroxynicotinic acid (500 mg, 3.6 mmol), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDCl) (689.4 mg, 3.6 mmol), HOBt (550.8 mg, 3.6 mmol), and (*S*)-(−)-2-amino-1,1,3-triphenyl-1-propanol (1000 mg, 3.6 mmol). The crude product was purified by crystallizing from ethyl acetate to give **5** (1300 mg, 85%) as an open yellow solid. M.p. 226.1-228.4 °C,$[\alpha]_D^{20} = -157.5$ (*c* 1, THF). IR (KBr): 3358, 3263, 3058, 2966, 1659, 1539, 1488, 1445, 1326, 1058, 773, 697, 567 cm^{-1} ,^{1}H NMR (DMSO-d_6): δ (ppm) 2.72 (d, *J*= 6.7 Hz, 2H, -CH_2), 5.33-5.39 (m, 1H, C*H*-NH), 6.29-6.40 (m, 2H, Ar-*H* and O*H*), 7.05-8.03 (m, 17H, Ar-*H*), 10.05 (d, *J*= 9.8 Hz, 1H, N*H*), 11.40 (s, 1H, Ar-*OH*). ^{13}C NMR (DMSO-d_6): δ(ppm) 37.20 (*C*H_2), 57.19 (CH), 80.69 (alph.-*C*), 106.35 (Ar-*C*), 120.57 (Ar-*C*), 126.20 (Ar-*C*), 126.24 (Ar-*C*), 126.48 (Ar-*C*), 126.52 (Ar-*C*), 126.89 (Ar-*C*), 127.80 (Ar-*C*), 128.29 (Ar-*C*), 128.63 (Ar-*C*), 129.45 (Ar-*C*), 139.52 (Ar-*C*), 139.70 (Ar-*C*), 144.20 (Ar-*C*), 146.61 (Ar-*C*), 146.98 (Ar-*C*), 162.45 (Ar-*C*-OH), 163.11 (C=0). Anal. Calcd. for $C_{27}H_{24}N_2O_3$ (mw: 424 g/mol): C, 76.40; H, 5.66; N, 6.60. Found: C, 76.40; H, 5.67; N, 6.61.

2-Hydroxy-*N*-[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl]pyridine-3-carboxamide 6. This compound was prepared as described above for **1** starting from 2-hHydroxynicotinic acid (695 mg, 5.0 mmol), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDCl) (957.5 mg, 5.0 mmol), HOBt (765 mg, 5.0 mmol), and (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (1000 mg, 4.7 mmol). The crude product was purified by crystallizing from ethyl acetate to give **6** (1100 mg, 70%) as a white solid. M.p. 238.2-240.4 °C,$[\alpha]_D^{20} = +117.3$ (*c* 1, THF).IR (KBr, cm^{-1}): 3347, 3217, 3080, 2969, 1669,1592, 1473, 1329,696. ^{1}H NMR (DMSO-d_6): δ (ppm) 4.97 (m, 1H,-C*H*-NH), 5.24 (q, 1H, C*H*-OH), 5.71 (d, 1H, *J*= 4.12 Hz, O*H*), 6.43-6.46

(m, 1H, Ar-*H*), 7.05-7.21 (m, 10H, Ar-*H*), 7.70-7.71 (m, 1H, Ar-*H*),8.25-8.27 (m, 1H, Ar-*H*),10.65 (d, 1H, *J* = 8.6 Hz, -N*H*)). ^{13}C NMR (DMSO-d_6): δ(ppm) 59.22 (*C*H-OH, 75.31(*C*H-NH), 106.67 (Ar-*C*), 120.74 (Ar-*C*), 127.07(Ar-*C*), 127.15(Ar-*C*),127.40 (Ar-*C*), 127.91(Ar-*C*), 127.93(Ar-*C*), 128.50(Ar-*C*), 139.94 (Ar-*C*), 140.02 (Ar-*C*), 142.51 (Ar-*C*), 144.34 (Ar-*C*, 162.87 (Ar-*C*-OH), 162.98 (C=0). Anal. Calcd. for $C_{20}H_{18}N_2O_3$ (mw: 334 g/mol): C, 71.86; H, 7.69; N,8.38. Found: C, 72.02; H, 7.74; N, 8.40.

2-Hydroxy-*N*-[(1*R*,2*S*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]pyridine-3-carboxamide 7. This compound was prepared as described above for **1** starting from 2-hydroxynicotinic acid (973 mg, 7.0 mmol), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDCl) (1340 mg, 7.0 mmol), HOBt (1071 mg, 7.0 mmol), and (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (1000 mg, 6.71 mmol). The crude product was purified by crystallizing from ethyl acetate to give **7** (1300 mg, 70%) as a white solid. M.p.247.7-249°C,[α] $_D^{20}$ = +8.2 (*c* 0.5, THF). IR (KBr): 3326, 3126, 3067, 2928, , 1680, 1626, 1566, 1523, 1436, 1311, 1243, 1088, 1054, 893, 774, 673, 578 cm^{-1} ,^{1}H NMR (DMSO-d_6): δ (ppm) A part of AB system: 2.82 (d, *J* = 16 Hz, 1H), B part of AB system, 3.10 (dd, *J*= 4.8 and 16 Hz, 1H), 4.47 (s, 1H, -C*H*-OH), 5.22 (s, 1H, O*H*), 5.39 (q, *J*= 5.0 and 8.3 Hz, 1H, C*H*-NH), 6.49 (t, *J*= 6.7 Hz, Ar-*H*), 7.16-7.27 (m, 4H, Ar-*H*), 7.70-7.72 (m, 1H, Ar-*H*), 8.42-8.45 (m, 1H, Ar-*H*), 10.26 (d, *J*= 8.4 Hz, 1H, N*H*), 12.43 (s, 1H, Ar-*OH*). ^{13}C NMR (DMSO-d_6): δ(ppm) 40.46 (*C*H$_2$, (from DEPT135 spect.)), 57.53 (−*C*NH), 72.45 (−*C*-OH), 106.52 (Ar-*C*), 121.07 (Ar-*C*), 124.36 (Ar-*C*), 125.39 (Ar-*C*), 126.82 (Ar-*C*), 127.71 (Ar-C), 139.87 (Ar-C), 141.18 (Ar-*C*), 143.14 (Ar-*C*), 144.49 (Ar-*C*), 162.65 (Ar-*C*-OH), 163.92 (C=0). Anal. Calcd. for $C_{15}H_{14}N_2O_3$ (mw: 270 g/mol): C, 66.60; H, 5.18; N, 10.37. Found: C, 66.65; H, 5.20; N, 10.40.

General Procedure for the Enantioselective Reduction of Ketones With Borane-Dimethyl Sulfide in the Presence of β-hydroxyamides 1–7

A 25-mL two-necked flask was charged with β-hydroxyamide **1–7** (0.05 mmol, 10%) in dry and fresh THF (3 mL), equipped with a magnetic stirrer and a connection to the combined nitrogen/vacuum line, and closed with a septum. The air in the flask was replaced by nitrogen. The β-hydroxyamides **1–7** were dissolved in THF (3 mL) under stirring and a solution of $BH_3.SMe_2$ (0.5 mmol, 10 M) complex was added at 0°C by a syringe. After the mixture was stirred for 1 h at 65°C, the freshly distilled ketone (0.5 mmol) in dry and fresh THF (2 mL) was added over a period of 1.5 h by a syringe at the same temperature. The reaction mixture was kept stirring at the 65°C until the ketone was completely consumed. After stirring a further 30 min at room temperature, the reaction mixture was quenched by the addition of MeOH (2 mL) and extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine and dried over $MgSO_4$. After evaporating the solvent under reduced pressure, the product was purified by column chromatography on silica gel using petroleum ether/EtOAc (5:1; for 4-nitroacetophenone: 5/3) as eluent. The *ee* value was determined by HPLC with Chiralcel AS-3 or Chiralcel OD-H columns.

RESULTS AND DISCUSSION

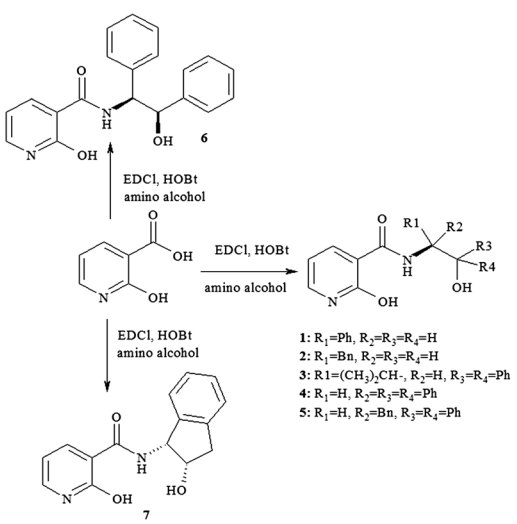
Amide bonds play a major role in the elaboration and composition of biological systems, representing, for example, the main chemical bonds that link amino acid building blocks together to give proteins.[31,32]

Peptides and proteins play an important role in modern biology. A key step in peptide production is the formation of the peptide bond, which involves amide bond formation.[33] The process usually requires activation of a carboxylic acid moiety in the presence of coupling reagents. Activation consists of the replacement of the hydroxyl group of the carboxylic acid with a leaving group, as the acid would otherwise simply form salts with the amine. The reaction of the activated intermediate and the amine is known as the coupling reaction and the activators are coupling reagents.[34]

N-(3-Dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDCl)/HOBt reagents have been widely used in amide synthesis to improve yields, because they show a moderate activity and they are reasonably cheap. When dicyclohexylcarbodiimide (DCC) was employed in the synthesis of the amides, the removal of dicyclohexylurea by product necessitated lengthy chromatography procedures. To avoid this, we preferred using *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDCl) as the coupling agent. This afforded a water-soluble urea byproduct which was easily removed by aqueous washes. As well as simplifying the work-up procedure, this modification also significantly increased the yields of the amides formed. Use of acid chlorides proved to be problematic since significant amounts of bisacylated product were formed under these conditions.

Considering the potential coordination and H-bond donation ability of β-hydroxyamide-based ligands, some of them have been applied to asymmetric catalysis as ligand or catalyst. With this analogy in mind, A series of novel chiral β-hydroxyamide ligands **1–7** with multicoordination groups were easily prepared from 2-hydroxynicotinic acid and commercially available amino alcohols (Scheme 1). Treatment of 2-hydroxynicotinic acid with *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimidehydrochloride (EDCl) and 1-hydroxybenzotriazole hydrate (HOBt) using amino alcohols in DMF afforded the corresponding chiral β-hydroxyamide ligands **1–7** as solid in 58-90% yields. Structures of all novel compounds were confirmed by spectral and elemental analyses.

It is known that the *ee* is sensitive to the solvent, amount of the catalyst, the catalyst generation period, and the reaction temperature. In our previous studies[35] we reported the optimization conditions for *ee* in the asymmetric borane reduction of prochiral ketone. Under optimized reaction conditions from our previous studies, we tested β-hydroxyamides **1–7**



Scheme 1. Synthesis of β-hydroxyamide-based ligands **1–7**.

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TABLE 1. Enantioselective ketone reduction using $BH_3.S(CH_3)_2$ as a reduction agent with β-hydroxyamides 1–7 as catalyst

		Catalyst **1**			Catalyst **2**			Catalyst **3**			Catalyst **4**			Catalyst **5**			Catalyst **6**			Catalyst **7**		
Entry	Ketones	Yield (%)[a]	Ee (%)[b]	Config.[c]	Yield (%)[a]	Ee (%)[b]	Config.[c]	Yield (%)[a]	Ee (%)[b]	Config.[c]	Yield (%)[a]	Ee (%)[b]	Config.[c]	Yield (%)[a]	Ee (%)[b]	Config.[c]	Yield (%)[a]	Ee (%)[b]	Config.[c]	Yield (%)[a]	Ee (%)[b]	Config.[c]
1	Acetophenone	98	37[d]	*(R)*	99	31	*(R)*	99	15	*(R)*	97	25	*(R)*	99	40	*(R)*	99	55	*(S)*	99	65	*(S)*
2	4'-Methylacetophenone	96	25[d]	*(R)*	96	32	*(R)*	98	15	*(S)*	96	26	*(R)*	98	36	*(R)*	98	15	*(R)*	98	59	*(S)*
3	4'-Methoxyacetophenone	90	29[d]	*(R)*	91	26	*(R)*	86	13	*(R)*	88	17	*(R)*	86	31	*(R)*	86	42	*(S)*	86	54	*(S)*
4	4'-Nitroacetophenone	93	33[e]	*(R)*	94	35	*(R)*	99	16	*(R)*	97	19	*(R)*	99	47	*(R)*	99	55	*(S)*	99	62	*(S)*
5	4'-Fluoroacetophenone	97	45[f]	*(R)*	98	42	*(R)*	99	20	*(R)*	99	38	*(R)*	99	43	*(R)*	99	58	*(S)*	99	76	*(S)*
6	4'-Chloroacetophenone	98	32[f]	*(R)*	98	33	*(R)*	99	19	*(R)*	99	32	*(R)*	99	42	*(R)*	99	60	*(S)*	99	60	*(S)*
7	4'-Bromoacetophenone	98	26[f]	*(R)*	98	38	*(R)*	99	24	*(R)*	99	31	*(R)*	99	45	*(R)*	99	50	*(S)*	99	66	*(S)*
8	α-Tetralone	95	28[g]	*(R)*	96	30	*(R)*	98	09	*(R)*	97	15	*(R)*	98	20	*(R)*	98	37	*(S)*	98	32	*(S)*
9	Isopropyl phenyl ketone	96	16[g]	*(S)*	94	17	*(S)*	95	15	*(R)*	95	09	*(S)*	95	15	*(R)*	95	13	*(S)*	95	23	*(S)*
10	2-Bromoacetophenone	99	35[g]	*(S)*	98	46	*(S)*	99	25	*(S)*	99	16	*(S)*	99	51	*(S)*	99	52	*(R)*	99	68	*(R)*
11	Ethyl phenyl ketone	94	32[g]	*(R)*	94	29	*(R)*	96	20	*(R)*	95	17	*(R)*	96	35	*(R)*	96	45	*(S)*	96	66	*(S)*
12	2,2,2-Trifluoroacetophenone	96	08[g]	*(S)*	95	07	*(S)*	95	07	*(S)*	94	09	*(S)*	94	10	*(R)*	94	08	*(S)*	96	09	*(R)*

[a]Yield determined after chromatographic purification.
[b]Ee determined by HPLC (Daicel Chiralcel OD-H Column, for 4-methylacetophenone and 4-nitroacetophenone Daicel Chiralcel AS-3 Column).
[c]Determined by comparison of the sign of the specific rotation with the literature value.
[1]1-Phenylethanol: [d]Eluent: *n*-hexane-2-propanol: 95/5 v/v; flow rate, 1 mL/min. 254 nm; t_R: 19.08 min and 20.05 min.
[2]1-(4-methylphenyl)ethanol: [d]Eluent: *n*-hexane-2-propanol: 95/5 v/v; flow rate, 1 mL/min. 254 nm; t_R: 9.02 min and 9.77 min.
[3]1-(4-methoxyphenyl)ethanol: [d]Eluent: *n*-hexane-2-propanol: 95/5 v/v; flow rate, 1 mL/min. 254 nm; t_R: 24.24 min and 31.96 min.
[4]1-(4-nitrophenyl)ethanol: [e]Eluent: *n*-hexane-2-propanol: 95/5 v/v; flow rate, 1 mL/min. 254 nm; t_R: 45,70 min and 56.55 min.
[5]1-(4-fluorophenyl)ethanol: [f]Eluent: *n*-hexane-2-propanol: 98/2 v/v; flow rate, 0.7 mL/min. 254 nm; t_R: 8.88 min and 9.74 min.
[6]1-(4-chlorophenyl)ethanol: [f]Eluent: *n*-hexane-2-propanol: 98/2 v/v; flow rate, 0.7 mL/min. 254 nm; t_R: 9.21 min and 9.99 min.
[7]1-(4-bromolphenyl)ethanol: [f]Eluent: *n*-hexane-2-propanol: 98/2 v/v; flow rate, 0.7 mL/min. 254 nm; t_R: 9.87 min and 10.82 min.
[8]1,2,3,4-Tetrahydro-1-naphthol: [g]Eluent: *n*-hexane-2-propanol: 98/2 v/v; flow rate, 1 mL/min. 254 nm; t_R: 19.11 min and 20.81 min.
[9]2-Methyl-1-phenylpropanol:[g]Eluent: *n*-hexane-2-propanol: 98/2 v/v; flow rate, 1 mL/min. 254 nm; t_R: 12.69 min and 15.23 min.
[10]2-Bromophenylethanol: [g]Eluent: *n*-hexane-2-propanol: 98/2, v/v; flow rate, 1 mL/min. 254 nm; t_R: 22.35 min and 27.52 min.
[11]1-Phenyl-1-propanol: [g]Eluent: *n*-hexane-2-propanol: 98/2, v/v; flow rate, 1 mL/min. 254 nm; t_R: 16.55 min and 19.55 min.
[12]2,2,2-trifluoro-1-phenylethanol: [g]Eluent: *n*-hexane-2-propanol: 98/2, v/v; flow rate, 1 mL/min. 254 nm; t_R: 38.67 min and 46.54 min.

in the asymmetric borane reduction of different substituted aromatic prochiral ketones; the results are summarized in Table 1.

In the asymmetric reduction studies for catalysts **1** and **2**, which contain a primary alcohol moiety, one chiral center, and a phenyl and benzyl moiety in the stereogenic center, the reduction yield is very high (from 90 to 99%), although enantioselectivity is very low. Absolute configurations of the products were found to be *R*, while those of the alcohols formed by the reduction of isopropyl phenyl ketone, 2-bromoacetophenone, and 2,2,2-trifluoroacetophenone were opposite (*S*) configuration.

In the asymmetric reduction studies with catalyst **3**, the best enantioselectivity was found for *S* isomer alcohol of 2-bromoacetophenone (25% *ee*) (Table 1, cat. **3**). For the examined ketones, the catalyst **3** gave very low enantioselectivities, but high chemical yields (Table 1, cat. 3). Catalyst **3** contains an isopropyl moiety and a tertiary alcohol carbon in the stereocenter and has two phenyl groups.

As can be seen in Table 1, when catalysts **1** and **2** are compared in enantioselectivity and yield, it can be stated that catalyst **2**, which is far from the stereocenter as a CH_2- group, is a better catalyst. This may be due to fact that the phenyl group is slightly further to the stereocenter during the formation of oxazaborolidine between catalyst **2** and boron. In Table 1, it is seen that catalyst **3**, which contains a secondary alcohol moiety and two stereogenic centers, is a good reduction catalyst in both enantioselectivity and yield.

Catalysts **4** and **5** were also employed as ligands in the reduction of a variety of prochiral ketones (Table 1), and *ee* values of up to 38% and 51% were obtained, respectively. From these results it can also be concluded that catalysts **4** and **5** are not good catalysts for enantioselective reduction of aromatic prochiral ketones.

By considering Table 1, one can see that the highest *ee* was obtained as 60% *ee* from 4-chloroacetophenone, whereas the lowest enantioselectivities were obtained as 13% and 8% *ee* from isopropyl phenyl ketone and 2,2,2-trifluoroacetophenone, respectively (Table 1, cat. **6**, entries 9 and 12). Except for 4-methoxy and 2-bromoacetophenone, the absolute configuration of the secondary alcohols were found to be (*S*).

In previous studies it has been reported that structural properties of electronic arrangement of the catalyst can change stereoselectivity in catalytic asymmetric reduction.[36] When catalyst **7**, which has two stereogenic centers and contains an indanol group, was used, the highest enantioselectivity (76% *ee*) and yield (99%) were obtained for 4-fluoroacetophenone, whereas the lowest enantioselectivity was found for 2,2,2-trifluoroacetophenone (9% *ee*) and isopropyl phenyl ketone (23% *ee*), as in the case of previous catalysts.

The stereochemical course of the reductions were the same, the (*S*) isomer of corresponding secondary alcohol was formed preferentially for all ketones tested except 4'-bromoacetophenone and 2,2,2-trifluoroacetophenone (Table 1, cat.**7**, entries10,12).

On the other hand, the enantioselectivity of α-tetralone, which has a cyclic structure, decreased to 3% *ee* and that of isopropyl phenyl ketone to be 23% *ee*, while the lowest enantioselectivity was found as 9% *ee* for 2,2,2-trifluoroacetophenone. A decrease in enantioselectivity was found in the case of the cyclic α-tetralone ketone (32% *ee*), which probably results from its rigid conformation.

From the above results obtained for the enantioselective prochiral reduction catalyzed by a series of chiral β-hydroxyamides **1–7**, it was found that chiral β-hydroxyamides **6** and **7** gave the best enantioselectivity, and the results are shown Table 1.

CONCLUSION

In conclusion, we have synthesized chiral β-hydroxyamide ligands **1–7** from 2-hydroxynicotinic acid and commercially available amino alcohols, for enantioselective ketone reduction with borane dimethyl sulfide as a reducing agent. Different prochiral ketones were reduced up to 76% *ee* and 99% yield. One can see that especially that ligand **7**, which is more rigid, has two chiral centers, and contains indanol ring and a secondary alcohol, as well as ligand **6**, which has also two chiral centers, and carries two phenyl groups in the chiral centers, exhibit better catalytic activity than the other ligands.

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