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Borane-Mediated Asymmetric Reduction of Acetophenone by Enantiopure Aminonaphthols and Aminoalcohols as Catalytic Source

CRISTINA CIMARELLI,* DAVIDE FRATONI, AND GIANNI PALMIERI
Department of Chemical Sciences, University of Camerino, Camerino, Italy

ABSTRACT Practical, cheap, and stereoselective synthetic methods were applied to the preparation of novel 1-(aminoalkyl)naphthol and γ-aminoalcohol tridentate ligands. The ligands obtained were conveniently applied with good results as catalytic sources in the borane-mediated enantioselective reduction of acetophenone with borane dimethylsulfide. Conformational analysis through molecular modeling allows the rationalization of observed stereochemical outcomes. *Chirality 22:655–661, 2010.*

KEY WORDS: asymmetric catalysis; borane; ketones; secondary alchohols; aminonaphthols; aminoalcohols

INTRODUCTION

Enantioselective reduction of ketones with borane, in the presence of chiral oxazaborolidines has emerged as standard method for the synthesis of chiral secondary alcohols.

This reaction has been widely studied by Corey and Helal[1] and has found wide application in the synthesis of natural products, nonnatural bioactive compounds and chiral intermediates, ligands and building blocks including a chiral alcohol functionality.[2–4] In the original articles of Itsuno and coworkers[5] and Corey and Link,[6] the reaction is catalyzed by monocyclic oxazaborolidines.

In principle bicyclic oxazaborolidines, obtained from tridentate ligands containing one nitrogen and two oxygen atoms, can increase the differentiation of the enantiotopic faces of the carbonyl compound and the affinity of the ketone binding to boron, because of the rigidity of the bicyclic skeleton and to the increased Lewis acidity of the coordinated boron atom.

So, it becomes interesting to prepare new tridentate chiral ligands to be tested in the borane enantioselective reduction of prochiral ketones.

In literature, it is known that tridentate aminophenols, derived from salicylaldehyde, catalyze the boron enantioselective reduction of ketones.[7,8] In the past, several diastereoselective, practical and cheap methods were developed to synthetize 1-(aminoalkyl)naphthol systems,[9–11] analogous to aminophenols. Sometimes these compounds were easily obtained, as single diastereomers, through the aromatic Mannich reaction of 2-naphthol, aldehydes, and chiral primary amines. These methods can be directly applied to the preparation of tridentate 1-(aminoalkyl)naphthols using aminoalcohols instead of simple amines.

Other convenient synthetic methodologies are available for the preparation of enantiopure γ-aminoalcohols, by reduction of the corresponding β-enaminoketones[12] or β-enaminoesters.[13] Also in this case introducing an hydroxy function in the starting β-enaminoketone or β-enaminoester, by choosing suitable aminoalcohols, allows the direct application of these reductive methods to the preparation of tridentate γ-aminoalcohols, potentially useful as ligands.

In this article, the application of such synthetic methodologies to the preparation of novel tridentate 1-(aminoalkyl)naphtols **4**, and γ-aminoalcohols **6** and the results from the use of these new compounds as ligands in the enantioselective reduction of prochiral ketones with borane are reported.

EXPERIMENTAL

General Methods

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with $CDCl_3$ as solvent at ambient temperature and were calibrated using residual undeuterated solvents as the internal reference. Coupling constants are given in Hertz. IR spectra were recorded using FTIR apparatus. Optical rotations were measured in a 1 dm cell at 20°C. GC-MS analyses were performed with an HP 59970 workstation formed by an HP-5890 gas chromatograph equipped with a methyl silicone capillary column and by an HP-5970 mass detector. Enantiomeric purities (% *ee*) were determined by GC analyses of the resulting alcohols on a MEGADEX DMP β capillary column (30% dimethylpentyl-β-cyclodextrin on OV 1701, 25 m, 0.25 mm ID, 0.25 μm film). All reagents were commercially available, pur-

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*Correspondence to: Cristina Cimarelli, Department of Chemical Sciences, University of Camerino, Via S. Agostino 1, 62032 Camerino, Italy.
E-mail: cristina.cimarelli@unicam.it
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TABLE 1. Borane-mediated asymmetric reduction of acetophenone by enantiopure tridentate aminonaphthols 4 and aminoalcohols 6 as catalytic source

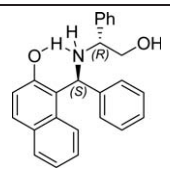
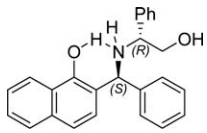
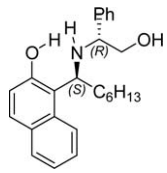
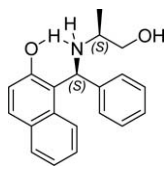
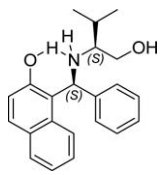
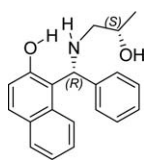
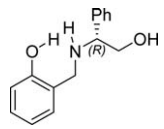
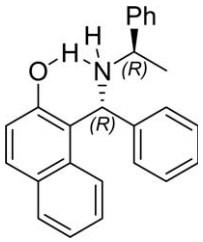
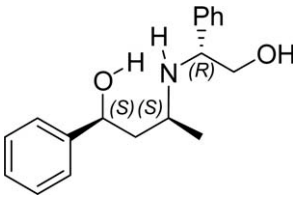
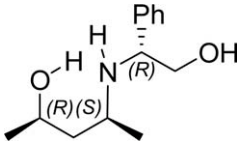
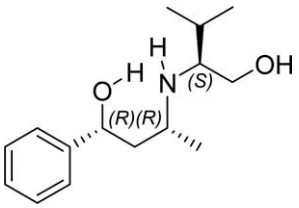
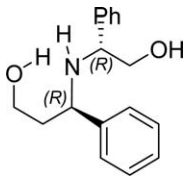
Entry	**4** or **6**	Ligand (yield %)[a]	Time (h)	Yield[b] (%)	*e.e.* (%)	Alcohol config.
1		(*S,R*)-**4a**[10] (63)	2	96	55	(*S*)
2		(*R,R*)-**4a**[10] (12)	2	98	8	(*S*)
3		(*S,R*)-**4b** (61)	4	75	41	(*S*)
4		(*R,R*)-**4b** (11)	4	65	6	(*S*)
5		(*S,R*)-**4c** (58)	2	>98	31	(*S*)
6		(*R,R*)-**4c** (14)	2	>98	7	(*S*)
7		(*S,S*)-**4d** (52)	2	97	17	(*S*)
8		(*S,R*)-**4d** (29)	2	95	9	(*S*)
9		(*S,S*)-**4e** (57)	5	83	0.6	(*S*)
10		(*S,S*)-**4f** (28)	2	97	21	(*S*)
11		(*R,S*)-**4f** (49)	2	>98	10	(*S*)
12		(*R*)-**4g**[14] (88)	6	>98	62	(*S*)

TABLE 1. Continued

Entry	**4** or **6**	Ligand (yield %)[a]	Time (h)	Yield[b] (%)	*e.e.* (%)	Alcohol config.
13		(*R,R*)-**4h**[9] (93)	1	>98	0.5	(*R*)
14		(*S,S,R*)-**6a** (53)	4	>98	38	(*S*)
15		(*R,S,R*)-**6b** (63)	4	>98	6	(*S*)
16		(*R,R,S*)-**6c** (54)	4	93	43	(*R*)
17		(*R,R*)-**6d** (62)	4	16	9	(*S*)

[a]Yield of the isolated pure ligand.
[b]Gascromatographic yield.

chased at the highest quality, and were purified by distillation when necessary prior to use.

Preparation of the Chiral Ligands 4 and 6

1-(Aminoalkyl)naphthols **4a–h**,[9–11] 1-(aminoalkyl)phenol **4g**[14] and g-aminoalcohols **6a–d**[12,13] were prepared according to the literature methods. Spectral data of ligands **4b–f** and **6a–d** follow.

1-{(*S*)-[(*R*)-2-Hydroxy-1-phenylethylamino](phenyl)methyl}naphthalen-2-ol (***S,R***)-**4a**:[10] colorless oil ^{1}H NMR (400 MHz, $CDCl_3$): δ3.88 (dd, 1 H, J = 15.1, 6.0 Hz); 3.93 (m, 1 H), 3.94 (dd, 1 H, J = 15.1, 4.3 Hz), 5.55 (s, 1 H), 6.20 (br s, 3 H), 7.15–7.75 (m, 16 H).

1-{(*R*)-[(*R*)-2-Hydroxy-1-phenylethylamino](phenyl)methyl}naphthalen-2-ol (***R,R***)-**4a**: compound (***R,R***)-**4a**[10] colorless oil (***R,R***)-**4a** ^{1}H NMR (400 MHz, $CDCl_3$): δ3.83 (dd, 1 H, J = 11.0, 4.8 Hz); 3.97 (dd, 1 H, J = 4.8, 4.0 Hz),

4.10 (dd, 1 H, J = 11.0, 4.0 Hz), 5.40 (br s, 3 H), 5.91 (s, 1 H), 7.15–7.75 (m, 16 H).

2-{(*S*)-[(*R*)-2-Hydroxy-1-phenylethylamino](phenyl)methyl}naphthalen-1-ol (***S,R*)-4b**:[10] colorless oil: $[\alpha]_D^{20}$ + 109.77 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3285, 1751, 1426, 1354, 1231, 1038, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ.2.40 (brs, 3 H), 3.76–4.00 (m, 3 H), 5.57 (s, 1 H), 7.20–7.80 (m, 16 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 60.1, 62.7, 66.5, 113.2, 120.35, 121.2, 122.6, 127.8, 127.9, 128.0, 128.2, 128.5, 128.8, 129.0, 129.2, 129.3, 130.0, 132.7, 139.0, 141.3, 156.9; Anal. Calcd. for $C_{25}H_{23}NO_2$ (369.46): C, 81.28; H, 6.27; N, 3.79. Found: C, 81.23; H, 6.37; N, 3.97.

2-{(*R*)-[(*R*)-2-Hydroxy-1-phenylethylamino](phenyl)methyl}naphthalen-1-ol (***R,R*)-4b**:[10] colorless oil; $[\alpha]_D^{20}$ + 4.87 (*c* 1.3, $CHCl_3$); IR (neat): ν_{max} 3294, 1783, 1371, 1233, 1019, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ1.60 (brs, 3 H), 3.87 (dd, 1 H, J = 10.8, 4.6 Hz), 3.98 (dd, 1 H, J = 4.6, 4.0 Hz), 4.15 (dd, 1 H, J = 10.8, 4.0 Hz), 5.92 (s, 1 H), 7.10–7.75 (m, 16 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 60.7, 61.7, 64.6, 109.6, 118.2, 120.2, 122.7, 123.5, 127.8, 127.9, 128.0, 128.5, 128.8, 129.0, 129.3, 130.0, 130.7, 131.5, 141.3, 154.2, 163.1; Anal. Calcd. for $C_{25}H_{23}NO_2$ (369.46): C, 81.28; H, 6.27; N, 3.79. Found: C, 81.19; H, 6.48; N, 3.92.

1-{(*S*)-1-[(*R*)-2-Hydroxy-1-phenylethylamino]heptyl}naphthalen-2-ol (***S,R*)-4c**:[10] colorless oil; $[\alpha]_D^{20}$ + 3.83 (*c* 0.73, $CHCl_3$); IR (neat): ν_{max} 3309, 1622, 1601, 1269, 1038, 736, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ0.85 (t, 3 H, J = 6.6 Hz), 1.00–1.80 (m, 10 H), 1.95 (br s, 3 H), 3.73 (t, 1 H, J = 5.1 Hz), 3.83 (dd, 1 H, J = 11.0, 5.1 Hz), 3.93 (dd, 1 H, J = 11.0, 5.1 Hz), 4. 48 (dd, 1 H, J = 7.9, 5.7 Hz), 7.00–8.03 (m, 11 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.8, 26.3, 29.2, 31.8, 35.1, 54.8, 61.7, 66.6, 115.8, 119.9, 121.1, 122.5, 126.3, 127.7, 128.3, 128.9, 129.0, 129.1, 129.3, 132.9, 139.5, 156.2. Anal. Calcd. for $C_{25}H_{31}NO_2$, (377.52): C, 79.54; H, 8.27; N, 3.71. Found: C, 79.71; H, 8.12; N, 3.51.

1-{(*S*)-1-[(*R*)-2-Hydroxy-1-phenylethylamino]heptyl}naphthalen-2-ol (***R,R*)-4c**:[10] colorless oil; $[\alpha]_D^{20}$ − 47.1 (*c* 0.15, $CHCl_3$); IR (neat): ν_{max} 3305, 1738, 1626, 1354, 1268, 1038, 735, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ0.84 (t, 3 H, J = 6.6 Hz), 1.10–1.58 (m, 10 H), 1.95 (br s, 3 H), 3.79 (dd, 1 H, J = 10.6, 4.8 Hz), 3.86 (dd, 1 H, J = 4.8, 3.8 Hz), 4.03 (dd, 1 H, J = 10.6, 3.8 Hz), 4.87 (t, 1 H, J = 6.6 Hz), 6.97–7.90 (m, 11 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.8, 26.4, 29.5, 31.8, 35.2, 55.9, 61.4, 64.1, 116.5, 120.0, 121.0, 122.4, 126.4, 127.2, 127.8, 128.7, 128.7, 128.9, 129.1, 132.7, 139.5, 156.0. Anal. Calcd. for $C_{25}H_{31}NO_2$, (377.52): C, 79.54; H, 8.27; N, 3.71. Found: C, 79.66; H, 8.08; N, 3.48.

1-{(*S*)-[(*S*)-1-Hydroxypropan-2-ylamino](phenyl)methyl}-naphthalen-2-ol (***S,S*)-4d**:[10] colorless oil; $[\alpha]_D^{20}$ + 157.1 (*c* 1.05, $CHCl_3$); IR (neat): ν_{max} 3297, 1621, 1266, 1231, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ1.12 (d, 3 H, J = 6.6 Hz); 1.70 (br s, 3 H), 3.10 (qdd, 1 H, J = 6.6, 5.5, 3.7 Hz), 3.54 (dd, 1 H, J = 10.8, 5.5 Hz), 3.95 (dd, 1 H, J = 10.8, 3.7 Hz), 5.82 (s, 1 H), 7.12–7.90 (m, 11 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 54.4, 61.7, 64.5, 114.3, 120.5, 121.3, 122.6, 126.7, 127.9, 128.2, 128.8, 129.0, 129.3, 129.8, 132.5, 141.9, 157.5; Anal. Calcd. for $C_{20}H_{21}NO_2$ (MW 307.39): C, 78.15; H, 6.89; N, 4.56. Found: C, 78.41; H, 7.06; N, 4.48.

1-{(*S*)-[(*S*)-1-Hydroxypropan-2-ylamino](phenyl)methyl}-naphthalen-2-ol (***S,R*)-4d**:[10] colorless oil; $[\alpha]_D^{20}$ − 19.8 (*c* 0.55, $CHCl_3$); IR (neat): ν_{max} 3304, 1721, 1626, 1254, 1229, 1041, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ1.31 (d, 3 H, J = 6.2 Hz), 2.40 (br s, 3 H), 3.00 (m, 1 H), 3.59 (dd, 1 H, J = 11.4, 4.8 Hz), 3.73 (dd, 1 H, J = 11.4, 4.0 Hz), 5.88 (s, 1 H), 7.14–7.82 (m, 11 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 54.5, 61.7, 64.4, 114.4, 120.4, 121.3, 122.6, 126.5, 126.7, 129.0, 129.3, 131.1, 132.5, 141.9, 154.4, 157.4, 162.0; Anal. Calcd. for $C_{20}H_{21}NO_2$, (MW 307.39): C, 78.15; H, 6.89; N, 4.56. Found: C, 78.12; H, 6.97; N, 4.72.

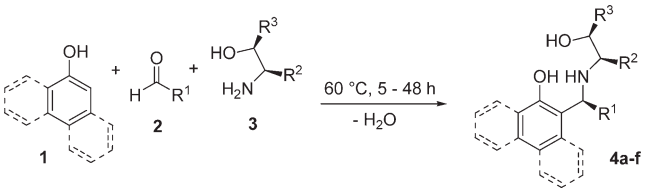
1-{(S)-[(S)-1-Hydroxy-3-methylbutan-2-ylamino](phenyl)-methyl}naphthalen-2-ol (***S,S*)-4e**:[10] colorless oil; $[\alpha]_D^{20}$ + 134.3 (*c* 0.23, $CHCl_3$); IR (neat): ν_{max} 3315, 1631, 1359, 1231, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ0.95 (d, 3 H, J = 6.8 Hz), 1.00 (d, 3 H, J = 6.8 Hz), 1.80 (br s, 3 H), 1.96 (sept d, 1 H, J = 6.8, 5.5 Hz), 2.63 (dt, 1 H, J = 5.5, 3.8 Hz), 3.74 (dd, 1 H, J = 11.5, 3.8 Hz), 4.04 (dd, 1 H, J = 11.5, 3.8 Hz), 6.00 (s, 1 H), 7.15–7.50 (m, 8 H), 7.70–7.80 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 19.7, 30.0, 59.6, 65.5, 64.7, 109.6, 118.1, 123.6, 126.5, 126.6, 128.0, 128.5, 128.8, 129.2, 129.8, 131.0, 141.7, 153.9, 162.5. Anal. Calcd. for $C_{22}H_{25}NO_2$, (MW 335.44): C, 78.77; H, 7.51; N, 4.18. Found: C, 78.51; H, 7.56; N, 4.01.

1-{(S)-[(S)-1-Hydroxy-3-methylbutan-2-ylamino](phenyl) methyl}naphthalen-2-ol (**R,S**)-**4e**:[10] ^1H NMR (400 MHz, $CDCl_3$, obtained from an enriched mixture of the two diastereomers): δ1.02 (d, 3 H, J = 6.8 Hz), 1.03 (d, 3 H, J = 6.8 Hz), 1.70 (br s, 3H), 2.16 (sept d, 1 H, J = 6.8, 5.1 Hz), 2.72 (td, 1 H, J = 5.1, 3.8 Hz), 3.64 (dd, 1 H, J = 12.0, 5.1 Hz), 3.73 (dd, 1 H, J = 12.0, 3.4 Hz), 5.81 (s, 1 H), 7.13–7.80 (m, 11 H).

1-{(*S*)-[(*S*)-2-Hydroxypropylamino](phenyl)methyl}naphthalen-2-ol (***S,S*)-4f**:[10] colorless oil; $[\alpha]_D^{20}$ + 66.9 (*c* 0.43, $CHCl_3$); IR (neat): ν_{max} 3297, 1633, 1391, 1222, 1041, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ1.24 (d, 3 H, J = 6.2 Hz), 1.95 (br s, 3 H), 2.76 (dd, 1 H, J = 12.8, 7.0 Hz), 2.90 (dd, 1 H, J = 12.8, 3.3 Hz), 4.15 (dqd, 1 H, J = 7.0, 6.2, 3.3 Hz), 5.75 (s, 1 H), 7.14–7.80 (m, 11 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 55.4, 63.3, 65.7, 113.5, 120.3, 121.3, 122.7, 126.7, 128.0, 128.1, 128.3, 129.1, 129.3, 130.0, 132.9, 141.6, 156.9. Anal. Calcd. for $C_{20}H_{21}NO_2$, (MW 307.512): C, 78.16; H, 6.88; N, 4.55. Found: C, 77.87; H, 6.90; N, 4.46.

1-{(*R*)-[(*S*)-2-Hydroxypropylamino](phenyl)methyl}naphthalen-2-ol (***R,S*)-4f**:[10] colorless oil; $[\alpha]_D^{20}$ + 155.8 (*c* 0.30, $CHCl_3$); IR (neat): ν_{max} 3317, 1602, 1429, 1237, 1052, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ1.19 (d, 3 H, J = 6.2 Hz), 1.70 (br s, 3 H), 2.75 (dd, 1 H, J = 11.7, 9.2 Hz), 2.85 (dd, 1 H, J = 11.7, 3.0 Hz), 4.07 (dqd, 1 H, J = 9.2, 6.2, 3.0 Hz), 5.66 (s, 1 H), 7.11–7.80 (m, 11 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 56.8, 64.7, 67.6, 113.6, 120.2, 121.4, 122.7, 126.7, 128.0, 128.3, 128.9, 129.0, 129.3, 129.9, 132.8, 141.6, 156.9.Anal. Calcd. for $C_{20}H_{21}NO_2$, (MW 307.39): C, 78.16; H, 6.88; N, 4.55. Found: C, 77.99; H, 6.73; N, 4.61.

(1*S*,3*S*)-3-[(*R*)-2-Hydroxy-1-phenylethylamino]-1-phenylbutan-1-ol (***S,S,R*)-6a**:[12] colorless oil; $[\alpha]_D^{20}$ − 26.9 (*c* 3.08, $CHCl_3$); IR (neat): ν_{max} 3294, 1493, 1453, 1062, 758, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ1.06 (d, 3 H, J = 6.2 Hz), 1.59 (dd, 1 H, J = 14.3, 9.8 Hz), 1.74 (dt, 1 H, J = 14.3, 3.4 Hz), 3.22 (dqd, 1 H, J = 9.9, 6.2, 3.3 Hz), 3.36 (bs, 3 H), 3.60–3.96 (m, 3 H), 4.98 (dd, 1 H, J = 9.9, 2.9 Hz), 7.00–7.50 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 46.3,



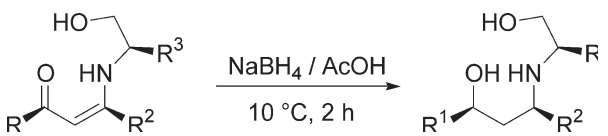
Scheme 1. Aromatic Mannich reaction for the synthesis of ligands **4a–f**.

54.0, 62.8, 66.9, 75.1, 125.7, 127.3, 127.4, 128.1, 128.5, 129.0, 142.0, 145.0; EI-MS m/z (%): 254 (57), 132 (100), 105 (21), 91 (23), 77 (27); Anal. Calcd. for $C_{18}H_{23}NO_2$, (285.38): C, 75.76; H, 8.12; N, 4.90. Found: C, 75.77; H, 7.91; N, 4.88.

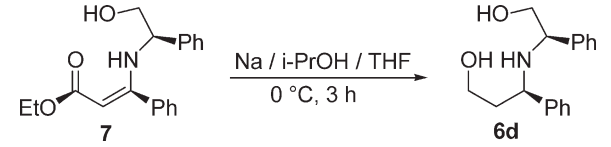
(2*R*,4*S*)-4-[(*R*)-2-Hydroxy-1-phenylethylamino]pentan-2-ol (***R,S,R*)-6b**[12] colorless oil; $[\alpha]_D^{20}$ + 15.5 (*c* = 2.84, $CHCl_3$). IR (neat): ν_{max} 3304, 1741, 1454, 1376, 1234, 1038, 762, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ0.94 (d, 3 H, *J* = 6.2 Hz), 1.09 (d, 3 H, *J* = 5.9 Hz), 1.22 (dt, 1 H, *J* = 14.3, 10.3 Hz), 1.45 (ddd, 1 H, *J* = 14.3, 3.1, 2.0 Hz), 2.97 (dqd, 1 H, *J* = 10.3, 6.2, 3.3 Hz), 3.40 (br s, 3 H), 3.86–4.09 (m, 2 H), 4.06–4.24 (m, 2 H), 7.20–7.40 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 23.9, 45.8, 53.6, 59.0, 67.3, 68.7, 127.2, 127.9, 128.8, 141.2. EI-MS m/z (%): 192 (100), 163 (26), 134 (56), 132 (56), 106 (85), 91 (45), 77 (25); Anal. Calcd. for $C_{13}H_{21}NO_2$, MW 223.31: C, 69.93; H, 9.47; N, 6.27%. Found: C, 69.81; H, 9.33; N, 6.50%.

(1*R*,3*R*)-3-[(*S*)-1-Hydroxymethyl-2-methyl-propylamino]-1-phenylbutan-1-ol (***R,R,S*)-6c**[12] colorless oil; $[\alpha]_D^{20}$ + 1.84 (*c* 0.68, $CHCl_3$); IR (neat): ν_{max} 3304, 1740, 1454, 1370, 1216, 1038, 762, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ0.95 (d, 3 H, *J* = 6.8 Hz), 0.99 (d, 3 H, *J* = 7.3, Hz), 1.15 (d, 3 H, *J* = 6.0 Hz), 1.69 (dt, 1 H, *J* = 14.5, 10.7 Hz), 1.77 (dt, 1 H, *J* = 14.5, 3.0 Hz), 1.93 (sept d, 1H, *J* = 6.8, 3.8 Hz), 2.72 (dt, 1 H, *J* = 9.0, 3.8 Hz), 3.12 (dqd, 1 H, *J* = 10.2, 6.4, 2.6 Hz), 3.43 (dd, 1 H, *J* = 10.7, 9.0 Hz), 3.72 (dd, 1 H, *J* = 10.7, 3.4 Hz), 3.85 (m, 3H), 4.90 (dd, 1 H, *J* = 10.2, 2.6 Hz), 7.20–7.40 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.4, 19.7, 20.9, 28.9, 46.1, 53.0, 61.7, 61.8, 75.5, 125.7, 127.2, 128.5, 145.0. Anal. Calcd. for $C_{15}H_{25}NO_2$, (251.36): C, 71.67; H, 10.02; N, 5.57. Found: C, 71.53; H, 10.08; N, 5.39%.

(*S*,*S*)-3-[(*S*)-1-Hydroxymethyl-2-methyl-propylamino]-1-phenylbutan-1-ol (***S,S,S*)-6c**[12]: colorless oil; ^1H NMR (400 MHz, $CDCl_3$, obtained from an enriched mixture of the two diastereomers): δ0.96 (d, 3H, *J* = 6.8 Hz), 0.98 (d, 3H, *J* = 6.8, Hz), 1.13 (d, 3H, *J* = 6.4 Hz), 1.59 (dt, 1H, *J* = 14.5, 10.7 Hz), 1.78 (dt, 1H, *J* = 14.5, 3.0 Hz), 1.85 (oct, 1H, *J* = 6.4Hz), 2.54 (q, 1H, *J* = 5.0 Hz), 3.18 (dqd, 1H, *J* = 9.4, 6.4, 3.0 Hz), 3.66 (dd, 1H, *J* = 11.5, 5.5 Hz), 3.75 (dd, 1H, *J* = 11.5, 3.8 Hz), 3.85 (m, 3H), 4.94 (dd, 1H, *J* = 10.7, 2.1 Hz), 7.20–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 19.6, 21.6, 29.4, 45.9, 53.5, 62.4, 75.5, 125.8, 127.3, 128.5, 145.2.



Scheme 2. Diastereoselective reduction of β-enaminoketones **5** to γ-aminoalcohols **6a–c**.



Scheme 3. Diastereoselective reduction of β-enaminoester **7** to γ-aminoalcohol **6d**.

(*R*)-3-[(*R*)-2-Hydroxy-1-phenylethylamino]-3-phenylpropan-1-ol (***R,R*)-6d**[13] colorless oil; $[\alpha]_D^{20}$ - 158.9 (*c* 0.69, $CHCl_3$); IR (neat): ν_{max} 3287, 1736, 1493, 1341, 1147, 1032, 758, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ1.70 (dq, 1H, *J* = 14.6, 3.4 Hz), 2.04 (ddt, 1H, *J* = 14.6, 10.8, 7.0 Hz), 3.64 (dd, 2H, *J* = 10.6, 3.4 Hz) 3.77 (dd, 4H, *J* = 6.6, 3.4 Hz), 3.90 (br s, 3H), 7.16–7.91 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.5, 60.7, 61.8, 63.2, 67.4, 126.8, 127.1, 127.5, 127.9, 128.4, 128.9, 139.7, 142.9. Anal. Calcd. for $C_{17}H_{21}NO_2$ (271,35): C, 75.25; H, 7.98; N, 5.16%. Found: C, 75.33; H, 7.70; N, 5.21%.

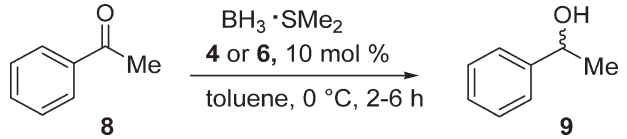
General Procedure for the Reduction of Acetophenone with Borane-Dimethylsulfide Catalyzed by Ligands 4a–h and 6a–d

Ligands **4a–h** or **6a–d** (0.2 mmol) were poured into a three-necked round-bottom flask equipped with magnetic stirring. Borane dimethyl sulfide 1 M in toluene (2.2 mmol, 1.1 mL) was added dropwise to the ligand at room temperature, under nitrogen atmosphere. After 30 min, the mixture was cooled to 0°C and acetophenone was added (0.240 g, 2 mmol in 2 mL toluene); the reaction mixture was allowed to stand until the reaction was complete, according to the reaction times reported in Table 1. Then the reaction mixture was quenched with 2 M NaOH (10 mL) and extracted twice with CH_2Cl_2 (10 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent removed under reduced pressure. The crude mixture obtained was filtered on a thin pad of silica gel with AcOEt/cyclohexane (20:80 v/v) and then submitted to gaschromatographic analysis.

RESULTS AND DISCUSSION

The aromatic Mannich reaction has been applied to the preparation of (aminoalkyl)naphtols **4a–g** by reaction of α- or β-naphthols **1** with aldehydes **2** and several β-aminoalcohols **3**.[9–11] The three-component reaction simply takes place by mixing the reagents and allowing the mixture to stand at 60°C for 5–48 h, as depicted in Scheme 1.

Secondary γ-aminoalcohols **6a–c** were instead prepared by diastereoselective reduction of β-enaminoketones with sodium borohydride in acetic acid,[12] as depicted in Scheme 2.



Scheme 4. Enantioselective borane reduction of acetophenone catalyzed by ligands **4** or **6**.

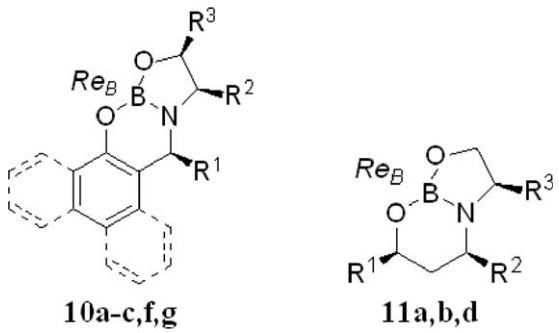


Fig. 1. Structures of the byciclic oxazaborolidines formed by ligands **10a–c,f,g** and **11a,b,d**.

Finally, primary γ-aminoalcohol **6d** was prepared by reduction of the corresponding β-enaminoester with sodium in THF, in the presence of isopropanol,[13] as reported in Scheme 3.

These tridentate ligands were applied to the catalyzed reduction of ketones with borane, as depicted in Scheme 4. The catalyst was prepared by dissolving ligands **4** or **6**, in 10% molar ratio with respect to the acetophenone, in a solution of borane-dimethylsulfide in toluene, at room temperature, under a nitrogen atmosphere. After 30 min, acetophenone was added at 0°C then the *ee* of the reaction was determined at completion by gas-chromatography on a chiral column. The ligands used and the results obtained are reported in Table 1.

The yields are >95% in the majority of the cases. The ligand reacts with a borane molecule forming the bicyclic oxazaborolidine **10** or **11**, that is the real catalytic specie. In the subsequent step, this complex coordinates the ketone at boron atom and borane at nitrogen atom. The subsequent hydride transfer step takes place through a cyclic six-membered transition state.

The reaction performed with ligand (*R,R*)-**4h** (entry 13) shows the need of a tridentate chelating structure to make the reduction enantioselective: although the yield of the reduction is as high as that obtained with ligand (*S,R*)-**4a** (entry 1) the *ee* is ~100 times larger in this last case, in which the ligand (*S,R*)-**4a** differs from (*R,R*)-**4h** only in the presence of the second hydroxy group.

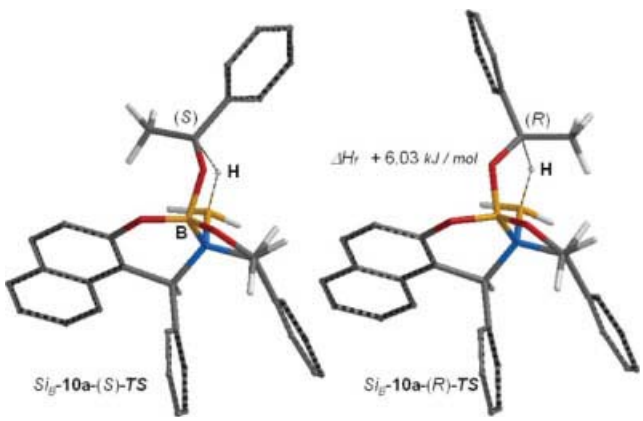


Fig. 2. Molecular modeling representations of the diastereoselective transition state (TS) of the reduction step with ligand (*S,R*)-4a (PM3 semiempirical minimization). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

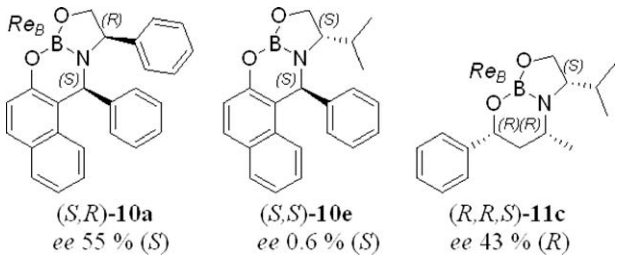


Fig. 3. Structures of oxazaborolidines (*S,R*)-**10a**, (*S,S*)-**10e** and (*R,R,S*)-**11c** and *ee* obtained in the corresponding reductions.

Stereochemistry

The stereochemistry of the ligand determines the preferred face of the ketone on which the reduction takes place. In fact, all the ligands that achieve the major enantioselectivitites show a similar structure of the byciclic oxazaborolidine, with the substituents R^1, R^2, and R^3 located on the same side of the complex, as shown in Figures 1 and 3. In the majority of the chelants reported in Table 1, the product is the bicyclic oxazaborolidine with the Re_B face of the chelated boron atom hindered by the substituents, whereas the Si_B face is open to coordinate both borane and acetophenone for the subsequent reduction step. This situation is common to both 1-(aminoalkyl)naphthols and γ-aminoalcohols (Fig. 1).

In the reduction step, acetophenone can approach to the catalyst in two different ways, to give (*R*) or (*S*)-1-phenylethanol. The molecular models of the two hypothetical transition states corresponding to the two situations are depicted in Figure 2, in the case of ligand (*S,R*)-**4a**. The transition state Si_B-**10a**-(*S*)-**TS**, that affords the (S) alcohol, is stabilized by 6.03 kJ/mol with respect to Si_B-**10a**-(*R*)-**TS** (PM3 semiempirical minimization*), reasonably because the hydride transfer takes places through a six member chair-like transition state in the first, whereas the second presents a boat-like conformation (Fig. 2). This model is in accord with the experimental data that show that the major enantiomer obtained is (*S*)-1-phenylethanol in the majority of the cases (Table 1).

These results are relative to oxazaborolidines with structures like (*S,R*)-**10a**, depicted in Figure 3. On the contrary, the reduction with ligand (*R,R,S*)-**6c** produces the (*R*) alcohol in 43% *ee*. Indeed the catalyst (*R,R,S*)-**11c**, obtained with this ligand, presents R^1 and R^2 substituents located on the Si_B face, resulting in the Re_B face being open for the reduction step, in a situation opposite to the previous (*S,R*)-**10a** (Fig. 3).

A confirmation of the hypothesis of induction mechanism is the reduction performed with ligand (*S,S*)-**4e**, that results in a very low *ee* with a slight preference for the (*S*) alcohol. In the corresponding bicyclic oxazaborolidine

*PM3 semiempirical minimization was performed with the Spartan '06 1,1,1 – Wavefunction Inc 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612.

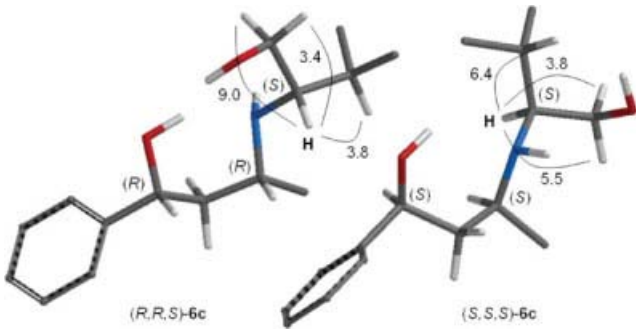


Fig. 4. Minimized conformations of diastereoisomers *syn*-γ-aminoalcohols (*R,R,S*)-6c and (*S,S,S*)-6c (PM3 semiempirical minimization). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

(*S,S*)-**10e**, the isopropyl group partially shields the Re_B face, while the phenyl group hinders the opposite Si_B face, making the two faces sterically not very different.

The absolute configuration of the ligands was established by comparing ^{1}H-NMR spectral data with the more stable conformations calculated by molecular modeling[9–13] (conformational analysis with PM3 semiempirical minimization*).

For example, ligand **6c** was synthesized by reduction of the corresponding β-enaminoketone, according to literature methods[12] obtaining in good yields only the two diastereomers of the *syn*-γ-aminoalcohol **6c**, and the major one was then used in the reduction reaction. The attribution of the configurations was made by the conformational analysis of the two *syn*-γ-aminoalcohols **6c**. The more populated conformations of the two *syn* isomers show a significant difference in the relative position of the two methine protons present on the side chain bonded to the nitrogen atom. Compound (***R,R,S***)-**6c** presents three more stable (more populated) conformations, the most stable of which is depicted in Figure 4, and all have both *anti* (J = 9.0 Hz) and *syn* (J = 3.8 Hz) protons. On the other hand, the more populated conformations of (***S,S,S***)-**6c** isomer are equilibrating *anti*/*gauche* conformations and consequently the coupling constants result lie between the *anti* and *gauche* standard values (J = 5.5, 6.4 Hz). According to this experimental data, the (*R,R,S*) absolute configuration was attributed to the major ligand **6c**, the one used in the reduction.

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