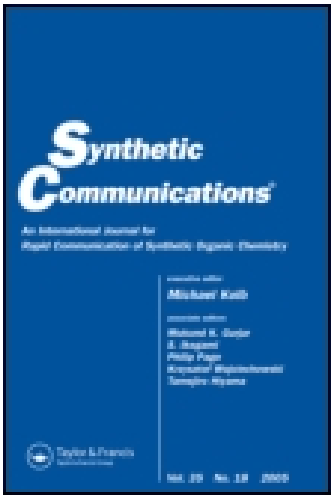

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Asymmetric Reduction of Prochiral Ketones with N-Sulfonylated Amino Alcohols as Catalysts

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Asymmetric Reduction of Prochiral Ketones with *N*-Sulfonylated Amino Alcohols as Catalysts

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Abstract: Novel *N*-sulfonylated amino alcohols were synthesized from L-amino acids and (+)-camphor, and their application to asymmetric reduction of prochiral ketones with $NaBH_4-BF_3 \cdot Et_2O$ is described.

Keywords: asymmetric reduction, ketone, *N*-sulfonylated amino alcohol

INTRODUCTION

Enantioselective reduction of prochiral ketones to enantiomerically pure secondary alcohols is an important reaction in asymmetric synthesis. The chiral oxazaborolidine-catalyzed reduction (CBS reduction) of prochiral ketones developed by Itsuno et al.[1] and then improved by Corey et al.[2] is one of the most important methods for generation of chiral secondary alcohols. However, the CBS reduction commonly requires borane, which is toxic and rather expensive. Chiral sulfonamides prepared from commercially available L-proline derivatives were also reported to be efficient catalysts for the highly enantioselective reduction of ketones with borane.[3,4] Jiang reported an enantioselective reduction of ketones

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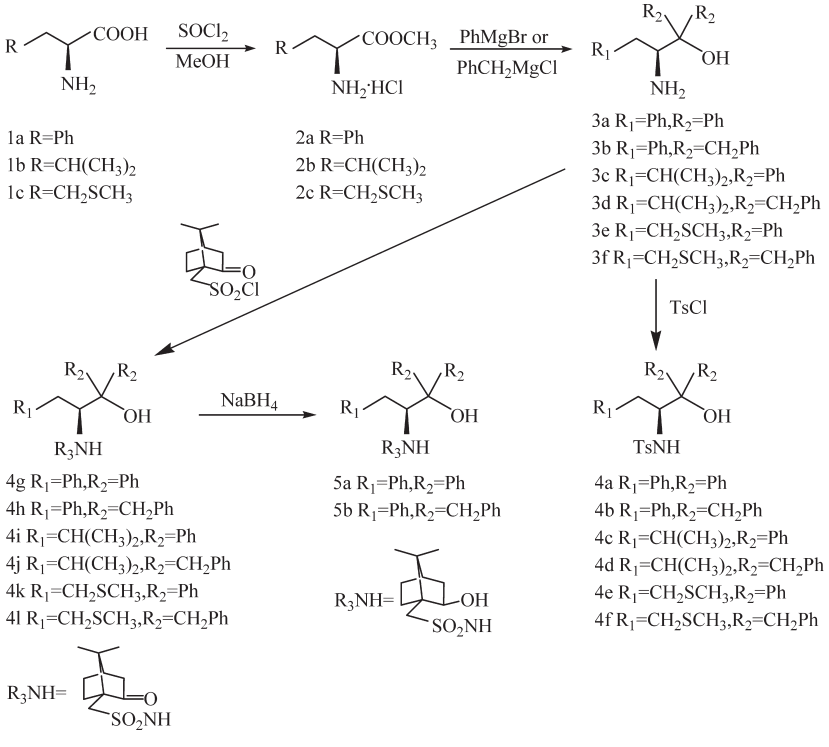
with the combined reagent of $NaBH_4/Me_3SiCl$ and a catalytic amount of (*S*)-α,α-diphenylpyrrolidinemethanol.[5] However, to the best of our knowledge, there are no reports on the use of $NaBH_4$-$BF_3 \cdot Et_2O$ for the enantioselective reduction of ketones. In this article, we report the synthesis of new *N*-sulfonylated amino alcohols from L-amino acid and (+)-camphor and their application in the catalytic enantioselective reduction of alkyl aryl ketones with the combined reagent of $NaBH_4$-$BF_3 \cdot Et_2O$.

RESULTS AND DISCUSSION

The synthetic route for *N*-sulfonylated amino alcohols is summarized in Scheme 1. After the typical methyl esteration of amino acid, the reaction of the Grignard reagents with **2a–c** afforded amino alcohols **3a–f**. The reaction of *p*-toluenesulfonyl chloride with amino alcohols **3a–f** in the presence of triethylamine produced compounds **4a–f**. The reaction of (1S)-(+)-10-camphorsulfonyl chloride,[6] which was prepared from the commercially available (+)-camphor with amino alcohols **3a–f**, catalyzed by



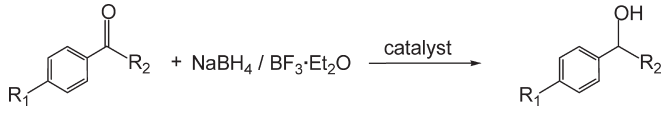
Scheme 1.

triethylamine gave camphorsulfonamides **4g–l**. Reduction of **4g** and **4h** with sodium borohydride at −15°C afforded the expected hydroxyl camphorsulfonamides **5a** and **5b** respectively.

A borane–tetrahydrofuran complex was reportedly formed when $NaBH_4$ was treated with $BF_3 \cdot Et_2O$ in THF,[7] and the asymmetric reduction of aromatic ketones with borane was catalyzed by a class of recoverable and highly stable chiral sulfonamides derived from (*S*)-proline to yield optically active secondary alcohols in high yields and with enantiomeric excesses of up to 91%.[3] This inspired us to investigate the possibility of carrying out the asymmetric reductions of ketones by $NaBH_4$–$BF_3 \cdot Et_2O$ and *N*-sulfonylated amino alcohols (Scheme 2).

Acetophenone was tested as substrate in the enantioselective reduction with $NaBH_4$–$BF_3 \cdot Et_2O$ using *N*-(*p*-toluenesulfonyl)amino alcohols **4a–f** as catalysts. As with previous reports,[3] when the reaction was carried out in THF, the best result could be achieved if the reaction mixture was at reflux. Hence, reactions were carried out in dry THF at reflux in the presence of 10 mol% chiral catalyst. The results are listed in Table 1. These catalysts afforded low enantioselectivities with the highest ee value of 16.9% when **4e** was used as a catalyst. Catalysts **4a**, **4c**, and **4e** derived from amino acid methyl ester hydrochloride and phenylmagnesium bromide show higher enantioselectivity than **4b**, **4d**, and **4f** derived from benzylmagnesium chloride and amino acid methyl ester hydrochloride.

Hoping to improve the enantioselectivity, *N*-sulfonylated amino alcohols **4g–l** and **5a–5b** containing chiral camphorsulfonyl group were synthesized and used as catalysts, the results are summarized in Table 2. To find optimum reaction conditions, we examined the reduction of acetophenone with chiral catalyst **4g** under various temperatures. In this study, obvious temperature effects were observed. When the reaction temperature was raised from room temperature to refluxing temperature, the ee value increased from 7.4 to 19.4% (entries 1 and 4). Hence, the best result could be achieved if the reaction mixture was at reflux. Based on the optimum reaction conditions, we chose acetophenone as substrate to examine the effect of various catalysts. All sulfonamide catalysts gave good chemical yields for acetophenone reduction by $NaBH_4$–$BF_3 \cdot Et_2O$. Among the catalysts examined, catalyst **4g** gave the best enantioselectivity. *N*-sulfonylated amino alcohols **4g**, **4i**, and **4k**, which derived from amino acid methyl ester hydrochloride and phenylmagnesium bromide provided the product



Scheme 2.

Table 1. Enantioselective reduction of acetophenone with catalysts **4a–4f**

Entry	Catalyst	Yield (%)[a]	%e.e.[b]	Configuration[c]
1	**4a**	92	12.2	R
2	**4b**	99	5.1	R
3	**4c**	95	11.3	R
4	**4d**	93	6.5	R
5	**4e**	94	16.9	R
6	**4f**	99	12.0	R

[a]Isolated yields.
[b]Determined by comparison of the optical rotation value with the literature[8] value.
[c]Determined by comparison of the specific rotation with the literature.[8]

with 19.4% ee, 14.7% ee, and 15.0% ee, (entries 4, 6, 8), respectively. For catalysts **4h**, **4j**, and **4l**, which derived from benzylmagnesium chloride and amino acid methyl ester hydrochloride, no enantioselectivity was observed (entries 5, 7, 9). Catalysts **4g** and **4h** containing a carbonyl group on the camphor moiety provided the product with 19.4% ee and 0 ee (entries 4 and 5), respectively. For catalysts **5a** and **5b** containing a hydroxy on the camphor moiety, enantioselectivities were 13.2% ee and 8.1% ee (entries 10 and 11), respectively. This study indicates that the camphor moiety could not improve enantioselectivity significantly.

We subsequently explored the scope of the asymmetric reduction of ketones using the best performing catalyst **4g**, and the results are shown in Table 3. For the examined ketones, the catalyst **4g** gave 0 to 33% ee and moderate to high

Table 2. Enantioselective reduction of acetophenone with catalysts **4g– l** and **5a–5b**

Entry	Catalyst	Temperature(°C)	Yield (%)[a]	%e.e.[b]	Configuration[c]
1	**4g**	rt(25)	98.0	7.4	R
2	**4g**	40	96.3	8.9	R
3	**4g**	50	97.1	12.6	R
4	**4g**	Reflux	99.0	19.4	R
5	**4h**	Reflux	89.3	0	—
6	**4i**	Reflux	85.1	14.7	R
7	**4j**	Reflux	97.6	0	—
8	**4k**	Reflux	95.4	15.0	R
9	**4l**	Reflux	87.0	0	—
10	**5a**	Reflux	97.6	13.2	R
11	**5b**	Reflux	98.2	8.1	R

[a]Isolated yields.
[b]Determined by comparison of the optical rotation value with the literature[8] value.
[c]Determined by comparison of the specific rotation with the literature.[8]

Table 3. Enantioselective reduction of prochiral ketones with catalyst **4g**

Entry	Catalyst	R_1	R_2	Yield (%)[a]	%e.e.[b]	Configuration[c]
1	**4g**	H	CH_3	99.0	19.4	R
2	**4g**	H	C_2H_5	65.7	8.6	R
3	**4g**	Cl	CH_3	78.6	16.2	R
4	**4g**	H	CH_2Br	72.8	32.2	S
5	**4g**	H	CH_2Cl	81.0	33.0	S
6	**4g**	Br	CH_3	73.5	18.9	R
7	**4g**	CH_3	CH_3	67.1	0	—

[a]Isolated yields.
[b]Determined by comparison of the optical rotation value with the literature[8] value.
[c]Determined by comparison of the specific rotation with the literature.[8]

chemical yields. The results show that the reduction of α-haloketone could give a higher enantioselectivity, which agrees with the results reported by other authors.[8] Moreover, the results also show that α-haloketone was reduced to the corresponding alcohol with (*S*)-configuration, whereas other ketones provided alcohols with (*R*)-configuration.

In summary, 14 chiral *N*-sulfonylated amino alcohols have been synthesized from readily available (+)-camphor and L-amino acids and used as catalysts for asymmetric reduction of prochiral ketones by $NaBH_4$–$BF_3 \cdot Et_2O$. These results reveal that *N*-sulfonylated amino alcohols containing one stereogenic center on the amino alcohol moiety do not provide the product with high enantioselectivities. Synthesis of a series of *N*-sulfonylated amino alcohols containing two stereogenic centers on the amino alcohol moiety, hoping to improve the enantioselectivity and to learn more about the structural features of the catalyst that influences the enantioselectivity and catalytic activity, is now in progress.

EXPERIMENTAL

Melting points are uncorrected. $[\alpha]_D$ values were recorded in a WZZ-3 digital polarimeter. FT-IR spectra were obtained on a Nexus 470 spectrophotometer. ^1H NMR spectra were recorded on a Varian Mercury 300 using $CDCl_3$ as solvent and TMS as internal standard. All solvents were purified according to standard procedures.

(S)-Phenylalanine Methyl Ester Hydrochloride (2a)

$SOCl_2$ (11 mL) was added dropwise to methanol (100 mL) in a 250-mL, round-bottomed flask cooled to $-10^\circ C$. After stirring for 15 min, L-phenylalanine (16.5 g, 100 mmol) was added. After warming up to room temperature and

stirring for 3 h, the reaction mixture was refluxed for 2 h. Then reaction mixture was condensed under reduced pressure; the residue was washed with ethanol and gave **2a**. Yield: 88.8%; mp 158–160°C; $[\alpha]_D^{25} = +39.0$ (c = 2, C_2H_5OH).

(S)-Leucine Methyl Ester Hydrochloride (2b)

This compound was prepared by procedures similar to those for **2a**. Yield: 96.33%; mp 149–151°C; $[\alpha]_D^{25} = +13.65$ (c = 2.0, H_2O).

(S)-Methionine Methyl Ester Hydrochloride (2c)

This compound was prepared by procedures similar to those for **2a**. Yield: 65.35%; mp 151–153°C; $[\alpha]_D^{25} = +21.6$ (c = 1.005, H_2O).

(S)-2-Amino-1,1,3-triphenyl-1-propanol (3a)

(S)-Phenylalanine methyl ester hydrochloride (2.16 g, 10 mmol) was added portionwise to freshly prepared Grignard reagent PhMgBr (80 mmol) in the usual way under 0°C and an argon atmosphere in diethyl ether. Then the mixture was stirred at ambient temperature overnight, and cold saturated NH_4Cl was dropped into it under vigorous stirring. The mixture was extracted with ethyl acetate three times. The combined organic layer was washed with brine and dried with anhydrous Na_2SO_4, then concentrated in vacuum. This residue was recrystallized with petroleum ether and gave **3a** as a colorless crystal. Yield: 65.3%; mp 144–145°C; $[\alpha]_D^{25} = -88.9$ (c = 1.53, CH_2Cl_2) [lit.[9]: mp 144–145°C; $[\alpha]_D^{25} = -88.5$ (c = 0.604, $CHCl_3$)].

(S)-2-Amino-1,1-dibenzyl-3-phenyl-1-propanol (3b)

Compound **3b** was prepared using a procedure similar to that of **3a** (Grignard reagent $PhCH_2MgCl$). After the usual workup, the residue was recrystallized with ethyl acetate and petroleum ether and gave **3b** as a colorless crystal. Yield: 63.4%; mp 134–136°C; $[\alpha]_D^{25} = +23.5$ (c = 2.0, $CHCl_3$); IR (KBr), ν: 3377, 3315, 3060, 3025, 2932, 1597, 1493, 1448, 1386, 1328, 1236, 1179, 1079, 1032, 878, 841, 753, 697 cm^{-1}; ^1H NMR: δ 7.39–6.99 (m, 15H, Ph), 3.83 (br, 1H), 3.26–3.28 (q, $J = 1.8$ Hz, $J = 13.2$ Hz, 1H), 2.97–3.01 (m, 2H), 2.69–2.84 (m, 3H), 2.42–2.47 (dd, 1H), 1.02 (s, 2H).

(S)-2-Amino-4-methyl-1,l-diphenyl-1-pentanol (3c)

Compound **3c** was prepared using a procedure similar to that of **3a** (Grignard reagent PhMgBr). After the usual workup, the residue was recrystallized with ethanol and gave **3c** as a colorless crystal. Yield: 52.45%; mp 136–138°C; $[\alpha]_D^{25} = -96.6$ (c = 1.00, $CHCl_3$) [lit.[9]: mp 132–134°C; $[\alpha]_D = -95.12$ (c = 1.01, $CHCl_3$)].

(S)-2-Amino-4-methyl-1,l-dibenzyl-1-pentanol (3d)

Compound **3d** was prepared using a procedure similar to that of **3a** (Grignard reagent $PhCH_2MgCl$). After the usual workup, the residue was recrystallized with ethanol and gave **3d** as a colorless crystal. Yield: 42.1%; mp 89–90°C; $[\alpha]_D^{25} = +17.44$ (c = 1.08, $CHCl_3$); IR (KBr), ν: 3402, 3354, 3062, 3024, 2863, 1601, 1494, 1455, 1405, 1323, 1241, 1185, 1157, 1085, 1046, 900, 856, 810, 753, 700 cm^{-1}; ^1H NMR: δ 7.49–7.17 (m, 10H), 3.92 (br, 1H), 2.88–2.81 (dd, J = 5.1 Hz, 13.8 Hz, 4H), 2.69–2.60 (m, 2H), 1.70–1.49 (m, 3H), 1.38–1.21 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.6 Hz, 3H).

(S)-2-Amino-4-methylthio-1,l-diphenyl-1-butanol (3e)

Compound **3e** was prepared using a procedure similar to that of **3a** (Grignard reagent PhMgBr). After the usual workup, the residue was recrystallized with petroleum ether and gave **3e** as a colorless crystal. Yield: 64.5%; mp 94–96°C; $[\alpha]_D^{25} = -110.55$ (c = 0.986, $CHCl_3$) [lit.[9]: mp 96–98°C; $[\alpha]_D = -108.57$ (c = 0.986, $CHCl_3$)].

(S)-2-Amino-4-methylthio-1,l-dibenzyl-1-butanol (3f)

Compound **3f** was prepared using a procedure similar to that of **3a** (Grignard reagent $PhCH_2MgCl$). After the usual workup, the residue was recrystallized with petroleum ether and gave **3f** as a colorless crystal. Yield: 63.5%; mp 130–134°C; $[\alpha]_D^{25} = -30$ (c = 0.60, $CHCl_3$); IR (KBr), ν: 3372, 3308, 3064, 3029, 2944, 2914, 2857, 1600, 1494, 1447, 1399, 1343, 1240, 1185, 1142, 1078, 1043, 963, 874, 817, 757, 703 cm^{-1}; ^1H NMR: δ 7.32–7.19 (m, 10H), 3.65 (br, 1H), 2.86 (d, J = 14.1 Hz, 2H), 2.71 (d, J = 13.8 Hz, 2H), 2.66–2.57 (m, 2H), 2.50–2.35 (m, 2H), 2.11 (s, 3H), 1.64–1.53(m, 1H), 1.08 (br, 2H).

(S)-2-(*p*-Toluenesulfonylamino)-1,1,3-triphenyl-1-propanol (4a)

p-Toluenesulfonyl chloride (5 mmol) in CH_2Cl_2 (10 mL) was added to a stirred solution of triethylamine (2.1 mL, 15 mmol) and (S)-2-amino-1,1,3-triphenylpropanol (1.52 g, 5.0 mmol) in CH_2Cl_2 (20 mL) at 0°C over a 1 h period. The reaction mixture was allowed to warm to room temperature and stirred for an additional 24 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 2 N HCl (2 × 5 mL), saturated aqueous $NaHCO_3$ (3 × 10 mL), and brine (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and recrystallized from ethanol to afford the sulfonylated amino alcohol. Yield: 72.9%; mp 129–132°C (lit.[10]: mp 120–121°C); $[\alpha]_D^{25} = +120.5$ (c = 0.518, CH_2Cl_2); IR (KBr), ν: 3526, 3364, 3062, 3030, 2929, 1599, 1494, 1449, 1314, 1148, 1087, 1058, 1035, 957, 909, 811, 745, 699, 670 cm^{-1}.

(S)-2-(*p*-Toluenesulfonylamino)-1,1-dibenzyl-3-phenyl-1-propanol (4b)

Compound **4b** was prepared using a procedure similar to that of **4a**. Yield: 75.6%; mp 167–169°C; $[\alpha]_D^{25} = -113.6$ (c = 0.494, CH_2Cl_2); IR (KBr), ν: 3503, 3341, 3029, 2926, 1599, 1493, 1450, 1411, 1343, 1318, 1156, 1086, 1049, 949, 912, 811, 754, 701, 665 cm^{-1}; ^1H NMR: δ 7.41–6.43 (m, 19H), 4.22(d, $J = 8.1$ Hz, 1H), 3.79 (s, 1H), 3.31–3.24 (m, 1H), 3.12–2.99 (m, 3H), 2.85–2.73 (m, 2H), 2.46–2.37 (m, 1H), 2.31 (s, 3H). Anal. calcd. for $C_{30}H_{31}NO_3S$: C, 74.20%; H, 6.43%; N, 2.88%. Found: C, 74.13%; H, 6.51%; N, 2.79%.

(S)-2-(*p*-Toluenesulfonylamino)-4-methyl-1,l-diphenyl-1-pentanol (4c)

Compound **4c** was prepared using a procedure similar to that of **4a**. Yield: 78.8%; mp 197–200°C; $[\alpha]_D^{25} = +14.6$(c = 0.520, CH_2Cl_2); IR (KBr), ν: 3520, 3261, 3027, 2958, 2869, 1600, 1495, 1448, 1304, 1150, 1094, 1063, 1019, 974, 948, 910, 879, 810, 743, 699 cm^{-1}; ^1H NMR: δ 7.47–7.11 (m, 14H), 4.58–4.51 (m, 2H), 2.93 (d, $J = 18.3$ Hz, 1H), 2.37 (s, 3H), 1.59–1.55 (m, 1H), 1.38–1.21 (m, 2H), 0.89 (d, $J = 6$ Hz, 3H), 0.74(d, $J = 6.6$ Hz, 3H). Anal. calcd. for $C_{25}H_{29}NO_3S$: C, 70.89%; H, 6.90%; N, 3.31%. Found: C, 70.98%; H, 6.93%; N, 3.26%.

(S)-2-(*p*-Toluenesulfonylamino)-4-methyl-1,l-dibenzyl-1-pentanol (4d)

Compound **4d** was prepared using a procedure similar to that of **4a**. Yield: 73.9%; mp 153–155°C; $[\alpha]_D^{25} = -21.4$ (c = 0.495, CH_2Cl_2); IR (KBr), ν: 3424, 3229, 3027, 2954, 2870, 1598, 1494, 1456, 1391, 1313, 1197, 1153, 1086, 1037, 1010, 957, 925, 811, 749, 701, 663 cm^{-1}; ^1H NMR:

δ 7.45–7.15 (m, 14H), 4.13 (s, br, 1H), 3.22–3.15 (m, 1H), 2.88–2.58 (m, 5H), 2.38 (s, 3H), 1.43–1.20 (m, 3H), 0.81 (d, $J = 6.6$ Hz, 3H), 0.22 (d, $J = 5.1$ Hz, 3H). Anal. calcd. for $C_{27}H_{33}NO_3S$: C, 71.81%; H, 7.37%; N, 3.10%. Found: C, 71.89%; H, 7.41%; N, 3.02%.

(S)-2-(*p*-Toluenesulfonylamino)-4-methylthio-1,l-diphenyl-1-butanol (4e)

Compound **4e** was prepared using a procedure similar to that of **4a**. Yield: 37.8%; mp 128–132°C; $[\alpha]_D^{25} = +38.8$(c = 0.520, CH_2Cl_2); IR (KBr), ν: 3465, 3279, 3058, 3028, 2974, 2918, 2857, 1597, 1495, 1434, 1292, 1151, 1077, 1027, 986, 868, 815, 746, 700 cm^{-1}; ^1H NMR: δ 7.51–7.11 (m, 14H), 5.00 (s, br, 1H), 4.62–4.56 (m, 1H), 3.05 (s, br, 1H), 2.39 (s, 3H), 1.83 (s, 3H), 1.68–1.57 (m, 2H), 1.37–1.32(m, 2H). Anal. calcd. for $C_{24}H_{27}NO_3S_2$: C, 65.28%; H, 6.16%; N, 3.17%. Found: C, 65.17%; H,6.08%; N, 3.23%.

(S)-2-(*p*-Toluenesulfonylamino)-4-methylthio-1,l-dibenzyl-1-butanol (4f)

Compound **4f** was prepared using a procedure similar to that of **4a**. Yield: 71.1%; mp 124–126°C; $[\alpha]_D^{25} = -20.2$ (c = 0.516, CH_2Cl_2); IR (KBr), ν: 3433, 3208, 3028, 2923, 1599, 1493, 1436, 1391, 1315, 1155, 1074, 978, 813, 753, 703, 662 cm^{-1}; ^1H NMR: δ 7.38–7.14 (m, 14H), 4.23 (d, $J = 9$ Hz, 1H), 3.12–3.06 (t, $J = 9$ Hz, 1H), 2.86–2.68 (m, 4H), 2.44 (s, 1H), 2.38 (s, 3H), 2.15–2.08 (m, 1H), 1.99 (s, 3H), 1.92–1.83 (m, 2H), 1.72–1.61 (m, 1H). Anal. calcd. for $C_{26}H_{31}NO_3S_2$: C, 66.49%; H, 6.65%; N, 2.98%. Found: C, 66.57%; H, 6.73%; N, 2.91%.

N-(1S)-(1-Benzyl-2-hydroxy-2,2-diphenyl-ethyl)-*C*-[(1S)-7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl]-methanesulfonamide (4g)

A solution of (1S)-(+)-10-camphorsulfonyl chloride (1.25 g, 5.0 mmol) in CH_2Cl_2 (10 mL) was added to a stirred solution of triethylamine (2.1 mL, 15 mmol) and (S)-2-amino-1,1,3-triphenylpropanol (1.52 g, 5.0 mmol) in CH_2Cl_2 (20 mL) at 0°C over a 1-h period. The reaction mixture was allowed to warm to room temperature and stirred for an additional 24 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 2 N HCl (2 × 5 mL), saturated aqueous $NaHCO_3$ (3 × 10 mL), and brine (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and recrystallized from ethanol to afford the sulfonamide. Yield: 58%; mp 173–174°C; $[\alpha]_D^{25} = +50$ (c = 2.0, CH_2Cl_2);

IR (KBr), ν: 3333, 3273, 2951, 1739, 1490, 1443, 1320, 1142, 1063, 969, 747, 697 cm^{-1}; ^1H NMR: δ 7.67–7.13 (m, 15H), 5.23 (d, $J = 9.3$ Hz, 1H), 5.00 (m, 1H), 3.22 (br, 1H), 2.99 (d, $J = 14.1$ Hz, 1H), 2.79 (dd, $J = 8.7$, 14.1 Hz, 1 H), 2.28 –1.61 (m, 8H), 1.35–1.28 (m, 1H), 0.79 (s, 3H), 0.49 (s, 3H). Anal. calcd. for $C_{31}H_{35}NO_4S$: C, 71.92%; H, 6.82%; N, 2.71%. Found: C, 71.77%; H, 6.89%; N, 2.82%.

N-(1S)-(1,2,2-Tribenzyl-2-hydroxy-ethyl)-*C*-[(1S)-7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl]-methanesulfonamide (4h)

Compound **4h** was prepared using a procedure similar to that of **4g**. Yield: 66.1%; mp 136–138°C; $[\alpha]_D^{25} = +16.2$(c = 1.1, $CHCl_3$); IR (KBr), ν: 3504, 3261, 3061, 3026, 2957, 1744, 1604, 1494, 1454, 1372, 1310, 1143, 1049, 964, 754, 703 cm^{-1}; ^1H NMR: δ 7.43–6.96 (m, 15H), 4.61 (d, $J = 9.6$ Hz, 1H), 3.62 (m, 1H), 3.48 (dd, $J = 7.2$, 14.4 Hz, 4H), 3.28 (d, 1H), 3.04 (d, $J = 13.8$ Hz, 2H), 2.87 (dd, $J = 7.2$, 14.4 Hz, 2H), 2.58 (dd, $J = 1.8$, 11.4 Hz, 2H), 2.27(d, 1H), 2.06–1.79 (m, 2H), 1.46–1.40 (m, 1H), 1.22–1.19 (m, 1H), 0.84 (s, 3H), 0.64 (s, 3H). Anal. calcd. for $C_{33}H_{39}NO_4S$: C, 72.63%; H, 7.20%; N, 2.57%. Found: C, 72.54%; H, 7.15%; N, 2.61%.

N-(1S)-[1-(2-Methyl)propyl-2-hydroxy-2,2-diphenyl-ethyl]-*C*-[(1S)-7,7-dimethyl-2-oxo-bicycle[2.2.1]hept-1-yl]-methanesulfonamide (4i)

Compound **4i** was prepared using a procedure similar to that of **4g**. Yield: 69.01%; mp 202–204°C; $[\alpha]_D^{25} = +9.30$ (c = 0.978, $CHCl_3$); IR (KBr), ν: 3447, 3373, 2957, 1723, 1449, 1326, 1143, 1071, 1020, 990, 804, 748, 701 cm^{-1}; ^1H NMR: δ 7.60 (d, $J = 8.1$ Hz, 2H), 7.44 (d, $J = 7.5$ Hz, 2H), 7.26–7.06 (m, 6H), 5.05 (d, $J = 9$ Hz, 1H), 4.84–4.77 (m, 1H), 3.19 (s, 1H), 2.25–1.76 (m, 6H), 1.53 (s, 2H), 1.43–1.06 (m, 4H), 0.98 (d, $J = 5.7$ Hz, 3H), 0.79 (d, $J = 6.6$ Hz, 3H), 0.75 (s, 3H), 0.45 (s, 3H). Anal. calcd. for $C_{28}H_{37}NO_4S$: C, 69.52%; H, 7.72%; N, 2.90%. Found: C, 69.59%; H, 7.75%; N, 2.83%.

N-(1S)-[1-(2-Methyl)propyl-2-hydroxy-2,2-dibenzyl-ethyl]-*C*-[(1S)-7,7-dimethyl-2-oxo-bicycle[2.2.1]hept-1-yl]-methanesulfonamide (4j)

Compound **4j** was prepared using a procedure similar to that of as **4g**. Yield: 52.18%; mp 149–151°C; $[\alpha]_D^{25} = +51.82$ (c = 0.961 $CHCl_3$); IR (KBr), ν: 3452, 3353, 3269, 2952, 1732, 1602, 1494, 1452, 1322, 1278, 1136, 1050, 1004, 964, 933, 820, 754, 702 cm^{-1}; ^1H NMR: δ 7.34–7.21 (m, 10H), 5.24 (d, $J = 9$ Hz, 1H), 3.77 (d, $J = 15.3$ Hz, 1H), 3.63–3.56 (dd, $J = 8.7$ Hz, 14.1 Hz,1H), 3.01–2.94 (m, 2H), 2.84–2.68 (m, 3H), 2.57

(s, 1H), 2.44–2.38 (m, 1H), 2.19–1.81 (m, 6H), 1.59 (s, 1H), 1.49–1.39 (m, 2H), 0.99 (s, 3H), 0.98 (d, $J = 6$ Hz, 3H), 0.92 (s, 3H), 0.74 (d, $J = 6.3$ Hz, 3H). Anal. calcd. for $C_{30}H_{41}NO_4S$: C, 70.40%; H, 8.08%; N, 2.75%. Found: C, 70.29%; H, 8.01%; N, 2.79%.

N-(1S)-[1-(2-Methylthio)ethyl-2-hydroxy-2,2-diphenyl-ethyl]-*C*-[(1S)-7,7-dimethyl-2-oxo-bicycle[2.2.1]hept-1-yl]-methanesulfonamide (4k)

Compound **4k** was prepared using a procedure similar to that of **4g**. Yield: 66.5%; mp 153–155°C; IR (KBr), ν: 3477, 3272, 3060, 2961, 1789, 1493, 1447, 1317, 1145, 1058, 987, 860, 753, 702 cm^{-1}; ^1H NMR: δ 7.66 (d, $J = 8.1$ Hz, 2H), 7.55 (d, $J = 8.1$ Hz, 2H), 7.34–7.14 (m, 6H), 5.48–5.39 (m, 1H), 4.97–4.92 (m, 1H), 3.46–3.32 (m, 1H), 2.79–2.64 (m, 2H), 2.43–2.08 (m, 4H), 2.00 (s, 3H), 1.92–1.68 (m, 4H), 1.59 (s, 2H),1.40–1.31 (m, 1H), 0.83 (s, 3H), 0.53 (s, 3H). Anal. calcd. for $C_{27}H_{35}NO_4S_2$: C, 64.64%; H, 7.03%; N, 2.79%. Found: C, 64.51%; H, 7.07%; N, 2.84%.

N-(1S)-[1-(2-Methylthio)ethyl-2-hydroxy-2,2-dibenzyl-ethyl]-*C*-[(1S)-7,7-dimethyl-2-oxo-bicycle[2.2.1]hept-1-yl]-methanesulfonamide (4l)

Compound **4l** was prepared using procedure similar to that of **4g**. After the usual workup, the residue was recrystallized with ethyl acetate and petroleum ether and gave **4l** as a colorless crystal. Yield: 63.01%; mp 130–131°C; $[\alpha]_D^{25} = +12.81$ (c = 0.960, $CHCl_3$); IR (KBr), ν: 3464, 3349, 3270, 3062, 3029, 2952, 1729, 1603, 1494, 1445, 1395, 1322, 1281, 1245, 1138, 1078, 1048, 971, 909, 851, 815, 758, 703 cm^{-1}; ^1H NMR: δ 7.35–7.17 (m, 10H), 5.48 (d, $J = 9.3$ Hz, 1H), 3.73 (d, $J = 15.3$ Hz, 1H), 3.46 (t, $J = 9.6$ Hz, 1H), 2.99–2.87 (m, 2H), 2.80–2.73 (m, 3H), 2.52 (s, 1H), 2.47–2.39 (m, 2H), 2.15 (s, 3H), 2.12–1.91 (m, 5H), 1.76–1.70 (m, 1H), 1.59 (s, 2H), 1.47–1.40 (m, 1H), 0.95 (s, 3H), 0.90 (s, 3H). Anal. calcd. for $C_{29}H_{39}NO_4S_2$: C, 65.75%; H, 7.42%; N, 2.64%. Found: C, 65.66%; H, 7.34%; N, 2.73%.

N-(1S)-(1-Benzyl-2-hydroxy-2,2-diphenyl-ethyl)-*C*-[(1S,2R)-7,7-dimethyl-2-hydroxyl-bicyclo[2.2.1]hept-1-yl]-methanesulfonamide (5a)

Compound **4g** (3 mmol) was dissolved in a 1:1 mixture of ethanol and THF (30 mL), and $NaBH_4$ (0.78 g, 21 mmol) was added portionwise over 5 min at −15°C. The reaction mixture was stirred for 10 h at −15°C, and then quenched carefully with saturated NH_4Cl (20 mL). After the organic solvent was removed in vacuo, the residue was extracted with $CHCl_3$ (3 × 20 mL).

The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and recrystallized from ethyl acetate to afford the sulfonamide. Yield: 84.7%; mp 94–96°C; $[\alpha]_D^{25} = +45$ (c = 1.0, CH_2Cl_2); IR (KBr), ν: 3471, 3399, 2930, 1494, 1448, 1295, 1135, 1061, 1030, 977, 743, 700 cm^{-1}; ^1H NMR: δ 7.61–7.14 (m, 15H), 4.76 (br, 1H), 4.62 (br, 1H), 3.88 (dd, $J = 4.2$, 8.4 Hz, 1H), 3.72 (dd, $J = 7.2$, 14.4 Hz, 1H), 3.15 (dd, $J = 3$, 14.4 Hz, 1H), 2.81 (dd, $J = 8.4$, 14.4 Hz, 1H), 2.35 (d, $J = 14.4$ Hz, 1H), 1.83–1.46 (m, 4H), 1.45–1.31 (m, 2H), 1.25–1.19 (m, 2H), 1.01–0.97 (m, 1H), 0.79 (s, 3H), 0.54 (s, 3H). Anal. calcd. for $C_{31}H_{37}NO_4S$: C, 71.65%; H, 7.18%; N, 2.70%. Found: C, 71.77%; H, 7.23%; N, 2.65%.

N-(1S)-(1,2,2-Tribenzyl-2-hydroxy-ethyl)-*C*-[(1S,2R)-7,7-dimethyl-2-hydroxyl-bicyclo[2.2.1]hept-1-yl]-methanesulfonamide (5b)

Compound **5b** was prepared from **4h** using a procedure similar to that of **5a**. After the usual workup, the residue was recrystallized with methanol and gave **5b** as a colorless crystal. Yield: 69.2%; mp 214–216°C; $[\alpha]_D^{25} = -32.5$ (c = 1.1, $CHCl_3$); IR (KBr), ν: 3497, 3263, 3063, 3025, 2947, 1493, 1452, 1360, 1305, 1132, 1073, 1048, 960, 753, 701 cm^{-1}; ^1H NMR: δ 7.49–6.94 (m, 15H), 3.88 (m, 1H), 3.72 (dd, J= 4.2, 7.8 Hz, 1H), 3.26 (dd, $J = 3$, 7.8 Hz, 1H), 3.32 (br, 1H), 3.11(d, $J = 14.4$ Hz, 1H), 2.97–2.89 (m, 3H), 2.62 (m, 1H), 1.92 (d, $J = 14.4$ Hz, 2H), 1.60–1.53 (m, 6H), 1.38–1.32 (m, 1H), 1.21–1.17 (m, 1H), 0.99–0.93 (m, 1H), 0.64 (s, 3H), 0.43 (s, 3H). Anal. calcd. for $C_{33}H_{41}NO_4S$: C, 72.36%; H, 7.55%; N, 2.56%. Found: C, 72.45%; H, 7.61%; N, 2.48%.

General Procedure for the Catalytic Reduction of Prochiral Ketones

The following procedure for the asymmetric reduction of acetophenone is representative. Under a nitrogen atmosphere, freshly distilled $BF_3 \cdot Et_2O$ (0.4 mL, 3.2 mmol) in THF (5 mL) was added dropwise to a suspension of $NaBH_4$ (91 mg, 2.4 mmol) in dry THF (10 mL) at 0°C. After the mixture was stirred at 0°C for 0.5 h and allowed to warm to refluxing temperature, a solution of **4a** (0.2 mmol) in THF (5 mL) was added dropwise. After refluxing for 1.5 h, a solution of acetophenone (240 mg, 2 mmol) in THF (4 mL) was added dropwise over 3 h at the same temperature. After refluxing for another hour, the reaction mixture was cooled to 0°C and quenched with 5 mL of saturated ammonium chloride solution. Ethyl acetate (3 × 10 mL) was added to extract the product, and the organic layer was separated. The combined organic layers were washed with brine, and dried with sodium sulfate. After removal of the solvent by distillation, chromatography of the residue afforded the chiral alcohol.

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