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Enantioselective addition of diethylzinc to aldehydes using 2-azanorbornylmethanols and 2-azanorbornylmethanethiol as a catalyst

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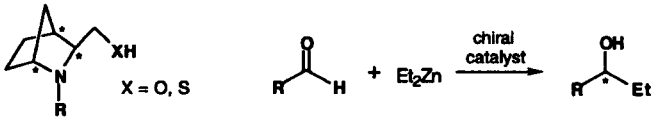
Abstract: Optically active 2-azanorbornylmethanols and 2-azanorbornylmethanethiol were prepared from ethyl (1*S*,3*S*,4*R*)-2-[(*R*)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate and catalyzed the enantioselective addition of diethylzinc to aldehydes to give optically active secondary alcohols. © 1997 Elsevier Science Ltd

Introduction

Catalytic asymmetric synthesis has been a challenging subject in organic synthesis. The development of efficient enantioselective catalysts applicable to a wide range of carbon–carbon bond forming reactions represents a pivotal challenge to the synthetic community. Among the catalysts, β-amino alcohols have proved to be extremely efficient catalysts in catalytic reactions.[1,2] Most recently, ephedrine- and pyrrolidine-based β-amino thiols also have been shown to be effective ligands similar to β-amino alcohols for the enantioselective alkylation.[3a–i] However, to the best of our knowledge, there are very few reports for the use of bicyclic β-amino thiols as a catalyst. 2-Azanorbornenes, 2-azabicyclo[2.2.1]heptenes, have great potential as synthetic intermediates for the syntheses of biologically active compounds.[4] We wish to report the synthesis of a series of new chiral ligands, 2-azanorbornylmethanols[5] **3–5**, **6a–f**, 2-azanorbornylmethanethiol **8**, and their use as chiral catalysts in the asymmetric addition to aldehydes. The asymmetric addition of diethylzinc to aldehydes in the presence of catalytic amounts of chiral ligands is a convenient method for the preparation of enantiomerically pure secondary alcohols. 2-Azanorbornylmethanols **3–5**, **6a–f** or 2-azanorbornylmethanethiol **8** are sterically constrained β-amino alcohols or β-amino thiols, and their bicyclo[2.2.1] ring system in the chiral ligands may block the approach of the attacking species to one of the enantiotopic faces of aldehydes.



Chiral Ligand

Synthesis of chiral ligands, 2-azanorbornylmethanols and 2-azanorbornylmethanethiol

Preparations of the chiral ligands, **3–5**, **6a–f** are described in Scheme 1. The chiral ligand **3** having a hydroxymethyl substituent in the side chain was obtained from catalytic hydrogenation of bicyclic amino acid ethylester **1**[6] followed by reduction with lithium aluminum hydride in 67% yield. Furthermore, the chiral ligand **4** bearing a diphenylmethanol moiety in the side chain was synthesized by the reaction of **2** with phenylmagnesium bromide in 80% yield. The chiral *N*-unsubstituted ligand

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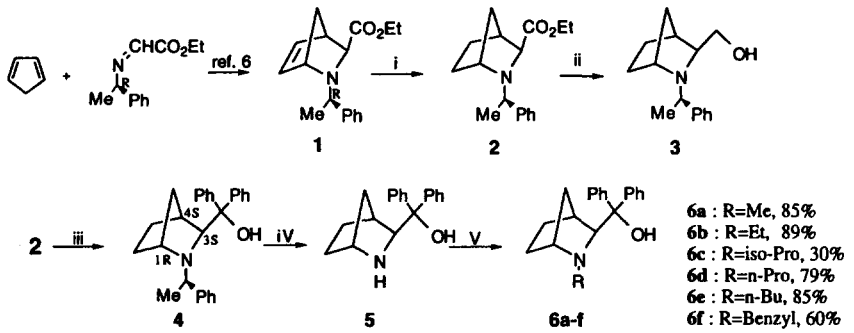
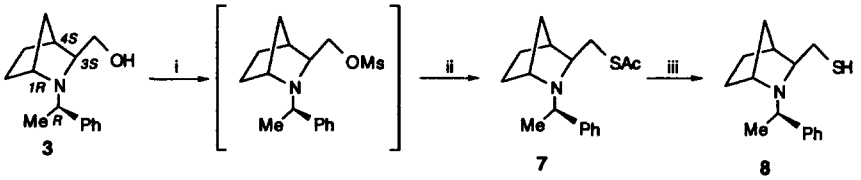
5 was obtained from **4** by hydrogenolysis with palladium hydroxide in a quantitative yield, and the reactions of **5** with various alkyl halides gave the corresponding chiral *N*-alkylated ligands **6a–f** in good yields (30–89%).



Reagents. i: H_2, Pd-C(10%), CH_3CO_2Et, rt, 24h, 96%; ii: $LiAlH_4$, THF, 15h, rt, 70%; iii: PhMgBr, THF, rt, 24h, 80%; iv: H_2, 20%$Pd(OH)_2$, CH_3CO_2Et, 45°C, 98%; v: RX, CH_3CN, reflux or CH_2Cl_2, rt, 12h

Scheme 1.

Next, the chiral ligand **8** of β-amino thiol type was also synthesized easily from the corresponding β-amino alcohol **3** (Scheme 2). The β-amino alcohol **3** was treated with methanesulfonylchloride (MsCl) and triethylamine to give the corresponding mesylate (not isolated), and subsequent displacement with potassium thioacetate gave the corresponding thioacetate **7**[7] in 86% yield from **3**. Finally, treatment of **7** with lithium aluminum hydride afforded the chiral ligand **8** in 86% yield. These structures of **2–5**, **6a–f**, **7**, **8** were characterized by IR, ^1H and ^{13}C NMR spectroscopy, high-resolution mass spectrometry (HRMS) and elemental analysis.



Reagents. i: MsCl, Et_3N,CH_2Cl_2, 0°C, 5h; ii: KSAc, EtOH, reflux, 15h, 86% from 3; iii: $LiAlH_4$, THF, rt, 12h, 86%

Scheme 2.

The absolute configuration within the chiral ligand (1*R*,3*S*,4*S*)-**4** was determined by single crystal X-ray analysis (Figure 1). Considering this result, the absolute configurations of the other chiral ligands **3**, **5**, **6a–f**, **8** also were assigned as 1*R*,3*S*, and 4*S*, respectively. The chiral ligand **4** showed usual bond lengths and angles. The phenyl substituents, A and B, in **4** were almost diagonal with the dihedral angle of 99.0°, and B and C were almost parallel with the dihedral angle of 9.0°. One interesting feature to be noted was the formation of intramolecular hydrogen bonding between hydroxyl group (O1–H) and nitrogen atom (N1) (the distance=1.769 Å, the angle=130.4°).

Enantioselective addition of diethylzinc to aldehydes catalyzed by optically active 2-azanorbornylmethanols and 2-azanorbornylmethanethiol

In order to examine the catalytic ability of the ligands, the enantioselective addition of diethylzinc to benzaldehyde was examined at 0°C in the presence of a catalytic amount (5 mol%) of various 2-azanorbornylmethanols **3–5**, **6a–f**. All catalysts gave optically active 1-phenyl-1-propanol **9** (entry 1–9, Table 1). The relation between the enantiomeric excess (ee) of the obtained alcohol and the catalysts are shown in Table 1. The *N*-phenylethylated ligand **3** possessing a primary alcohol moiety

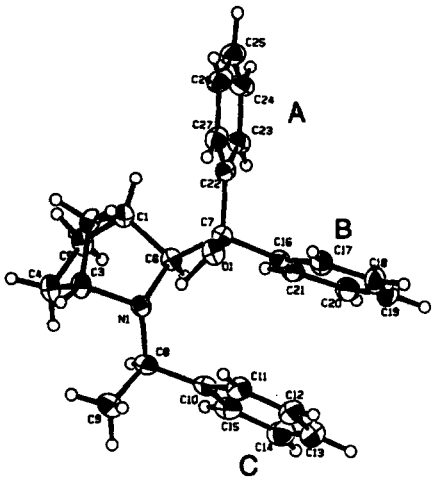


Figure 1. ORTEP drawing of compound **4**.

afforded (*R*)-**9** in low enantiomeric excess (22%ee) (entry 1). Although the most bulky ligand **4**, *N*-unsubstituted ligand **5** and *N*-alkylated ligands **6b–f** having a diphenylmethanol moiety, respectively, also were less effective (28–68%ee) (entry 2, 3, 5–9) as catalysts in this reaction similar to **3**, the *N*-methylated ligand **6a** having a diphenylmethanol moiety proved to be a better catalyst (65%, 78%ee) (entry 4) than the others. Next, the reaction of β-naphthylaldehyde with diethylzinc using the chiral ligands **4**, **6a–c** (entry 10–13) under the above reaction conditions was performed to give optically active 1-(2-naphthyl)-1-propanol, and the best result (81%, 92%ee) was obtained by using the *N*-methylated chiral ligand **6a** (entry 11) similar to the case of benzaldehyde (entry 4). Furthermore, the enantioselective addition of 2-ethoxybenzaldehyde with diethylzinc in the presence of the ligand **6a** gave also enantioselectively (*S*)-1-(2-ethoxyphenyl)-1-propanol in high chemical yield and enantiomeric excess (97%, 82%ee) (entry 14). However, the enantioselective ethylation of 4-methoxybenzaldehyde and cyclohexanecarboxaldehyde only proceeded with moderate selectivity, respectively (entry 15 and 16). From these results, the *N*-methylated chiral ligand **6a** was found to be superior to the chiral ligands **3**, **4**, **5**, **6b–f** in terms of enantioselectivity.

Next, the asymmetric catalytic capability of 2-azanorbornylmethanethiol **8** was also investigated in the same reaction described above. The sulfur atoms have high affinity toward zinc atoms as compared to oxygen atoms, and the metal thiolate complex formed is expected to block strongly a specific prochiral face of coordinated aldehydes. The reaction of benzaldehyde with diethylzinc was examined in the presence of a catalytic amount (5 mol%) of the chiral ligand **8**. As shown in Table 2, the best result (95%, 97%ee) was obtained from the reaction using β-amino thiol ligand **8** (entry 1) in contrast to the unsatisfactory results of the reaction using the corresponding β-amino alcohol ligand **3** (53%, 22%ee) and the others (28–78%ee). Under the same reaction conditions, several aromatic aldehydes were examined by using the best ligand **8**, and afforded the corresponding secondary alcohols in high chemical yields and enantiomeric excess (94–100%, 94–98%ee) (entry 2–4). Similarly, cyclohexanecarboxaldehyde was also ethylated in >99%ee (entry 7). Furthermore, 2-furylaldehyde afforded (*R*)-1-(2-furyl)-1-propanol in 74%ee (entry 6). However, (*E*)-cinnamaldehyde and *n*-octylaldehyde were ethylated only in 10%ee and 60%ee, respectively (entry 5 and 8).

Optically active phthalides are naturally occurring substances, many of which possess biologically activity.[8] Recently, (*R*)-1-(2-bromophenyl)-1-propanol **11** was synthesized in high enantiomeric excess (90%ee) from the addition of dialkylzinc to 2-bromobenzaldehyde **10** using *N*,*N*-dibutylnorephedrine [(1*R*,2*S*)-DBNE] as a chiral catalyst by Soai *et al.*[9] and was converted to (*R*)-3-ethylphthalide **12** in 90%ee. We applied the new chiral ligand **8** as a catalyst for the reaction to **10**. The reaction of **10** with

Table 1. Enantioselective addition of diethylzinc to aldehydes using **3–5**, and **6a–f** as a catalyst[a]

entry	aldehyde	catalyst	yield, %[b]	$[\alpha]_D$, deg (c, solvent)	ee, %	config
1	benzaldehyde	**3**	53	+11.6 (1.9, $CHCl_3$)[c]	22[d]	*R*
2	benzaldehyde	**4**	29	-20.9 (1.0, $CHCl_3$)	28	*S*
3	benzaldehyde	**5**	42	+17.3 (1.1, $CHCl_3$)	36	*R*
4	benzaldehyde	**6a**	65	-36.5 (3.1, $CHCl_3$)	78	*S*
5	benzaldehyde	**6b**	95	-22.0 (1.3, $CHCl_3$)	54	*S*
6	benzaldehyde	**6c**	86	-29.6 (2.1, $CHCl_3$)	68	*S*
7	benzaldehyde	**6d**	88	-18.3 (2.1, $CHCl_3$)	43	*S*
8	benzaldehyde	**6e**	92	-20.5 (1.8, $CHCl_3$)	51	*S*
9	benzaldehyde	**6f**	46	-17.7 (1.0, $CHCl_3$)	49	*S*
10	2-naphthylaldehyde	**4**	57	-22.0 (0.5, $CHCl_3$)[e]	72[d]	*S*
11	2-naphthylaldehyde	**6a**	81	-22.3 (4.0, $CHCl_3$)	92	*S*
12	2-naphthylaldehyde	**6b**	95	-15.0 (0.8, $CHCl_3$)	67	*S*
13	2-naphthylaldehyde	**6c**	75	-18.9 (3.6, $CHCl_3$)	75	*S*
14	2-ethoxybenzaldehyde	**6a**	97	-41.4 (2.8, $C_6H_5CH_3$)[f]	82[g]	*S*
15	4-methoxybenzaldehyde	**6a**	80	-27.5 (1.2, C_6H_6)[h]	73[g]	*S*
16	cyclohexanecarboxaldehyde	**6a**	20	-6.0 (1.0, $CHCl_3$)[i]	71[j]	*S*

[a] The reaction was carried out in hexane-toluene (1:1) with 5mol% of catalysts **3-5,6a-f** 2.0equiv of diethylzinc to aldehydes. [b] Isolatedyield. [c] $[\alpha]^{25}_D$+45.5 (c5.15, $CHCl_3$) for (*R*)-1-phenylpropanol in 100%ee: see ref 2e. [d] Determined by HPLC analysis using Chiralcel OD. [e] $[\alpha]^{22}_D$-26.6 (c3.35, C_6H_6) for (*S*)-1-(2-naphthyl)propanol in 97%ee: see ref 2f. [f] $[\alpha]^{27}_D$+46.3 (c1.20, $C_6H_5CH_3$) for (*R*)-1-(2-ethoxyphenyl)propanol in 97%ee: see ref 2a. [g] Determined by HPLC analysis using Chiralcel OB. [h] $[\alpha]^{24}_D$-34.6 (c5.00, $CHCl_3$) for (*S*)-1-(2-methoxyphenyl)propanol in 90%ee: see ref 2e. [i] $[\alpha]^{24}_D$+8.1 (c2.00, $CHCl_3$) for (*R*)-1-cyclohexylpropanol in 100%ee: see ref 2m. *d* Determined by ^{13}C-NMR analysis of the corresponding (*R*)-MTPA ester.

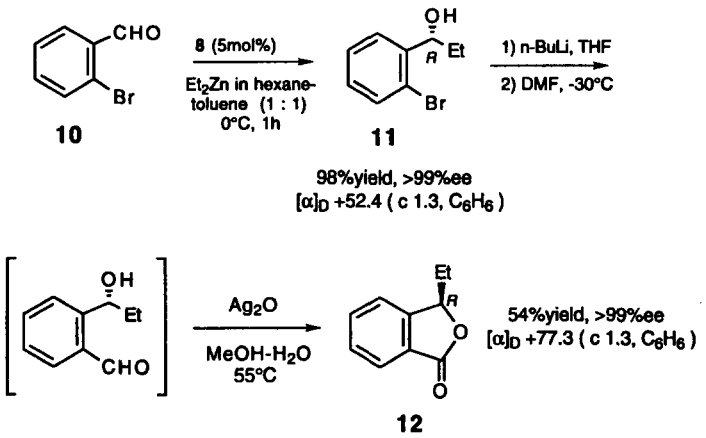
diethylzinc was carried out at 0°C in the presence of a catalytic amount (5 mol%) of the chiral ligand **8**, and (*R*)-**11** of >99%ee was obtained in 98% yield. The chiral alcohol (*R*)-**11** obtained was converted to (*R*)-3-ethylphthalide **12** in 54% yield and >99%ee according to the method of the previous report (Scheme 3).[10]

To investigate the capability and selectivity of the ligands, we studied the reaction path of the addition of diethylzinc to benzaldehyde in the presence of chiral ligand **8**. We considered the reaction path as follows[1,11] (Scheme 4). At first, the ligand **8** reacts with diethylzinc and makes ethylzinc thioalkoxide **13**. Next, the compound **13** coordinates diethylzinc and benzaldehyde, and forms some mixed ligands. We regard the compound **13**, diethylzinc, and benzaldehyde as the initial state of this system. We optimized in vacuum the structures of diethylzinc, benzaldehyde, ethylzinc thioalkoxide, and the mixed ligands using the semi-empirical molecular orbital method, PM3.[12] After optimizing the mixed ligands, we calculated vibrational frequencies and performed an intrinsic reaction coordinate calculation. Then, we obtained the lowest energy transition state (TS), **14** or **15**, which generates *R*-

Table 2. Enantioselective addition of diethylzinc to aldehydes using **8** as a catalyst[a]

entry	aldehyde	yield, %[b]	$[\alpha]_D$, deg (c, solvent)	ee, %	config
1	benzaldehyde	95	+43.6 (1.1, $CHCl_3$)[c]	97[d]	*R*
2	2-naphthylaldehyde	95	+25.8 (1.2, C_6H_6)[e]	98[d]	*R*
3	2-ethoxybenzaldehyde	100	+45.0 (2.8, $C_6H_5CH_3$)[f]	97[g]	*R*
4	4-methoxybenzaldehyde	94	+36.0 (1.0, C_6H_6)[h]	94[g]	*R*
5	(E)-cinnamaldehyde	100	+ 4.5 (2.2, $CHCl_3$)[i]	10[d]	*R*
6	2-furylaldehyde	83	+12.0 (1.0, $CHCl_3$)[j]	74[k]	*R*
7	cyclohexanecarboxaldehyde	97	+ 7.1 (0.7, $CHCl_3$)[l]	>99[m]	*R*
8	octylaldehyde	87	-5.0 (0.8, EtOH)[n]	60[o]	*R*

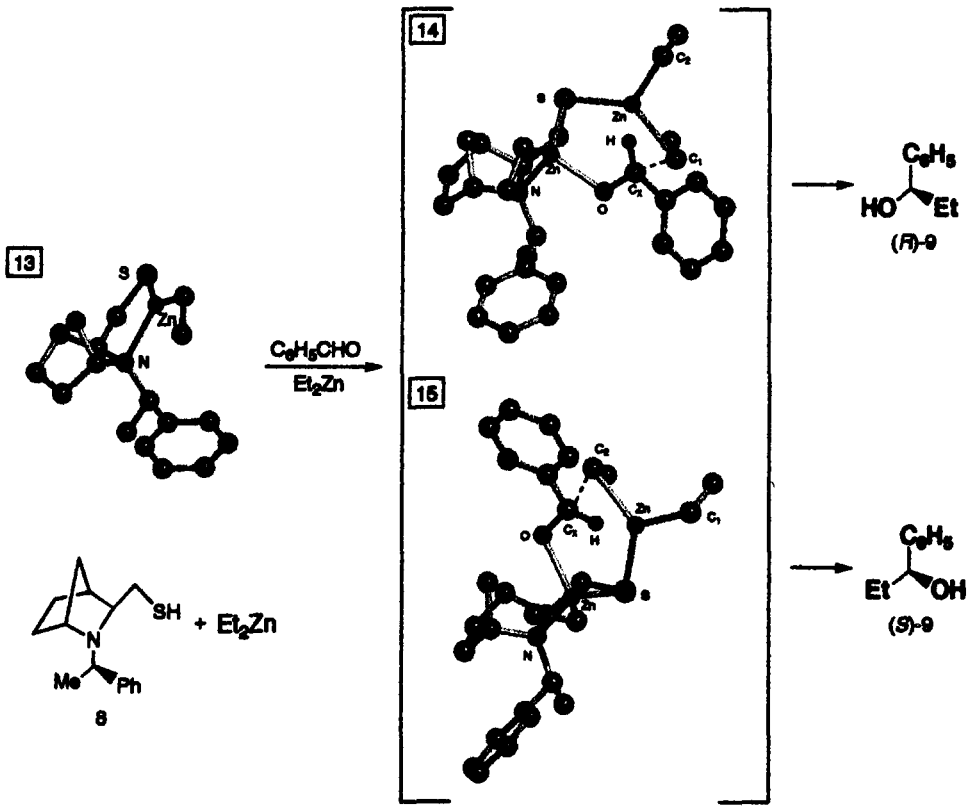
[a]See footnote a in Table 1. [b]Isolated yield. [c]See footnote c in Table 1. [d]Determined by HPLC analysis using Chiralcel OD. [e]See footnote e in Table 1. [f]See footnote f in Table 1. [g]Determined by HPLC analysis using Chiralcel OB. [h]See footnote h in Table 1. [i]$[\alpha]^{23}_D$ -6.6 (c3.20, $CHCl_3$) for (*S*)-1-Phenyl-1-penten-3-ol in 75%ee: see ref 2e. [j]$[\alpha]^{22}_D$ -17.9 (c1.75, $CHCl_3$) for (*R*)-1-(2-furyl)- propanol in 91%ee: see ref 2f. [k]Determined by HPLC analysis of the corresponding (S)-MTPA ester. [l]$[\alpha]^{24}_D$ +8.1 (c2.00, $CHCl_3$) for (*R*)-1-cyclohexyl- propanol in 100%ee: see ref 2m. [m]Determined by ^{13}C-NMR analysis of the corresponding (R)-MTPA ester. [n]$[\alpha]_D$ -6.3 (EtOH) for (*R*)-undecanol in 100%ee: see ref 2m. [o]Determined by specific rotation value.



Scheme 3.

or *S*-type alcohols, respectively. The bond to be formed between C_1 and C_X in **14** and that between C_2 and C_X in **15** are shown as dotted lines and those distances are obtained to be 2.07 and 2.08 Å, respectively. We regard the energy difference between TS and the initial state as the activation energy of the reaction. The activation energy of TS that is catalyzed by the ligand **8** having a thiol moiety and leads to *R*-type adduct, is about 14 kcal/mol. This value is small enough to explain the high rate of reaction[13] (short reaction time and high yield of alcohols). The energy difference between the transition states **14** and **15** is 3.6 kcal/mol, which is large enough to explain the experimental *R* to *S* ratio of 66 (Table 3).

In conclusion, we have succeeded in developing that 2-azanorbornylmethanethiol **8** exhibits high asymmetric inductions in zinc-catalyzed asymmetric addition of aldehydes. Moreover, the theoretical



Scheme 4.

Table 3. The calculated activation energy and the experimental yield of alcohols for the chiral ligand **8**

ligand (entry)	initial state[b] (kcal/mol)	TS[c] (kcal/mol) (*R*)	(*S*)	Ea[d] (kcal/mol) (*R*)	(*S*)	r.t[e] (hour)	yield (%)	*R* to *S* ratio (%ee)	config
8 (1)[a]	24.7	38.6	42.2	13.9	17.5	1	95	66 (97)	*R*

[a] See in Table 2. [b] Sum of the heat of formation of diethylzinc, benzaldehyde, and ethylzinc thioalkoxide. [c] Heat of formation of transition state. *R* (*S*) indicates TS which generates *R*-type (*S*-type) alcohols. [d] Activation energy. [e] Reaction time.

calculations also support the experimental results that the β-amino thiol **8** shows the catalytic capability and selectivity in this reaction.

Experimental

General

IR spectra were measured with a Perkin Elmer 1725X spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-GSX 270 spectrometers with TMS as an internal standard. MS were taken on a Hitachi RMG-6MG and a JEOL-JNM-DX 303 spectrometers. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter. Diethylzinc in hexane was obtained from Kanto Chemical Co. Reactions with diethylzinc were performed under an argon atmosphere by using Schlenk-type glassware. Thin layer chromatography was performed with Merk F-254 silica gel plates. Preparative thin layer chromatography was carried out on Merk PSC-Fertirplatten Kieselgel 60 F254 plates.

*Ethyl (1R,3S,4S)-2-[(R)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane-3-*exo*-carboxylate* **2**

A mixture of **1** (760 mg, 2.9 mmol) and 10% Pd–C (50 mg), in ethyl acetate (20 mL) was stirred under a hydrodgen atmosphere at room temperature for 24 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to afford the residue. The residue was chromatographed on a silica gel column eluted with ether–hexane (1:5) to give **2** (732 mg, 96%) as a colorless oil: $[\alpha]_D^{23}$=+2.1 (c 4.8, $CHCl_3$). IR (film) cm^{-1}: 1738, 1605; ^1H NMR ($CDCl_3$) δ: 7.34–7.16 (m, 5H), 3.76–3.66 (m, 2H), 3.50 (q, J=6.3 Hz, 2H), 2.55 (s, 1H), 2.27 (d, J=4.0 Hz, 1H), 2.15–1.94 (m, 2H), 1.67–1.59 (m, 1H), 1.45–1.25 (m, 5H), 1.34 (d, J=6.6 Hz, 3H), 0.91 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 173.73, 144.18, 128.07, 127.93, 127.02, 70.21, 61.17, 59.83, 57.91, 43.10, 35.90, 29.41, 22.72, 22.16, 13.93; HRMS calcd for $C_{17}H_{23}NO_2$ 273.17290, found 273.1700.

*(1R,3S,4S)-2-[(R)-1-Phenylethyl]-2-azabicyclo[2.2.1]heptane-3-*exo*-methanol* **3**

To a stirred suspension of lithium aluminum hydride (122 mg, 4.0 mmol) in dry tetrahydrofuran (THF) (5 mL) was added a solution of **2** (500 mg, 1.74 mmol) in dry THF (15 mL) at 0°C. The mixture was stirred at room temperature for 15 h, quenched by addition to water, and filterated through celite 545. The filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to afford the residue. The residue was chromatographed on a silica gel column eluted with ether to give **3** (434 mg, 70%) as a colorless oil: $[\alpha]_D^{23}$=+60.6 (c 1.6, $CHCl_3$). IR (film) cm^{-1}: 3625, 1605. ^1H NMR ($CDCl_3$) δ: 7.34–7.22 (m, 5H), 3.62 (s, 1H), 3.51 (q, J=6.6 Hz, 1H), 2.73 (dd, J=2.0, 10.6 Hz, 1H), 2.37–2.31 (m, 2H), 2.15 (d, J=3.9 Hz, 1H), 2.07–1.94 (m, 2H), 1.83 (d, J=10.0 Hz, 1H), 1.65–1.54 (m, 1H), 1.43–1.18 (m, 6H), 1.33 (d, J=6.6 Hz, 3H), 1.19 (d, J=10.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 145.86, 128.34, 127.73, 127.46, 69.18, 64.15, 60.86, 58.53, 42.17, 35.87, 29.49, 22.57, 22.32. HRMS calcd for $C_{15}H_{21}NO$, 231.16230, found 231.1675.

*(1R,3S,4S)-2-[(R)-1-Phenylethyl]-2-azabicyclo[2.2.1]heptane-3-*exo*-diphenylmethanol* **4**

Phenyl magnesium bromide (23 mL of a 2M solution in THF, 45 mmol) was added to a THF (30 mL) solution of **2** (1.5 g, 5.5 mmol) at 0°C, and the mixture was stirred at room temperature for 24 h. The mixture was cooled to 0°C, EtOAc added, and the mixture was quenched with saturated aqueous NH_4Cl (10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on a silica gel column eluted with ether to give **4** (1.7 g, 80%) as colorless prisms (ether), mp 143–144°C. $[\alpha]_D^{23}$=−22.6 (c 0.9, $CHCl_3$). IR (KBr) cm^{-1}: 3631, 1665, 1596. ^1H NMR ($CDCl_3$) δ: 7.66–7.54 (m, 4H), 7.28–7.03 (m, 11H), 5.64 (s, 1H), 3.64 (s, 1H), 3.45 (q, J=7.1 Hz, 1H), 3.29 (s, 1H), 2.05–1.95 (m, 2H), 1.78 (d, J=9.2 Hz, 1H), 1.56 (s, 1H), 1.56–1.29 (m, 2H), 1.30 (d, J=6.9 Hz, 3H), 0.85 (bd, J=9.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 149.27, 146.88, 143.23, 128.12, 127.96, 127.76, 126.88, 125.98, 125.86, 127.37, 75.90, 70.94, 57.43, 56.69, 41.19, 36.28, 29.20, 28.68, 15.96. Anal. Calcd for $C_{27}H_{29}NO$: C, 84.55; H, 7.62; N, 3.65. Found: C, 84.63; H, 7.57; N, 3.49.

*(1R,3S,4S)-2-Azabicyclo[2.2.1]heptane-3-*exo*-diphenylmethanol* **5**

A mixture of **4** (1.0 g, 2.61 mmol) and 20% $Pd(OH)_2$ (50 mg) in ethyl acetate (25 mL) was stirred under a hydrodgen atmosphere at 45°C for 48 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give the residue, which was chromatographed on a silica gel column eluted with MeOH to afford **5** (714 mg, 98%) as colorless prisms (ether), mp 133–134°C. $[\alpha]_D^{23}$=−78.9 (c 0.1, $CHCl_3$). IR (KBr) cm^{-1}: 3467, 1739, 1598. ^1H NMR ($CDCl_3$) δ: 7.54–7.45 (m, 4H), 7.38–7.12 (m, 6H), 3.74 (s, 1H), 3.44 (s, 1H), 2.15 (d, J=2.3 Hz, 1H), 1.90 (d, J=9.9 Hz, 1H), 1.72–1.36 (m, 4H), 1.00 (d, J=9.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 148.28, 145.41, 128.05, 127.94, 126.32, 126.27, 126.18, 125.86, 76.57, 66.57, 55.69, 38.81, 35.22, 32.70, 30.37. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.68; H, 7.77; N, 4.84.

General procedure for the synthesis of N-*alkylated (1R,3S,4S)-2-azabicyclo[2.2.1]heptane-3-diphenylmethanols* ***6a–e***

A mixture of **5** (200 mg, 0.72 mmol) and alkyl iodide (2 equiv., 1.2 mmol) in acetonitrile (15 mL) was refluxed for 12 h under Ar. The solvent was removed, and the residue was chromatographed on a silica gel column eluted with ether to give **6a–e**.

*(1R,3S,4S)-2-Methyl-2-azabicyclo[2.2.1]heptane-3-*exo-*diphenylmethanol* ***6a***

85% yield, colorless prisms (ether), mp 102–103°C. $[\alpha]_D^{23}$=+19.0 (c 0.1, $CHCl_3$). IR (KBr) cm^{-1}: 3334, 1598. ^1H NMR ($CDCl_3$) δ: 7.62 (dd, J=1.0, 8.0 Hz, 2H), 7.52 (dd, J=1.0, 8.0 Hz, 2H), 7.30–7.23 (m, 4H), 7.17–7.10 (m, 2H), 4.88 (s, 1H), 3.20 (s, 1H), 2.94 (s, 1H), 2.10 (s, 1H), 1.98–1.81 (m, 5H), 1.81 (s, 3H), 1.55–1.45 (m, 1H), 1.37–1.24 (m, 2H), 0.97 (d, J=9.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 148.55, 146.11, 127.98, 127.89, 126.13, 125.82, 125.64, 76.57, 76.46, 63.27, 41.09, 37.89, 36.19, 30.33, 21.79. Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.87; H, 7.84; N, 4.49.

*(1R,3S,4S)-2-Ethyl-2-azabicyclo[2.2.1]heptane-3-*exo-*diphenylmethanol* ***6b***

89% yield, colorless prisms (ether), mp 102–103°C. $[\alpha]_D^{23}$=−27.5 (c 0.4, $CHCl_3$). IR (KBr) cm^{-1}: 3294, 1595. ^1H NMR ($CDCl_3$) δ: 7.63 (dd, J=1.3, 7.3 Hz, 2H), 7.51 (dd, J=1.3, 7.3 Hz, 2H), 7.30–7.10 (m, 6H), 5.29 (s, 1H,), 3.46 (s, 1H), 3.02 (s, 1H), 2.33–2.23 (m, 1H), 2.07 (s, 1H), 1.94–1.72 (m, 3H), 1.56–1.44 (m, 1H), 1.34–1.21 (m, 2H), 0.99 (d, J=9.6 Hz, 1H), 0.76 (t, J=7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 148.86, 146.36, 127.92, 127.83, 126.11, 126.05, 125.82, 125.78, 75.90, 57.11, 43.52, 40.57, 35.56, 30.13, 21.65, 14.19. Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.11; H, 8.45; N, 4.46.

*(1R,3S,4S)-2-Isopropyl-2-azabicyclo[2.2.1]heptane-3-*exo-*diphenylmethanol* ***6c***

30% yield, colorless prisms (ether), mp 97–98°C. $[\alpha]_D^{23}$=−230.0 (c 0.1, $CHCl_3$). IR (KBr) cm^{-1}: 3411, 1598. ^1H NMR ($CDCl_3$) δ: 7.69–7.55 (m, 4H), 7.30–7.11 (m, 6H), 6.38 (s, 1H), 3.58 (s, 1H), 3.34 (s, 1H), 2.57–2.48 (m, 1H), 2.02 (s, 1H), 1.90–1.72 (m, 2H), 1.54–1.47 (m, 2H), 1.36–1.26 (m, 3H), 0.93 (d, 3H, J=6.7 Hz), 0.85 (d, J=9.9 Hz, 1H), 0.70 (d, 3H, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 150.17, 146.92, 128.28, 127.80, 127.64, 126.27, 125.99, 125.78, 75.43, 72.59, 57.89, 48.89, 41.33, 35.52, 28.55, 26.34, 22.80, 21.16. Anal. Calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 81.93; H, 8.66; N, 4.17.

*(1R,3S,4S)-2-*n-*Propyl-2-azabicyclo[2.2.1]heptane-3-*exo-*diphenylmethanol* ***6d***

79% yield, colorless prisms (ether), mp 93–94°C. $[\alpha]_D^{23}$=−25.6 (c 0.9, $CHCl_3$). IR (KBr) cm^{-1}: 1598 (aromatic). ^1H NMR ($CDCl_3$) δ: 7.61 (dd, J=1.7, 8.6 Hz, 2H), 7.52 (dd, J=1.7, 8.6 Hz, 2H), 7.31–7.10 (m, 6H), 5.27 (s, 1H), 3.40 (s, 1H), 3.01 (s, 1H), 2.34–2.25 (m, 1H), 2.10 (d, J=3.9, 1H), 1.96–1.79 (m, 2H), 1.63–1.43 (m, 2H), 1.36–1.12 (m, 4H), 0.99 (d, J=9.6 Hz, 1H), 0.62 (t, J=7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 148.75, 146.36, 127.92, 127.80, 126.11, 126.05, 125.91, 125.77, 75.88, 59.78, 57.47, 51.03, 40.50, 35.65, 30.15, 21.92, 21.82, 11.57. Anal. Calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 81.98; H, 8.54; N, 4.16.

*(1R,3S,4S)-2-*n-*Butyl-2-azabicyclo[2.2.1]heptane-3-*exo-*diphenylmethanol* ***6e***

85% yield, colorless prisms (ether), mp 97–98°C. $[\alpha]_D^{23}$=−27.5 (c 0.4, $CHCl_3$). IR (KBr) cm^{-1}: 1598 (aromatic). ^1H NMR ($CDCl_3$) δ: 7.62 (d, J=1.3, 8.2 Hz, 2H), 7.52 (d, J=1.3, 8.2 Hz, 2H), 7.30–7.09 (m, 10H), 5.26 (s, 1H), 3.41 (s, 1H), 3.01 (s, 1H), 2.32–2.23 (m, 1H), 2.08 (d, J=3.7, 1H), 1.95–1.79 (m, 2H), 1.74–1.63 (m, 1H), 1.56–1.42 (m, 2H), 1.35–0.96 (m, 6H), 0.66 (t, J=7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 148.77, 146.38, 127.92, 127.81, 126.11, 126.04, 125.90, 125.73, 75.96, 57.52,

48.95, 40.50, 35.63, 30.94, 30.17, 21.78, 20.13, 13.75. Anal. Calcd for $C_{23}H_{29}NO$: C, 82.34; H, 8.71; N, 4.18. Found: C, 82.22; H, 8.74; N, 4.15.

*(1R,3S,4S)-2-Benzyl-2-azabicyclo[2.2.1]heptane-3-*exo*-diphenylmethanol* ***6f***

To a solution of **5** (50 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.15 mL, 0.54 mmol) and benzylbromide (0.05 mL, 0.36 mmol) under Ar at 0°C and the reaction mixture was stirred at room temperature for 12 h. The solvent was removed, and the residue was chromatographed on a silica gel column eluted with ether to give **6f** (60%, 40 mg), colorless prisms (ether), mp 174–175°C. $[\alpha]_D^{23}$=+56.6 (c 0.6, $CHCl_3$). IR (KBr) cm^{-1}: 3299 (OH), 1597 (aromatic). ^1H NMR ($CDCl_3$) δ: 7.72 (dd, J=1.3, 8.6 Hz, 2H), 7.57 (dd, J=1.3, 8.6 Hz, 2H), 7.33–7.06 (m, 11H), 5.15 (s, 1H), 3.33–3.27, 2.96 (d, J=13.0, 2H), 3.22 (s, 1H), 3.09 (s, 1H), 2.19 (s, 1H), 2.06–1.90 (m, 2H), 1.61–1.19 (m, 3H), 0.94 (d, J=9.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 148.48, 146.23, 139.37, 128.77, 128.19, 128.08, 128.05, 126.84, 126.38, 126.20, 125.82, 125.70, 125.49, 75.09, 57.59, 53.44, 40.79, 35.62, 30.28, 21.73. Anal. Calcd for $C_{26}H_{27}NO$: C, 84.51; H, 7.37; N, 3.79. Found: C, 84.63; H, 7.36; N, 3.54.

*(1R,3S,4S)-3-*exo*-Acetylthiomethyl-2-[(R)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane* ***7***

To a solution of **3** (0.5 g, 2.16 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.3 mL, 4.33 mmol) and MsCl (0.3 mL, 3.25 mmol) at 0°C under Ar. The reaction mixture was stirred for 5 h at 0°C. The mixture was concentrated *in vacuo*. Ethanol (30 mL) and KSAc (742 mg, 6.49 mmol) were added to the crude product and the mixture was refluxed for 15 h under Ar. Solvent was removed under reduced pressure. The residue was dissolved in ether (20 mL) and the ether solution was washed with water (10 mL × 3). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue was chromatographed on a silica gel column eluted with ether to give **7** (540 mg, 86%) as colorless oil: $[\alpha]_D^{23}$=+110.0 (c 1.1, $CHCl_3$). IR (film) cm^{-1}: 1682, 1600. ^1H NMR ($CDCl_3$) δ: 7.31–7.19 (m, 5H), 3.55 (t, J=4.6 Hz, 1H), 3.48–3.45 (m, 1H), 3.36 (q, J=6.6 Hz, 1H), 2.61 (dd, J=4.3, 13.2 Hz), 2.46 (d, J=13.2 Hz, 1H), 2.33–2.25 (m, 4H), 2.25 (s, 3H, s), 1.93 (d, J=11.5 Hz, 1H), 1.82–1.69 (m, 2H), 1.51–1.27 (m, 6H), 1.28 (d, J=6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 196.00, 145.44, 128.25, 127.26, 126.70, 62.28, 56.24, 49.84, 45.25, 39.83, 36.53, 30.61, 29.34, 22.74, 21.34. HMRS calcd for $C_{17}H_{23}NOS$, 289.15010. Found: 289.1460.

*(1R,3S,4S)-2-[(R)-1-Phenylethyl]-2-azabicyclo[2.2.1]heptane-3-*exo*-methanethiol* ***8***

To a stirred suspension of lithium aluminum hydride (50 mg, 1.12 nmmol) in dry THF (10 mL) was added a solution of **7** (162 mg, 0.56 mmol) in dry THF (15 mL) at 0°C. The mixture was stirred at room temperature for 12 h, quenched by addition with water (1 mL), and filterated through celite 545. The filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to afford the residue. The residue was chromatographed on a silica gel column eluted with ether–hexane (1:5) to give **8** (110 mg, 86%) as colorless oil: $[\alpha]_D^{23}$=+50.0 (c 0.5, $CHCl_3$). IR (film) cm^{-1}: 1600. ^1H NMR ($CDCl_3$) δ: 7.33–7.15 (m, 5H), 3.54 (t, J=4.6, 5.0 Hz, 1H), 3.35 (q, J=6.6 Hz, 1H), 2.77 (bs, 1H), 2.54–2.44 (m, 2H), 2.31–2.22 (m, 2H), 1.99 (m, 1H), 1.95–1.67 (m, 2H), 1.42–1.22 (m, 6H), 1.30 (d, J=6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 145.46, 128.19, 127.19, 126.63, 62.14, 56.42, 52.07, 42.48, 40.46, 34.05, 29.59, 21.99, 21.33. HRMS calcd for $C_{15}H_{21}NS$, 247.13950. Found: 247.1389.

General procedure for the enantioselective addition of diethylzinc to aldehydes

To a solution of chiral ligands [**3**, **4**, **5**, **6a–f**, **8** (0.0175 mmol)] in toluene (0.7 mL), diethylzinc (0.7 mmol, 0.7 mL of 1 M solution in hexane) was added at room temperature. After the mixture had been stirred at room temperature for 30 min, aldehyde (0.35 mmol) was introduced. The homogeneous solution was stirred for 7 h at room temperature and quenched with 10% HCl. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was dried ($MgSO_4$) and then evaporated under reduced pressure. The residue was purified by preparative tlc over silica gel with $CHCl_3$ to afford the corresponding chiral alcohols, respectively. The products were identified by comparing the ^1H NMR and IR spectra with those of authentic samples, and the

optical rotation was measured. Enantiomeric excesses (%ee) were determined by HPLC analyses of the resulting secondary alcohols or the corresponding (*S*)-MTPA ester on a chiral column.

Enantioselective addition of diethylzinc to o-bromobenzaldehyde in the presence of chiral ligand 8

Ethylation was carried out in a manner similar to the above procedure. To a solution of chiral ligand **8** (3 mg, 0.05 mmol) in toluene (0.7 mL), diethylzinc (0.5 mmol, 0.5 mL of 1M solution in hexane) was added at 0°C. After the mixture had been stirred at room temperature for 20 min, 2-bromobenzaldehyde **10** (46 mg, 0.25 mmol) was introduced. The homogeneous solution was stirred for 1 h at 0°C and quenched with 10% HCl. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was dried ($MgSO_4$) and then evaporated under reduced pressure. The residue was purified by preparative tlc over silica gel with $CHCl_3$ to afford 1-(2-bromophenyl)-1-propanol **11** (52 mg, 98%) of >99%ee. The enantiomeric excess was determined by HPLC analysis using chiral column [Chiralcel OD, hexane–isopropanol (98:2), flow rate: 0.5 mL/1 min, Rt (min): 16 min for (*R*)-**11**, 19 min for (*S*)-**11**].

To a solution of (*R*)-**11** (51 mg, 0.23 mmol) in THF (5 mL), butyllithium (0.23 mmol, 0.14 mL of 1M solution in hexane) was added at −30°C. After 1 h, dry DMF (0.03 mL, 0.5 mmol) was added at −30°C, and the mixture had been stirred at −30°C for 5 h and quenched with 10% HCl. The resulting mixture was extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was converted to (*R*)-3-ethylphthalide **12** by oxidation using silver oxide according to the reported procedure. 54%, >99%ee, $[\alpha]_D^{23}$=+77.3 (c 1.3, $CHCl_3$) [lit.[10] $[\alpha]_D$=+76.9 (c 1.47, $CHCl_3$), 98%ee].

Absolute structure determination of (−)-4

$C_{27}H_{29}NO$, M=383.53. orthorhombic, a=15.406(2), b=22.827(4), c=5.977(2) Å, V=2102.0(7) Å (cell constants are determined by least-squares refinement on diffractometer angles, $50° < 2\theta < 66°$ for 25 automatically centered reflections, λ=1.5418 Å). Space group=$P2_12_12_1$ (No. 19), Z=4, DX=1.212 g/cm^3, μ(CuKα)=5.23 cm^{-1}, Colorless prism, Crystal size=0.25×0.25×0.3 mm, Rigaku AFC5PR diffractometer (45 kV, 200 mA), temperature=283 K, graphite monochromated Cu–Kα radiation, 2θ-ω scan mode, scan width=1.2+0.35 tanθ, 2θ scan speed=8°min^{-1}, a total of 1979 reflections in the range of $5° < 2\theta < 128°$ measured. Absorption correction employed using the empirical psi-scan method (max, min transition factors=1.0, 0.876). The structure was solved by the direct method and refined by full-matrix least-squares method employed with anisotropic thermal parameters for non-hydrogen atoms. All hydrogen atoms found in the difference Fourier syntheses and included without refinement. 1726 [Io>3σ(Io)] reflections used in the refinement of 272 parameters. The weighting scheme w=4Fo^2/σ2 (Fo^2) with σ(Fo) from counting statistics. Goodness-of-fit=2.13. Average shift/error=0.038. The Δρmax and Δρmin are 0.30 and −0.32 eÅ^{-3}. Refinement was converged to give the final R value of 0.041 (Rw=0.043). All calculations were performed by MICRO VAX II computer using Rigaku "TEXAN" Package Program System (1985). Atomic Scattering and Anomalous Dispersion Factors were applied from *"International Tables for x-ray Crystallography"*, Vol. IV, Kynoch Press, Birmingham (1974). Full details of crystal data, fractional atomic coordinates, bond lengths, bond angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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