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Enantioselective addition of diethylzinc to aldehydes in the presence of chiral hydrazone and imine ligands

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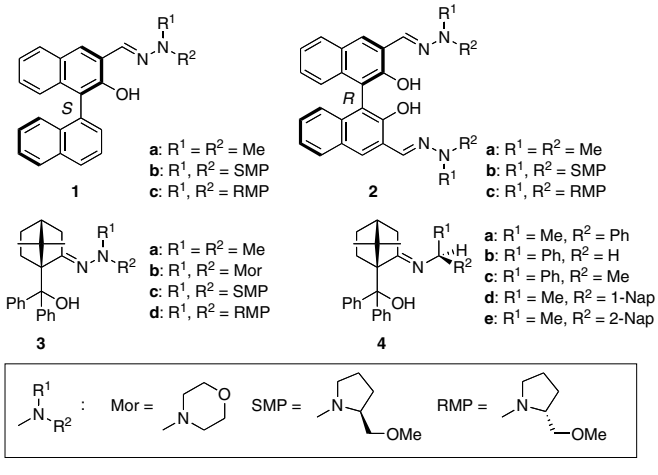
Abstract

Optically active hydrazone and imine were found to act as effective ligands for enantioselective addition of diethylzinc to aldehydes. This reaction provided optically active secondary alcohols with ee up to 71%.

Keywords: Hydrazone; Imine; Enantioselective addition; Diethylzinc; Secondary alcohol

1. Introduction

Enantioselective addition of organozinc reagent such as diethylzinc to aryl aldehyde in the presence of a catalytic amount of chiral ligand has emerged as an attractive method for the synthesis of optically active secondary alcohols [1]. The enantioselectivity of this process is mainly dependent on the chiral ligand, and therefore the search of new ligands for the asymmetric catalysis is a field of continuous interest. The catalysts used for the reaction have been based on chiral ligands such as diols [2], diamines [3], and amino alcohols [4]. We also reported chiral amino alcohol type ligands for enantioselective addition of diethylzinc to aryl aldehyde [5]. Imine type [6] ligands have been scarcely studied in this addition of diethylzinc to aldehyde. On the other hand, over the past few years, we have developed chiral hydrazones as ligands for palladium-catalyzed asymmetric allylic substitutions [7]. To the best of our knowledge, hydrazone has never been employed as chiral ligand in enantioselective addition of diethylzinc to aryl aldehyde. Thus, it should be of interest to explore the catalytic ability of hydrazone and imine ligands. Herein, we present new chiral hydrazone ligands **1**–**3** and imine ligands **4**, together with their catalytic applicability in the diethylzinc–aldehyde addition.



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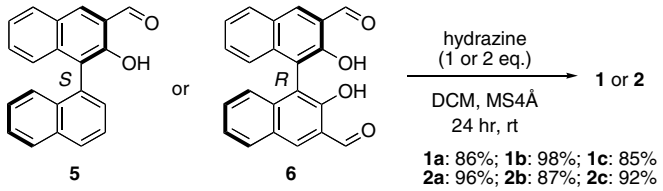
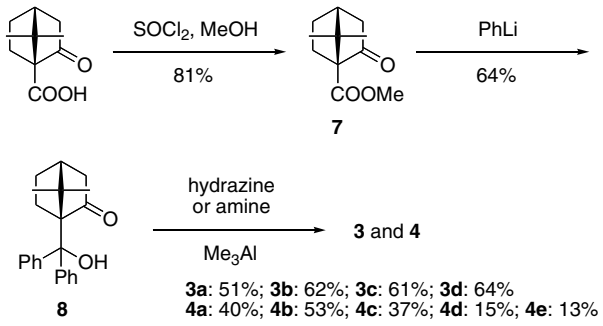
2. Results and discussion

Chiral hydrazones **1** and **2** were easily prepared from (*S*)-2-hydroxy-1,1′-binaphthalene-3-carboaldehyde (**5**) [8] or (*R*)-2,2′-dihydroxy-1,1′-binaphthalene-3,3′-dicarboaldehyde (**6**) [9] with various hydrazines such as *N*,*N*-dimethylhydrazine, (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP), or (*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP) in good yields (Scheme 1).

Chiral hydrazones **3** and imines **4** were also easily prepared from the ketopinic acid (Scheme 2). After esterification of ketopinic acid using methanol and thionyl chloride, treatment of ketopinic acid methyl ester (**7**) with 2.2 equivalent of phenyllithium afforded hydroxyl ketone **8** in good yield. Hydrazones **3** and imines **4** were obtained from the ketone **8** with chiral hydrazines or amines with trimethylaluminium. We successfully conducted X-ray crystallographic analysis of imine **4d**. The ORTEP drawing of **4d** is shown in Fig. 1.



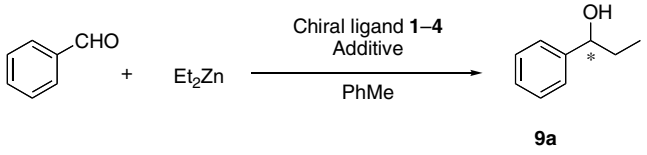
Scheme 1.



Scheme 2.

The chiral hydrazones **1**–**3** and imines **4** were applied to the chiral ligand for the enantioselective addition of diethylzinc to aldehydes.

Using 5 mol% of hydrazone **1a** as a ligand with diethylzinc in toluene (Scheme 3), the reaction proceeded smoothly at room temperature and the corresponding product (*S*)-**9a** was obtained from benzaldehyde in a good chemical yield with 23% ee (Entry 1, Table 1). In order to improve the enantioselectivity, we examined the effect of reaction temperature. The reaction at −35 °C slightly improved the enantioselectivity to 28% ee (Entry 2). When **1b** and diastereomer of **1b**, such as hydrazone **1c**, were used, the enantioselectivity of the products were not increased in comparison with **1a** (Entries 3 and 4). Using 5 mol% of bishydrazone type ligand **2a**, the product (*R*)-**9a** was obtained in a good chemical yield with 36% ee (Entry 6). Ligand **2b** was a very poor chiral ligand for this ethylation (Entry 7). We investigated the effect of diastereoisomer of **2b** in this reaction. The reaction proceeded smoothly using **2c** as a ligand, and the enantioselectivity of **9a** was increase to 60% ee (Entry 8). When the reaction



Scheme 3.

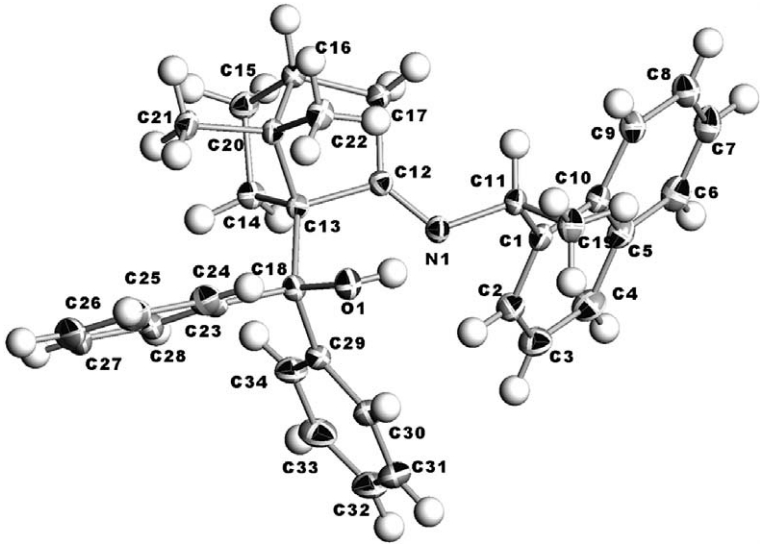


Fig. 1. ORTEP drawing of **4d**.

Table 1
Enantioselective addition of benzaldehyde using diethylzinc and ligands **1** and **2**

Entry	Ligand	Temperature/°C	Additive	Yield[a]/%	Ee[b]/%	Conf.
1	**1a**	r.t.	–	92	23	*S*
2	**1a**	−35	–	94	28	*S*
3	**1b**	−35	–	75	28	*S*
4	**1c**	−35	–	93	29	*S*
5	**1c**	−35	$Ti(O^iPr)_4$ (1 eq.)	64	20	*S*
6	**2a**	−35	–	46	36	*R*
7	**2b**	−35	–	36	16	*R*
8	**2c**	−35	–	58	60	*R*
9	**2c**	−35	$Ti(O^iPr)_4$ (1 eq.)	36	29	*R*

[a] GC yields.
[b] The ee values were determined by chiral GC analysis.

was carried out in the presence of $Ti(O^iPr)_4$, the enantioselectivity decreased (Entries 5 and 9).

We next investigated the activity of ligand **3** and**4** in this reaction at room temperature. Using 4 mol% of SAMP hydrazone **3a** as a ligand with diethylzinc in the presence of *n*-butyllithium in toluene, the reaction proceeded smoothly and the corresponding product (*S*)-**9a** was obtained in a good chemical yield with 58% ee (Entry 1, Table 2). When **3b** and **3c** were used, the enantioselectivity of the products decrease in comparison with **3a** (Entries 2 and 3). Using diastereomer of **3c**, such as hydrazone **3d**, the yield of **9a** was decreased to 74% with moderate enantioselectivity (50% ee) (Entry 4). On the other hand, using 5 mol% of imine type ligand **4a**, the product (*S*)-**9a** was obtained in a good chemical yield with moderate enantioselectivity (48% ee) (Entry 5). When the reaction was carried out without addition of *n*-butyllithium, the enantioselectivity increased without the decrease of the reactivity (Entry 6). Ligand **4b** was a very poor chiral ligand for this ethylation (Entry 7). We next investigated the effect of diastereoisomer of **4a** in this reaction (Entry 2 vs. 8). Although the reaction proceeded smoothly using **4c** as a ligand, the enantioselectivity of **9a** was decrease to 48% ee (Entry 6 vs. Entry 8). We also investigated the effect of R^2 of **4a** (Entries 9 and 10). When imine **4d** was used instead of **4a**, the enantioselectivity of **9a** was increased with good yield (Entry 9). In order to improve the enantioselectivity, we further examined the effect of reaction temperature using the ligand **4d**. The reaction at 0 °C further improved the enantioselectivity to 71% ee (Entry 11).

The use of ligand **4d** was extended to the asymmetric ethylation of other aromatic aldehydes with diethylzinc at room temperature, and the results were summarized in Table 3. The enantioselectivities for the substituted benzaldehydes were moderate to good with good yields (Entries 2–4). Ethylation of 1-naphthaldehyde was occurred 57% ee with 51% chemical yield (Entry 5).

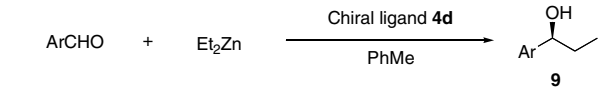
In conclusion, we have prepared chiral hydrazone and imine type ligands **1**–**4** from binaphthalene type aldehyde **5**, bisaldehyde **6**, and ketopinic acid. These ligands such as **4d** can be used in the ethylation of diethylzinc to aromatic aldehydes with moderate enantioselectivities.

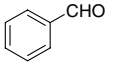
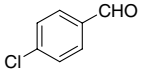
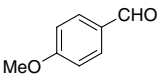
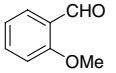
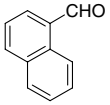
Table 2
Enantioselective addition of benzaldehyde using diethylzinc and ligands **3** and **4**

Entry	Ligand	Additive	Yield[a]/%	Ee[b]/%
1[c]	**3a** (4 mol%)	*n*-BuLi (4 mol%)	91	58
2[c]	**3b** (4 mol%)	*n*-BuLi (4 mol%)	90	34
3[c]	**3c** (4 mol%)	*n*-BuLi (4 mol%)	98	49
4[c]	**3d** (4 mol%)	*n*-BuLi (4 mol%)	74	50
5	**4a** (5 mol%)	*n*-BuLi (5 mol%)	98	48
6	**4a** (5 mol%)	–	98	63
7	**4b** (5 mol%)	–	88	18
8	**4c** (5 mol%)	–	97	48
9	**4d** (5 mol%)	–	99	67
10	**4e** (5 mol%)	–	98	47
11[d]	**4d** (5 mol%)	–	57	71

[a] GC yields.
[b] The ee values were determined by chiral HPLC analysis (Chiralcel OD-H).
[c] This reaction was carried out using 2 mL of toluene.
[d] This reaction was carried out at 0 °C.

Table 3
Enantioselective addition of aryl aldehydes using diethylzinc and ligands **4d**



Entry	Aldehyde	Yield[a]/%	Ee[b]/%	Conf.
1		99 (**9a**)	67	*S*
2		99 (**9b**)	65	*S*
3		90 (**9c**)	55	*S*
4		81 (**9d**)	68	*S*
5		51 (**9e**)	57	*S*

[a] GC yields.
[b] The ee values were determined by chiral HPLC analysis (Chiralcel OD-H).

3. Experimental

3.1. General methods

All the experiments were carried out under an argon atmosphere. NMR spectra were recorded on a JEOL LA-400 spectrometer, A-400 spectrometer or a Bruker DPX-300 spectrometer. Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^1H and ^{13}C NMR. Mass spectra were recorded on a JEOL JMS-HX110, JMS-700, a Shimadzu GCMS-QP2000A, or a Hitachi M-80B. Optical rotations were measured on a JASCO DIP-370 or a HORIBA SEPA-200.

3.2. Typical procedure for the preparation of **1** and **2**

To solution of aldehyde **5** or **6** (1 mmol) in DCM (3 mL) was added hydrazine (1 or 2 mmol) under an argon atmosphere. After 24 hr, the reaction mixture was diluted with DCM and water. The organic layer was washed with sat. $NaHCO_3$ aq., brine and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator and the residue was purified by column chromatography.

3.2.1. (*S*)-2-Hydroxy-1,1′-binaphthalenyl-3-carbaldehyde DMH hydrazone (**1a**)

$[\alpha]^{25}_D + 276$ ($c = 1.0$, $CHCl_3$); m.p. 180–182 °C; ^1H-NMR ($CDCl_3$) δ: 2.95 (s, 6H), 7.10–7.96 (m, 13H), 11.75 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 42.6, 120.6, 121.8, 123.2, 125.0, 125.6, 125.7, 126.0, 126.1, 126.6, 127.7, 127.8, 128.3, 128.4, 128.7, 132.8, 133.7, 133.9, 134.5, 136.3, 152.0; IR (KBr): 1560 cm^{-1}; FAB-MS *m/z* 340 (M^+, 100); HR-MS Calc. for $C_{23}H_{20}N_2O$ (M^+): 340.1576. Found: 340.1552.

3.2.2. (*S*)-2-Hydroxy-1,1′-binaphthalenyl-3-carbaldehyde SAMP hydrazone (**1b**)

$[\alpha]^{25}_D + 103$ ($c = 1.0$, $CHCl_3$); m.p. 181–183 °C; ^1H-NMR ($CDCl_3$) δ: 1.85–2.09 (m, 4H), 3.00 (dd, $J = 8.9$ and 16.2 Hz, 1H), 3.27 (s, 3H), 3.39–3.48 (m, 2H), 3.52–3.57 (m, 1H), 3.60–3.63 (m, 1H), 7.07–7.96 (m, 13H), 11.50 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 22.5, 26.6, 49.0, 59.2, 63.3, 74.0, 120.47, 122.2, 123.1, 125.0, 125.7, 125.7, 125.8, 126.3, 126.4, 127.6, 127.8, 127.9, 128.2, 128.3, 128.4, 133.5, 133.8, 134.6, 140.6, 151.9; IR (KBr): 1560 cm^{-1}; FAB-MS *m/z* 411 ($M^+ + 1$, 82); Anal. Calc. for $C_{27}H_{26}N_2O_2$: C, 79.00; H, 6.38; N, 6.82. Found: C, 79.06; H, 6.47; N, 6.81%.

3.2.3. (*S*)-2-Hydroxy-1,1′-binaphthalenyl-3-carbaldehyde RAMP hydrazone (**1c**)

$[\alpha]^{25}_D + 398$ ($c = 1.0$, $CHCl_3$); m.p. 147–149 °C; ^1H-NMR ($CDCl_3$) δ: 1.85–2.09 (m, 4H), 3.00 (dd, $J = 8.1$ and 16.9 Hz, 1H), 3.29 (s, 3H), 3.39–3.49 (m, 2H), 3.52–3.57 (m, 1H), 3.60–3.63 (m, 1H), 7.09–7.96 (m, 13H), 11.48 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 22.3, 26.7, 49.0, 59.2, 63.2, 74.1, 120.5, 122.2, 123.1, 124.9, 125.7, 125.7, 125.9, 126.1, 126.2, 126.4, 127.6, 127.8, 127.9, 128.3, 128.5, 132.8, 133.6, 133.8, 134.5, 136.1, 151.8; IR (KBr): 1560 cm^{-1}; FAB-MS *m/z* 411 ($M^+ + 1$, 78) ; Anal. Calc. for $C_{27}H_{26}N_2O_2$: C, 79.00; H, 6.38; N, 6.82. Found: C, 79.75; H, 6.30; N, 6.57%.

3.2.4. (*R*)-2,2′-Dihydroxy-1,1′-binaphthalenyl-3,3′-dicarbaldehyde bis DMH hydrazone (**2a**)

$[\alpha]^{25}_D - 80.0$ ($c = 1.0$, $CHCl_3$); m.p. 289–291 °C; ^1H-NMR ($CDCl_3$) δ: 2.93 (s, 12H), 7.16–7.81 (m, 10H), 7.64 (s, 2H), 11.76 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 42.6, 116.5, 121.9, 123.1, 124.6, 126.7, 127.9, 128.2, 128.9, 133.4, 136.8, 152.3; IR (KBr): 1575 cm^{-1}; FAB-MS *m/z* 426 (M^+, 76); Anal. Calc. for $C_{26}H_{26}N_4O_2$: C, 73.22; H, 6.14; N, 13.14. Found: C, 73.17; H, 6.11; N, 12.85%.

3.2.5. (*R*)-2,2′-Dihydroxy-1,1′-binaphthalenyl-3,3′-dicarbaldehyde bis SAMP hydrazone (**2b**)

$[\alpha]^{25}_D - 613$ ($c = 1.0$, $CHCl_3$); m.p. 131–133 °C; ^1H-NMR ($CDCl_3$) δ: 1.84–2.16 (m, 8H), 3.06 (dd, $J = 8.6$ and 17.3 Hz, 2H), 3.27 (s, 6H), 3.37–3.48 (m, 4H), 3.52–3.59 (m, 2H), 3.68–3.60 (m, 2H), 7.14–7.80 (m, 12H), 11.47 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 22.3, 26.8, 49.2, 59.5, 63.3, 74.2, 116.6, 122.3, 123.1, 123.7, 124.7, 126.6, 127.9, 128.3, 128.6, 129.8, 133.8, 136.7, 152.2; IR (KBr): 1560 cm^{-1}; FAB-MS *m/z* 567 ($M^+ + 1$, 100) ; Anal. Calc. for $C_{34}H_{38}N_4O_4$: C, 72.06; H, 6.76; N, 9.89. Found: C, 71.76; H, 6.68; N, 9.59%.

3.2.6. (*R*)-2,2′-Dihydroxy-1,1′-binaphthalenyl-3,3′-dicarbaldehyde bis RAMP hydrazone (**2c**)

$[\alpha]^{25}_D + 270$ ($c = 1.0$, $CHCl_3$); m.p. 142–145 °C; ^1H-NMR ($CDCl_3$) δ: 1.84–2.06 (m, 8H), 3.10 (dd, $J = 8.6$ and 17.3 Hz, 2H), 3.30 (s, 6H), 3.38–3.48 (m, 4H), 3.49–3.54 (m, 2H), 3.55–3.60 (m, 2H), 7.16–7.80 (m, 12H), 11.45 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 22.3, 26.7, 49.2, 59.2, 63.2, 74.1, 112.5, 122.3, 123.1, 124.7, 126.5, 127.8, 128.2, 128.6, 133.2, 136.7, 152.1; IR (KBr): 1560 cm^{-1}; FAB-MS *m/z* 567 ($M^+ + 1$, 100); HR-MS Calc. for $C_{34}H_{39}N_{44}$ ($M^+ + H$): 567.2950. Found: 567.2971.

3.3. Preparation of (*S*)-ketopinic acid methyl ester (**7**)

To solution of thionyl chloride (2 mL) in MeOH (30 mL) was added (*S*)-ketopinic acid (1.1 g, 6.1 mmol) at 0 °C. After being stirred for 18 h at room temperature, the reaction mixture was concentrated with a rotary evaporator and the residue was purified by column chromatography: 81%; $[\alpha]_D^{20} = +36.6$ ($c = 1.0$, $CHCl_3$); ^1H-NMR ($CDCl_3$) δ: 1.08 (s, 3H), 1.16 (s, 3H), 1.41–1.46 (m, 1H), 1.75–1.85 (m, 2H), 1.96 (d, $J = 18.4$ Hz, 1H), 2.01–2.14 (m, 2H), 2.29–2.49 (m, 1H), 2.50–2.52 (m, 1H), 3.76 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 19.8, 21.2, 26.3, 26.4, 43.9, 44.3, 49.3, 51.9, 68.0, 170.3, 211.0; IR (KBr): 1766 and 1725 cm^{-1}; EI-MS *m/z* (rel. intensity): 196 (M^+, 15); HR-MS Calc. for $C_{11}H_{17}O_3$ ($M^+ + H$) 197.1178. Found 197.1183.

3.4. Preparation of (1R,4R)-7,7-dimethyl-1-(hydroxydiphenylmethyl)-bicyclo[2,2,1]heptan-2- one (**8**) [10]

To solution of ketoester **7** (0.99 g, 5.0 mmol) in THF (20 mL) was added phenyl lithium (11.0 mmol) in THF (1.1 M, 9.6 mL) at −78 °C under an argon atmosphere. After being stirred for 18 h, the reaction mixture was diluted with ether and water. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator and the residue was purified by column chromatography: 64%; $[\alpha]_D^{20} = +183$ ($c = 0.3$, $CHCl_3$); m.p. 186–187 °C; ^{1}H-NMR ($CDCl_3$) δ: 0.26 (s, 3H), 1.07 (s, 3H), 1.39–1.45 (m, 1H), 1.78 (t, $J = 4.8$ Hz, 1H), 1.90–1.99 (m, 2H), 2.05–2.32 (m, 1H), 2.48–2.54 (m, 2H), 3.83 (br, 1H), 7.17–7.47 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ: 21.6, 22.6, 25.5, 26.9, 43.5, 44.5, 50.2, 69.2, 79.8, 126.8, 126.9, 127.1, 127.3, 128.2, 129.1, 144.5, 147.1, 220.2; IR (film): 3498 and 1714 cm^{-1}; EI-MS *m/z* (rel. intensity): 320 (M^+, 8); HR-MS Calc. for $C_{22}H_{24}O_2$ (M^+) 320.1776. Found 320.1768.

3.5. Typical procedure for the preparation of **3** and **4**

To solution of hydrazine or amine (0.5 mmol) in toluene (1 mL) was added trimethylaluminium (0.5 mmol) in hexane (1.0 M, 0.5 mL) under an argon atmosphere. The mixture was heated under reflux for 3 h, and then the solution of ketoalcohol **8** (0.080 g, 0.25 mmol) in toluene (1 mL) was added. After the mixture was heated under reflux for 4 h, the reaction mixture was diluted with ether and water. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator and the residue was purified by column chromatography.

3.5.1. (1R,4R)-7,7-Dimethyl-1-(hydroxydiphenylmethyl)-bicyclo[2,2,1]heptan-2-one DMH hydrazone (**3a**)

51%; $[\alpha]_D^{20} = +275$ (c = 0.31, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.07 (s, 3H), 1.08 (s, 3H), 1.25–1.34 (m, 1H), 1.57 (t, $J = 4.5$ Hz, 1H), 1.76–1.81 (m, 1H), 2.01 (dd, $J = 4.5$ Hz and 17.7 Hz, 1H), 2.27–2.48 (m, 2H), 2.47 (s, 6H), 2.69–2.78 (m, 1H), 6.18 (br, 1H), 7.14–7.26 (m, 6H), 7.36–7.52 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ: 21.1, 21.8, 26.6, 27.6, 34.5, 45.7, 47.3, 50.2, 62.4, 80.7, 126.0, 126.5, 126.6, 126.9, 127.2, 127.3, 128.8, 129.1, 130.2, 145.3, 148.6, 177.9; IR (film): 3365 and 1651 cm^{-1}; FAB-MS *m/z* (rel. intensity): 363 ($M^+ + 1$, 70); HR-MS Calc. for $C_{24}H_{31}N_2O$ ($M^+ + H$) 363.2436. Found 363.2441.

3.5.2. (1R,4R)-7,7-Dimethyl-1-(hydroxydiphenylmethyl)-bicyclo[2,2,1]heptan-2- one 1-aminomorpholine hydrazone (**3b**)

62%; $[\alpha]_D^{20} = +221$ ($c = 1.0$, $CHCl_3$); m.p. 149–152 °C; ^{1}H-NMR ($CDCl_3$) δ: 0.08 (s 3H), 1.08 (s 3H), 1.28–1.32 (m, 1H), 1.57–1.61 (m 1H), 1.75–1.84 (m 1H), 1.95 (d, $J = 17.9$ Hz, 1H), 2.26–2.44 (m, 1H), 2.48–2.50 (m 1H), 2.70–2.80 (m 5H), 3.52–3.75 (m 4H), 6.02 (br 1H), 7.13–7.52 (m 10H); ^{13}C-NMR ($CDCl_3$) δ: 21.5, 22.4, 27.0, 28.0, 35.1, 46.1, 50.6, 55.4, 63.0, 66.4, 81.0, 126.5, 127.0, 127.3, 129.2, 130.4, 145.6, 148.9, 179.4, 182.8; IR (film): 3392 and 1639 cm^{-1}; FAB-MS *m/z* (rel. intensity): 405 ($M^+ + 1$, 38); HR-MS Calc. for $C_{26}H_{33}N_2O$ ($M^+ + H$) 405.2542. Found 405.2558.

3.5.3. (1R,4R)-7,7-Dimethyl-1-(hydroxydiphenylmethyl)-bicyclo[2,2,1]heptan-2-one SAMP hydrazone (**3c**)

61%; $[\alpha]_D^{20} = +288$ (c = 0.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.12 (s, 3H), 1.09 (s, 3H), 1.24–1.29 (m, 1H), 1.55–1.58 (m, 2H), 1.82–1.89 (m, 5H), 2.46–2.59 (m, 4H), 3.00–3.10 (m, 1H), 3.29–3.33 (m, 6H), 6.30 (br, 1H), 7.26–7.28 (m, 3H), 7.45–4.45 (m, 4H), 7.48–7.49 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ: 21.6, 22.3, 22.7, 26.3, 27.0, 28.4, 35,9, 46.3, 50.6, 54.9, 59.4, 62.6, 66.1, 76.2, 80.9, 126.1, 126.8, 126.8, 127.2, 128.9, 130.4, 145.9, 149.6, 171.9; IR (film): 3389 and 1658 cm^{-1}; FAB-MS *m/z* (rel. intensity): 433 ($M^+ + 1$, 75); HR-MS Calc. for $C_{28}H_{37}N_2O$ ($M^+ + H$) 433.2855. Found 433.2859.

3.5.4. (1R,4R)-7,7-Dimethyl-1-(hydroxydiphenylmethyl)-bicyclo[2,2,1]heptan-2-one RAMP hydrazone (**3d**)

64%; $[\alpha]_D^{20} = +165$ (c = 0.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.09 (s, 3H), 1.11 (s, 3H), 1.21–1.27 (m, 2H), 1.52–1.58 (m, 1H), 1.73–1.79 (m, 4H), 2.03 (d, $J = 17.5$ Hz, 1H), 2.23–2.51 (m, 2H), 2.53–2.79 (m, 2H), 2.98–3.23 (m, 4H), 3.25 (s, 3H), 5.83 (br, 1H), 7.11–7.48 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ: 21.5, 22.6, 22.7, 26.4, 27.8, 27.9, 36.3, 46.5, 50.7, 54.3, 59.5, 63.3, 66.9, 74.9, 80.8, 126.3, 126.9, 127.1, 127.3, 129.1, 130.2, 145.8, 149.5, 173.8; IR (film): 3368 and 1637 cm^{-1}; FAB-MS *m/z* (rel. intensity): 433 ($M^+ + 1$, 78); HR-MS Calc. for $C_{28}H_{37}N_2O_2$ ($M^+ + H$) 433.2855. Found 433.2849.

3.5.5. (1R,4R)-7,7-Dimethyl-1-(hydroxydiphenylmethyl)-bicyclo[2,2,1]heptan-2-ylidene)-(S)-1-phenylethanamine (**4a**)

40%; $[\alpha]_D^{20} = +123$ ($c = 1.0$, $CHCl_3$); m.p. 77–78 °C; ^{1}H-NMR ($CDCl_3$) δ: 0.07 (s, 3H), 1.14 (s, 3H), 1.20–1.25 (m, 1H), 1.37 (d, $J = 16.5$ Hz, 3H), 1.55–1.62 (m, 1H), 1.68–1.80 (m, 1H), 1.87 (d, $J = 17.0$ Hz, 1H), 2.18–2.29 (m, 1H), 2.41–2.43 (m, 1H), 2.61–2.62 (m, 1H), 4.55 (q, $J = 6.5$ Hz, 1H), 6.13 (br, 1H), 7.07–7.69 (m, 15H); ^{13}C-NMR ($CDCl_3$) δ: 21.0, 21.8, 24.8, 26.8, 27.4, 34.4, 45.7, 49.6, 60.7, 63.4, 65.8, 80.7, 126.0, 126.3, 126.4, 126.5, 126.7, 126.8, 128.4, 128.7, 130.1, 144.8, 145.2, 148.7, 180.8; IR (film): 2964 and 1670 cm^{-1}; EI-MS *m/z* (rel. intensity): 423 (M^+, 10); HR-MS Calc. for $C_{30}H_{34}NO$ ($M^+ + H$) 424.2640. Found 424.2627.

3.5.6. (1R,4R)-7,7-Dimethyl-1-(hydroxydiphenylmethyl)-bicyclo[2,2,1]heptan-2- ylidene)(phenyl)methanamine (**4b**)

53%; $[\alpha]_D^{20} = +277$ (c=1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.08 (s, 3H), 1.06 (s, 3H), 1.17–1.29 (m, 1H), 1.60–1.63 (m, 1H), 1.76–1.80 (m, 1H), 1.92 (d, $J = 17.2$ Hz, 1H),

2.33–2.36 (m, 1H), 2.44–2.59 (m, 2H), 4.48 (q, $J = 16.5$ Hz, 2H), 7.11–7.25 (m, 12H), 7.48–7.52 (m, 3H), 7.56 (br, 1H); ^{13}C-NMR ($CDCl_3$) δ: 21.1, 22.1, 26.8, 27.4, 34.9, 45.5, 50.0, 55.0, 63.9, 80.3, 125.9, 126.3, 126.4, 126.7, 126.9, 127.4, 128.2, 128.5, 129.7, 139.6, 145.1, 148.8, 183.5; IR (film): 2964 and 1671 cm^{-1}; EI-MS *m/z* (rel. intensity): 409 (M^+, 20); HR-MS Calc. for $C_{29}H_{32}NO$ ($M^+ + H$) 410.2484. Found 410.2463.

3.5.7. (1R,4R)-7,7-Dimethyl-1-(hydroxydiphenylmethyl)-bicyclo[2,2,1]heptan-2-ylidene)-(R)-1-phenylethanamine (**4c**)

37%; $[\alpha]_D^{20} = +128$ ($c = 1.0$, $CHCl_3$); m.p. 70–71 °C; ^{1}H-NMR ($CDCl_3$) δ: 0.07 (s, 3H), 0.87 (s, 3H), 1.22–1.38 (m, 1H), 1.39 (d, $J = 3.4$ Hz, 3H), 1.57–1.58 (m, 2H), 1.71–1.86 (m, 1H), 2.01 (d, $J = 17.0$ Hz, 1H), 2.35–2.61 (m, 3H), 4.52 (q, $J = 6.6$ Hz, 1H), 6.71 (br, 1H), 7.09–7.25 (m, 11H), 7.47–7.51 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ: 21.2, 21.8, 24.8, 26.8, 27.5, 34.4, 45.7, 49.6, 60.7, 63.4, 80.7, 126.0, 126.4, 126.5, 126.6, 126.7, 126.9, 128.5, 128.7, 130.2, 144.9, 145.3, 148.7, 180.8; IR (film): 2965 and 1670 cm^{-1}; EI-MS *m/z* (rel. intensity): 423 (M^+, 12); HR-MS Calc. for $C_{30}H_{34}NO$ ($M^+ + H$) 424.2640, found 424.2655.

3.5.8. (1R,4R)-7,7-Dimethyl-1-(hydroxydiphenylmethyl)-bicyclo[2,2,1]heptan-2-ylidene)-(S)-1-α-naphthylethanamine (**4d**)

15%; $[\alpha]_D^{20} = +195$ ($c = 1.0$, $CHCl_3$); m.p. 173–174 °C; ^{1}H-NMR ($CDCl_3$) δ: 0.11 (s, 3H), 1.15–1.26 (m, 1H), 1.18 (s, 3H), 1.52 (d, $J = 6.5$ Hz, 3H), 1.61–1.65 (m, 1H), 1.76–1.81 (m, 1H), 1.90 (d, $J = 17.0$ Hz, 1H), 2.24–2.30 (m, 1H), 2.44–2.48 (m, 1H), 2.78–2.80 (m, 1H), 5.32 (q, $J = 6.5$ Hz, 1H), 6.67 (br, 1H), 7.13–8.05 (m, 17H); ^{13}C-NMR ($CDCl_3$) δ: 21.2, 22.2, 24.0, 26.6, 27.5, 34.3, 45.5, 50.0, 56.7, 63.8, 80.3, 122.9, 124.9, 125.1, 125.7, 125.8, 125.9, 126.5, 126.9, 127.0, 127.1, 128.4, 129.0, 129.7, 130.3, 133.8, 140.9, 145.2, 149.2, 180.6; IR (film): 2960 and 1675 cm^{-1}; FAB-MS *m/z* (rel. intensity): 474 ($M^+ + 1$, 50); HR-MS Calc. for $C_{34}H_{36}NO$ ($M^+ + H$) 424.2797. Found 474.2782.

3.5.9. (1R,4R)-7,7-Dimethyl-1-(hydroxydiphenylmethyl)-bicyclo[2,2,1]heptan-2- ylidene)-(S)-1-β-naphthylethanamine (**4e**)

13%; $[\alpha]_D^{20} = +140$ ($c = 1.0$, $CHCl_3$); m.p. 68–70 °C; ^{1}H-NMR ($CDCl_3$) δ: 0.08 (s, 3H), 1.16 (s, 3H), 1.17–1.26 (m, 2H), 1.45 (d, $J = 6.5$ Hz, 3H), 1.60–1.64 (m, 1H), 1.90 (d, $J = 17.0$ Hz, 1H), 2.21–2.27 (m, 1H), 2.35–2.45 (m, 1H), 2.65–2.77 (m, 1H), 4.71 (q, $J = 6.5$ Hz, 1H), 6.72 (br, 1H), 7.16–7.74 (m, 17H); ^{13}C-NMR ($CDCl_3$) δ: 21.5, 22.5, 25.5, 26.9, 27.9, 34.7, 45.9, 50.3, 61.2, 64.0, 80.9, 125.3, 125.8, 125.9, 126.2, 126.4, 126.9, 127.4, 128.0, 128.2, 128.3, 130.4, 132.9, 133.8, 143.2, 145.6, 149.6, 181.0; IR (film): 2964 and 1668 cm^{-1}; FAB-MS *m/z* (rel. intensity): 474 ($M^+ + 1$, 20); HR-MS Calc. for $C_{34}H_{36}NO$ ($M^+ + H$) 424.2797. Found 474.2770.

3.6. General procedure for the enantioselective addition of aldehydes using diethylzinc

Procedure A (Table 1): to a solution of ligand **1** or **2** (0.05 mmol) in toluene (5 mL) at −78 °C, diethylzinc (2 mmol) in hexane solution (1 M, 2 mL) was added and stirring was continued at same temperature. After 20 min., benzaldehyde (1 mmol, 0.1 mL) was added and the mixture was stirred at −35 °C for 24 hr. The reaction mixture was quenched with 2 M hydrochloric acid, and then extracted with ether. The organic layers were washed with sat. $NaHCO_3$ aq. and brine, and dried over $MgSO_4$ anhydrous. The solvent was evaporated and the residue was purified by column chromatography (hexane: EtOAc = 4:1).

Procedure B (Tables 2 and 3): To a solution of ligand **3** or **4** (0.025 mmol) in toluene (1 mL), diethylzinc (1 mmol) in hexane solution (1 M, 1 mL) was added and stirring was continued at room temperature. After 0.5 h, benzaldehyde (0.5 mmol, 0.05 mL) was added and the mixture was stirred for 24 h. The reaction mixture was quenched with 2 M hydrochloric acid, and then extracted with ether. The organic layers were washed with sat. $NaHCO_3$ aq. and brine, and dried over $MgSO_4$ anhydrous. The solvent was evaporated and the residue was purified by column chromatography (hexane:EtOAc = 4–12:1). The ee values were determined by HPLC with a Chiralcel OD-H [11]. The yield was determined by GC (Shimadzu GC-14B using CPB20-m25–025 column).

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