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Enantioselective addition of dialkylzinc to aldehydes catalyzed by (*S*)-2-(*N*,*N*-disubstituted aminomethyl)indoline

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Abstract

Chiral di- or triamines, (*S*)-2-(*N*,*N*-disubstituted aminomethyl)indoline **1a**–**d**, derived from (*S*)-indoline-2-carboxylic acid were efficient chiral catalysts for the enantioselective addition of dialkylzincs to aldehydes. The best results were obtained by employing 15 mol% of (*S*)-2-(4-methylpiperazin-1-ylmethyl)indoline **1c**, and chiral secondary alcohols were obtained in up to 97% ee.

1. Introduction

The catalytic enantioselective alkylation of aldehydes is a potentially important method for preparing chiral secondary alcohols.[1] To date, various types of catalyst such as chiral alcohols, amines, or amino alcohols, have been developed as chiral auxiliaries for the enantioselective addition of dialkylzinc to aldehydes.[2] Most of the successful results were obtained by using sterically constrained β-amino alcohols[2] and several amino sulfur compounds[3] and diols[4] were recently reported to show high selectivity. Although chiral amines have also been used as catalysts,[5,6] the selectivity has not been high except for a few cases.[5b,c,e]

We recently reported that chiral β-diamines derived from (*S*)-proline catalyze the enantioselective addition of diethylzinc to aldehydes, but the selectivity of the reaction is not high.[6] We anticipated that higher selectivity would be achieved using a more acidic amine to ensure the bond formation between the catalyst and dialkylzinc. Thus we synthesized chiral di- or triamines, (*S*)-2-(*N*,*N*-disubstituted aminomethyl)indoline **1a**–**d**, derived from (*S*)-indoline-2-carboxylic acid, and examined the reaction. The amines **1a**–**d** showed high selectivity in the reaction and various secondary alcohols were obtained in good yields with 59–97% ee (Scheme 1).

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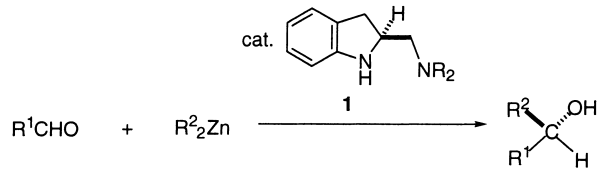
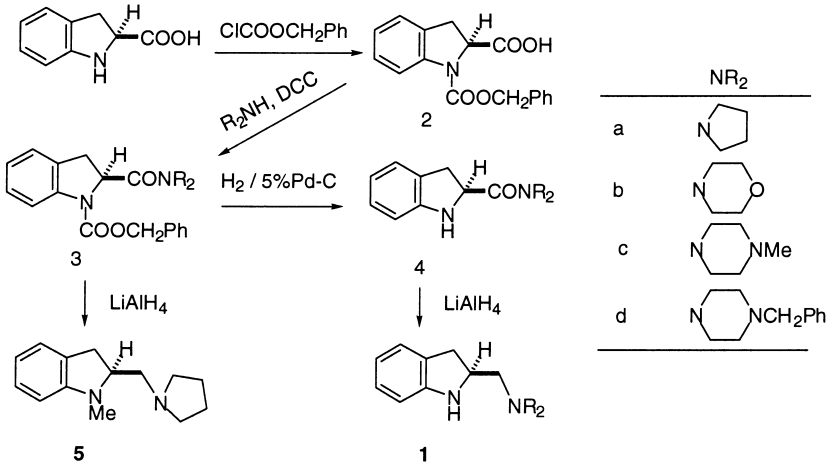


Scheme 1.

2. Results and discussion

Chiral di- or triamines, (*S*)-2-(*N*,*N*-disubstituted aminomethyl)indoline **1a**–**d**, were synthesized as shown in Scheme 2. (*S*)-*N*-(Benzyloxycarbonyl)indoline-2-carboxylic acid **2** was coupled with amines using dicyclohexylcarbodiimide (DCC) as the condensing reagent in dichloromethane to afford corresponding amides **3a**–**d**, respectively. Catalytic hydrogenation of **3a**–**d** under a hydrogen atmosphere in the presence of 5% Pd–C in methanol gave *N*,*N*-disubstituted (*S*)-indoline-2-carboxamides **4a**–**d**, which were then reduced with lithium aluminum hydride to give the chiral amines **1a**–**d**. The reduction of **3a** with lithium alminum hydride afforded (*S*)-1-methyl-2-(pyrrolidin-1-ylmethyl)indoline **5** (Scheme 2).

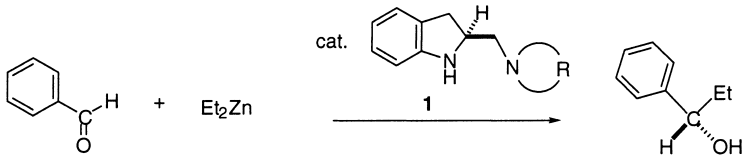


Scheme 2.

In the first place, the reaction of diethylzinc and benzaldehyde was examined in the presence of (*S*)-2-(pyrrolidin-1-ylmethyl)indoline **1a** under a variety of reaction conditions. As shown in Table 1, the selectivity of the reaction was highly dependent on the amount of catalyst, and (*S*)-1-phenyl-1-propanol was obtained with 91% ee in 89% yield, when the reaction was carried out in cyclohexane–hexane at rt for 15 h using 15 mol% of **1a** (Table 1, entries 1–8). The selectivity was further improved by using (*S*)-2-(morpholinomethyl)indoline **1b** or (*S*)-2-(4-methylpiperazin-1-ylmethyl)indoline **1c** in lieu of **1a** (Table 1, entries 9, 10), and the highest selectivity was achieved by conducting the reaction at 0°C using **1c** (Table 1, entry 12).

The reaction of diethylzinc and various aldehydes was then examined. In the presence of 15 mol% of **1c**, aromatic aldehydes were enantioselectively ethylated at 0°C for 15 h to afford the corresponding alcohols in relatively high ees (Table 2, entries 1–4). Although in the cases of cinnamaldehyde and sterically less hindered aliphatic aldehydes the selectivity was moderate (Table 2, entries 5–7), the best results were obtained by the reaction of cyclohexanecarbaldehyde to yield (*S*)-1-cyclohexyl-1-propanol in 97% ee (Table 2, entry 8). The reaction of dimethyl- and diisopropylzinc with benzaldehyde was also examined. The reaction became slow and the yield of the corresponding alcohols was 34% (Me_2Zn) or

Table 1
Enantioselective addition of diethylzinc to benzaldehydes in the presence of **1**[a]



Entry	**1** (mol%)	R	Solvent	Yield/%[b]	Ee/%[c]
1	**a** (5)	$-(CH_2)_4-$	Cyclohexane-Hexane	78	49
2	**a** (10)	$-(CH_2)_4-$	Cyclohexane-Hexane	87	88
3	**a** (15)	$-(CH_2)_4-$	Cyclohexane-Hexane	89	91
4	**a** (20)	$-(CH_2)_4-$	Cyclohexane-Hexane	89	91
5	**a** (15)	$-(CH_2)_4-$	Hexane	95	90
6	**a** (15)	$-(CH_2)_4-$	Toluene-Hexane	84	88
7	**a** (15)	$-(CH_2)_4-$	Ether-Hexane	90	89
8	**a** (15)	$-(CH_2)_4-$	Dichloromethane-Hexane	64	81
9	**b** (15)	$-(CH_2)_2-O-(CH_2)_2-$	Cyclohexane-Hexane	82	93
10	**c** (15)	$-(CH_2)_2-N(Me)-(CH_2)_2-$	Cyclohexane-Hexane	92	94
11	**c** (15)	$-(CH_2)_2-N(Me)-(CH_2)_2-$	Ether-Hexane	87	94
12[d]	**c** (15)	$-(CH_2)_2-N(Me)-(CH_2)_2-$	Cyclohexane-Hexane	85	95
13	**d** (15)	$-(CH_2)_2-N(CH_2Ph)-(CH_2)_2-$	Cyclohexane-Hexane	74	90

[a] The reaction was carried out at rt for 15 h after an addition of 1.0 M hexane solution of diethylzinc (2.7 mmol) to cyclohexane, hexane, toluene, ether, or dichloromethane (6 ml) solution of benzaldehyde (1.5 mmol) and **1** (0.225 mmol) at 0°C unless otherwise noted.

[b] Isolated yield.

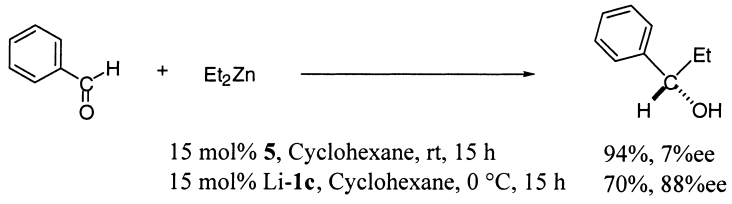
[c] Ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel OD-H).

[d] The reaction was carried out at 0°C for 15 h.

0% (i-Pr_2Zn) at 0°C, even after 63 h, respectively. However, the corresponding *S*-alcohols were obtained in good yields and high ees by conducting the reaction at rt for 15 h (Table 2, entries 9, 10).

In the enantioselective addition of dialkylzinc species to aldehydes catalyzed by chiral amino alcohols, diols, and amino sulfur compounds, the zinc–oxygen or zinc–sulfur bond formed by the reaction of the dialkylzinc and catalyst was considered to be important for realizing high selectivity.[2a,3a,d,e,4b] With regard to amine catalysts, moderate selectivity was achieved by the coordination of an aprotic ligand,

(*S*)-*N*,*N*,*N*′,*N*′-tetramethyl-2,2-diamino-1,1-binaphthyl.[5a] However, zinc–nitrogen bond formation was essential to achieve high selectivity when 2-[(2*S*)-2-pyrrolidinyl]pyridine was employed as the catalyst.[5c] We thus carried out a ^{1}H NMR study of a 1:1 mixture of **1a** and diethylzinc in toluene-d_8. The ^{1}H NMR signal (δ=0.48 ppm, q, *J*=8.3 Hz) relating to the methylene group attached to zinc integrated to two protons after 5 min at room temperature after solution preparation. This indicated that a zinc–nitrogen bond was formed rapidly at room temperature by the protonolysis of a zinc–carbon bond by the free secondary amine in **1a**. We next carried out the reaction of benzaldehyde and diethylzinc in the presence of an aprotic diamine, (*S*)-1-methyl-2-(1-pyrrolidin-1-ylmethyl)indoline **5**, under similar reaction conditions. (*S*)-1-Phenyl-1-propanol was obtained in high yield (94%), but the ee of the alcohol was very low (7%). The lithium salt of **1c** was also examined, since some amine catalysts were reported to give better selectivity when they were used as the corresponding lithium salts.[5b,e] However, the selectivity was not improved. Thus it appears that the Zn–N sigma bond played an important role in order to realize high selectivity in the reaction using **1** as the catalyst (Scheme 3).



Scheme 3.

We postulate a similar stereochemical course of the reaction to the one proposed previously for (*S*)-2-(*N*,*N*-disubstituted aminomethyl)pyrrolidine. Thus, a *cis*-fused 5-membered bicyclic complex is initially formed by the reaction of **1** and the dialkylzinc.[6] Another dialkylzinc molecule is chelated with the nitrogen atom on the indoline ring to form the dinuclear zinc complex. The carbonyl oxygen of the aldehyde approaches the more Lewis acidic diamine-chelated Zn_A in such a manner as to prevent a non-bonding repulsion between R^1 in the aldehyde and a terminal alkyl group (R^2) attached to Zn_B. The bridging alkyl group (R^2) attached to Zn_A then migrates to the aldehyde. The significant improvement of the selectivity compared with (*S*)-2-(*N*,*N*-disubstituted aminomethyl)pyrrolidine would be attributed to a more definite formation of the complex depicted in Fig. 1 as a result of the higher acidity of the aromatic amine.

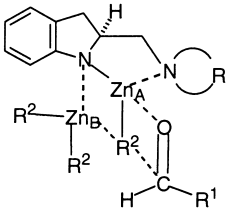
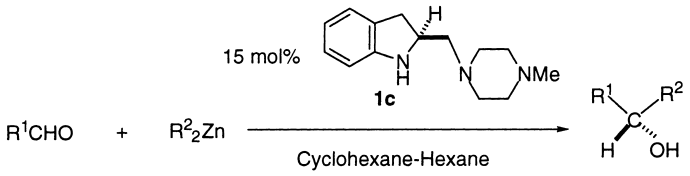


Figure 1.

In summary, new chiral di- and triamines **1** derived from (*S*)-indoline-2-carboxylic acid were found to promote the enantioselective alkylation of aldehydes efficiently to afford the corresponding secondary alcohols in up to 97% ee.

Table 2
Enantioselective addition of diethylzinc to aldehydes catalyzed by **1c**[a,7,8]



Entry	R^1	R^2	Yield/% [b]	$[\alpha]_D$ (*c*, temp.(C), solv)	Ee/%
1	Ph	Et	85	–44.4 (1.01, 22, $CHCl_3$)	95[c]
2	*p*-$MeOC_6H_4$	Et	80	–25.8 (1.10, 20, benzene)	74[d]
3	*o*-$MeOC_6H_4$	Et	71	–52.9 (1.02, 22, toluene)	91[d]
4	*p*-ClC_6H_4	Et	91	–23.6 (1.73, 20, benzene)	93[c]
5	(*E*)-PhCH=CH	Et	80	–4.25 (1.03, 20, $CHCl_3$)	59[c]
6	$PhCH_2CH_2$	Et	67	+16.2 (1.04, 20,C_2H_5OH)	66[d]
7	*n*-C_6H_{13}	Et	71	+5.87 (1.00, 20, $CHCl_3$)	60[e]
8	*c*-C_6H_{11}	Et	70	–6.39 (1.05, 24, $CHCl_3$)	97[f]
9[g]	Ph	Me	84	–56.6 (1.02, 23, cyclopentane)	96[c]
10[g]	Ph	*i*-Pr	80	–41.3 (1.04, 17, ether)	87[c]

[a] The reaction was carried out at 0°C for 15 h after an addition of 1.0 M hexane solution of diethylzinc (2.7 mmol) to cyclohexane (6 ml) solution of aldehyde (1.5 mmol) and **1c** (0.225 mmol) at 0°C unless otherwise noted. All products are of *S*-configuration based on the specific rotation.[2h,7]

[b] Isolated yield.

[c] Ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel OD-H).

[d] Ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel OB).

[e] Ee was determined by ^{13}C NMR spectroscopy after esterification with (−)-MTPACl.[8]

[f] Ee was determined by GC using capillary column (Shimadzu CBP-M25-025) after esterification with (−)-MTPACl.

[g] The reaction was carried out at rt.

3. Experimental section

3.1. General

Melting points were obtained on a Büchi 535 apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 260-10 spectrometer or Perkin–Elmer Paragon 1000. ^1H and ^{13}C NMR spectra

were measured with a JEOL JNM-EX-270 spectrometer, using tetramethylsilane as the internal standard. $CDCl_3$ was used as the solvent. Mass spectra (MS) were determined on a JEOL JMS SX102QQ mass spectrometer. Specific rotations were measured on a Horiba SEPA-200 polarimeter in the indicated solvent. GC analyses were carried out with Shimadzu GC-14A. HPLC analyses were carried out with Tosoh instruments (pump, CCPS; detector, UV-8020).

3.2. (S)-N-(Benzyloxycarbonyl)indoline-2-carboxylic acid **2**

To (*S*)-indoline-2-carboxylic acid (32.64 g, 0.2 mol) in water (280 ml) was slowly added benzyloxycarbonyl chloride (18.77 g, 0.11 mol) in toluene (60 ml) at 0°C. After addition of sodium hydrogen carbonate (40.0 g, 0.4 mol) the mixture was stirred at room temperature for 2 h and benzyloxycarbonyl chloride (18.77 g, 0.11 mol) in toluene (60 ml) was again added to the mixture at 0°C and the mixture was stirred overnight at room temperature. The aqueous layer was washed several times with ether, acidified with 6 N HCl, and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydous sodium sulfate. The solvent was removed under reduced pressure and the residue was recrystallized from toluene to give (*S*)-*N*-benzyloxycarbonylindoline-2-carboxylic acid (57.25 g, 96%) (mp 116.2–117.0°C). $[\alpha]_D^{25}$ −67.4 (*c* 1.00, $CHCl_3$); IR (KBr) ν: 1714 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.19 (dd, *J*=3.8, 16.5 Hz, 1H, 1×H-3), 3.54 (dd, *J*=11.7, 16.5 Hz, 1H, 1×H-3), 4.85–5.45 (m, 3H, H-2, CH_2Ph), 6.98 (dd, *J*=7.3, 7.6 Hz, 1H, H-5), 7.12 (d, *J*=7.3 Hz, 1H, H-4), 6.90–8.05 (m, 7H, H-6, H-7, C_6H_5), 10.39 (s, 1H, COOH). Found: C, 68.74; H, 5.09; N, 4.71%. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71%.

3.3. Preparation of N,N-disubstituted (S)-N^{α}-(benzyloxycarbonyl)indoline-2-carboxamide **3a–d**

To a dichloromethane solution (100 ml) of (*S*)-*N*-benzyloxycarbonylindoline-2-carboxylic acid **2** (14.87 g, 50 mmol) was added a dichloromethane solution (50 ml) of *N*,*N*′-dicyclohexylcarbodiimide (10.32 g, 50 mmol) at 0°C under an argon atmosphere. After stirring for 30 min, a dichloromethane solution (30 ml) of amine (50 mmol) was slowly added to the reaction mixture at 0°C. The reaction temperature was then gradually warmed to room temperature and stirring was continued overnight. After removal of the precipitate, the filtrate was washed successively with 2% HCl, 4% sodium hydrogencarbonate, water, and brine. The organic layer was dried over anhydous sodium sulfate and the solvent was removed under reduced pressure. The crude product was recrystallized from ethyl acetate to give the *N*,*N*-disubstituted N^{α}-(benzyloxycarbonyl)indoline-2-carboxamide **3**.

3.3.1. (S)-1-[N-(Benzyloxycarbonyl)indoline-2-carbonyl]pyrrolidine **3a**

Yield: 66%; mp 131.3–131.9°C; $[\alpha]_D^{20}$ −32.4 (*c* 1.00, $CHCl_3$); IR (KBr) ν: 1711, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.50–2.14 (m, 4H, 2×H-3′, 2×H-4′), 3.07 (dd, *J*=4.8, 16.0 Hz, 1H, 1×H-3), 3.15–3.90 (m, 4H, 2×H-2′, 2×H-5′), 3.48 (dd, *J*=11.0, 16.0 Hz, 1H, 1×H-3), 4.90–5.45 (m, 3H, H-2, CH_2Ph), 6.95 (dd, *J*=6.6, 7.3 Hz, 1H, H-5), 7.10 (d, *J*=7.3 Hz, 1H, H-4), 7.00–8.05 (m, 7H, H-6, H-7, C_6H_5). Found: C, 71.99; H, 6.30; N, 7.96%. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99%.

3.3.2. (S)-4-[N-(Benzyloxycarbonyl)indoline-2-carbonyl]morpholine **3b**

Yield: 62%; mp 183.0–183.6°C; $[\alpha]_D^{20}$ −61.7 (*c* 1.02, $CHCl_3$); IR (KBr) ν: 1712, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.00 (dd, *J*=4.1, 16.2 Hz, 1H, 1×H-3), 3.49 (dd, *J*=11.2, 16.2 Hz, 1H, 1×H-3), 3.25–3.90 (m, 8H, 2×H-2′, 2×H-3′, 2×H-5′, 2×H-6′), 5.05–5.50 (m, 3H, H-2, CH_2Ph), 6.96 (dd, *J*=6.6,

7.3 Hz, 1H, H-5), 7.10 (d, *J*=7.3 Hz, 1H, H-4), 7.00–8.05 (m, 7H, H-6, H-7, C_6H_5). Found: C, 68.87; H, 5.99; N, 7.62%. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65%.

*3.3.3. (S)-4-Methyl-1-[*N*-(benzyloxycarbonyl)indoline-2-carbonyl]piperazine* ***3c***

Yield: 61%; mp 163.6–164.4°C; $[\alpha]_D^{20}$ −66.5 (*c* 1.00, $CHCl_3$); IR (KBr) ν: 1702, 1656 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.24 (s, 3H, NCH_3), 1.95–2.65 (m, 4H, 2×H-3′, 2×H-5′), 2.98 (dd, *J*=4.0, 16.2 Hz, 1H, 1×H-3), 3.49 (dd, *J*=11.4, 16.2 Hz, 1H, 1×H-3), 3.30–3.80 (m, 4H, 2×H-2′, 2×H-6′), 5.05–5.50 (m, 3H, H-2, CH_2Ph), 6.80–8.10 (m, 9H, H-4, H-5, H-6, H-7, C_6H_5). Found: C, 69.73; H, 6.70; N, 11.04%. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07%.

*3.3.4. (S)-4-Benzyl-1-[*N*-(benzyloxycarbonyl)indoline-2-carbonyl]piperazine* ***3d***

Yield: 82%; mp 172.6–173.6°C; $[\alpha]_D^{20}$ −63.2 (*c* 1.02, $CHCl_3$); IR (KBr) ν: 1708, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.10–2.70 (m, 4H, 2×H-3′, 2×H-5′), 2.98 (dd, *J*=4.1, 16.0 Hz, 1H, 1×H-3), 3.45 (s, 2H, NCH_2Ph), 3.20–3.80 (m, 5H, 1×H-3, 2×H-2′, 2×H-6′), 5.05–5.50 (m, 3H, H-2, OCH_2Ph), 6.94 (dd, *J*=6.9, 7.3 Hz, 1H, H-5), 7.09 (d, *J*=7.3 Hz, 1H, H-4), 7.00–8.05 (m, 12H, H-6, H-7, 2×C_6H_5). Found: C, 73.95; H, 6.44; N, 9.20%. Calcd for $C_{28}H_{29}N_3O_3$: C, 73.82; H, 6.42; N, 9.22%.

*3.4. Preparation of (S)-2-(*N,N*-disubstituted aminomethyl)indoline* ***1a–d***

N,*N*-Disubstituted N^{α}-(benzyloxycarbonyl)indoline-2-carboxamide **3** (30 mmol) and 5% Pd–C catalyst (0.75 g) were stirred vigorously in methanol (60 ml) under a hydrogen atmosphere overnight. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give crude *N*,*N*-disubstituted (*S*)-indoline-2-carboxamide **4**. Crude **4** in THF (75 ml) was slowly added to a THF (60 ml) suspension of lithium aluminum hydride (3.42 g, 90 mmol) at 0°C, under an argon atmosphere, and the reaction mixture was refluxed for 15 h. Saturated sodium sulfate solution was added to the reaction mixture. After removal of the inorganic material, the organic layer was concentrated in vacuo. Fractional distillation, bulb-to-bulb distillation, or column chromatography of the resulting material afforded (*S*)-2-(*N*,*N*-disubstituted aminomethyl)indoline **1**.

3.4.1. (S)-2-(Pyrrolidin-1-ylmethyl)indoline ***1a***

Yield: 83%; bp 103–106°C/0.18 mmHg; $[\alpha]_D^{20}$ +133.2 (*c* 1.00, $CHCl_3$); IR (neat) ν: 3350 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.65–1.90 (m, 4H, 2×H-3′, 2×H-4′), 2.25 (dd, *J*=4.0, 11.9 Hz, 1H, 1×C_2-CH_2N), 2.35–2.80 (m, 6H, 2×H-2′, 2×H-5′, 1×H-3, 1×C_2–CH_2N), 3.15 (dd, *J*=9.1, 15.7 Hz, 1H, 1×H-3), 3.85–4.05 (m, 1H, H-2), 4.45 (s, 1H, NH), 6.63 (d, *J*=7.6 Hz, 1H, H-7), 6.69 (dd, *J*=7.3, 7.6 Hz, 1H, H-5), 7.01 (t, *J*=7.6 Hz, 1H, H-6), 7.07(d, *J*=7.3 Hz, 1H, H-4). Found: m/z 202.1449. Calcd for $C_{13}H_{18}N_2$: M, 202.1470.

3.4.2. (S)-2-(Morpholinomethyl)indoline ***1b***

Yield: 87%; bp 165°C (bath temperature)/0.3 mmHg (bulb-to-bulb distillation); $[\alpha]_D^{20}$ +138.8 (*c* 1.10, $CHCl_3$); IR (neat) ν: 3352 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.26 (dd, *J*=3.8, 12.0 Hz, 1H, 1×C_2–CH_2N), 2.30–2.70 (m, 4H, 2×H-3′, 2×H-5′), 2.47 (dd, *J*=10.4, 12.0 Hz, 1H, 1×C_2–CH_2N), 2.66 (dd, *J*=5.0, 15.8 Hz, 1H, 1×H-3), 3.15 (dd, *J*=9.1, 15.8 Hz, 1H, 1×H-3), 3.53–3.80 (m, 4H, 2×H-2′, 2×H-6′), 3.90–4.05 (m, 1H, H-2), 4.44 (s, 1H, NH), 6.66 (d, *J*=7.6 Hz, 1H, H-7), 6.70 (dd, *J*=7.3, 7.6 Hz, 1H, H-5), 7.02 (t, *J*=7.6 Hz, 1H, H-6), 7.08 (d, *J*=7.3 Hz, 1H, H-4). Found: m/z 219.1515. Calcd for $C_{13}H_{19}N_2O$: M+H, 219.1498.

3.4.3. (S)-2-(4-Methylpiperazin-1-ylmethyl)indoline ***1c***

Yield: 95%; bp 122–123°C/0.2 mmHg; $[\alpha]_D^{20}$+138.6 (*c* 1.00, $CHCl_3$); IR (neat) ν: 3353 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.15–2.80 (m, 9H, 2×H-2′, 2×H-3′, 2×H-5′, 2×H-6′, 1×C_2–CH_2N,), 2.29 (s, 3H, NCH_3), 2.49 (dd, *J*=10.2, 12.2 Hz, 1H, 1×C_2–CH_2N), 2.64 (dd, *J*=4.8, 15.7 Hz, 1H, 1×H-3), 3.14 (dd, *J*=9.1, 15.7 Hz, 1H, 1×H-3), 3.90–4.05 (m, 1H, H-2), 4.46 (s, 1H, NH), 6.64 (d, *J*=7.6 Hz, 1H, H-7), 6.69 (dd, *J*=7.3, 7.6 Hz, 1H, H-5), 7.01 (t, *J*=7.6 Hz, 1H, H-6), 7.07 (d, *J*=7.3 Hz, 1H, H-4). Found: m/z 231.1750. Calcd for $C_{14}H_{21}N_3$: M, 231.1735.

3.4.4. (S)-2-(4-Benzylpiperazin-1-ylmethyl)indoline ***1d***

Yield: 68%; mp 59.3–59.8°C (column chromatography); $[\alpha]_D^{20}$ +138.8 (*c* 1.00, $CHCl_3$); IR (KBr) ν: 3348 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.22 (dd, *J*=4.0, 12.2 Hz, 1H, 1×C_2–CH_2N), 2.28–2.75 (m, 8H, 2×H-2′, 2×H-3′, 2×H-5′, 2×H-6′), 2.47 (dd, *J*=10.4, 12.2 Hz, 1H, 1×C_2–CH_2N), 2.63 (dd, *J*=4.8, 15.7 Hz, 1H, 1×H-3), 3.13 (dd, *J*=9.1, 15.7 Hz, 1H, 1×H-3), 3.51 (s, 2H, CH_2Ph), 3.87–4.02 (m, 1H, H-2), 4.45 (s, 1H, NH), 6.63 (d, *J*=7.6 Hz, 1H, H-7), 6.69 (dd, *J*=7.3, 7.6 Hz, 1H, H-5), 7.01 (t, *J*=7.6 Hz, 1H, H-6), 7.06 (d, *J*=7.3 Hz, 1H, H-4), 7.20–7.38 (m, 5H, C_6H_5). Found: m/z 307.2048. Calcd for $C_{20}H_{25}N_3$: M, 307.2048.

3.5. (S)-1-Methyl-2-(pyrrolidin-1-ylmethyl)indoline ***5***

(*S*)-1-[*N*-(Benzyloxycarbonyl)indoline-2-carbonyl]pyrrolidine **3a** (1.00 g, 2.8 mmol) in THF (10 ml) was slowly added to a THF (5 ml) suspension of lithium aluminum hydride (0.26 g, 6.8 mmol) at 0°C under an argon atmosphere. The reaction mixture was refluxed for 15 h, and saturated sodium sulfate solution was added to the reaction mixture. After removal of the inorganic material, the organic layer was concentrated in vacuo. The crude product was purified by column chromatography followed by bulb-to-bulb distillation to afford (*S*)-1-methyl-2-(pyrrolidin-1-ylmethyl)indoline **5** (0.45 g, 78%); bp 140°C (bath temperature)/0.3 mmHg (bulb-to-bulb distillation); $[\alpha]_D^{20}$ −80.0 (*c* 1.18, $CHCl_3$); IR (neat) ν: 2795, cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.70–1.90 (m, 4H, 2×H-3′, 2×H-4′), 2.48–2.66 (m, 6H, 2×H-2′, 2×H-5′, 1×C_2–CH_2N, 1×H-3), 2.80 (s, 3H, NCH_3), 2.89 (dd, *J*=4.5, 12.1 Hz, 1H, 1×C_2–CH_2N), 3.24 (dd, *J*=8.8, 15.7 Hz, 1H, 1×H-3), 3.42–3.55 (m, 1H, H-2), 6.46 (d, *J*=7.9 Hz, 1H, H-7), 6.65 (dt, *J*=1.0, 7.4 Hz, 1H, H-5), 6.99–7.11 (m, 2H, H-6, H-4). Found: m/z 217.1722. Calcd for $C_{14}H_{21}N_2$: M, 217.1705.

3.6. The enantioselective addition of diethylzinc to aldehydes catalyzed by ***1****: typical procedure (Table 1, entry 3)*

To a cyclohexane (6.0 ml) solution of benzaldehyde (159.2 mg, 1.5 mmol) and **1a** (45.5 mg, 0.225 mmol) was added a hexane (2.7 ml) solution of diethylzinc (2.7 mmol) at 0°C, and the reaction mixture was stirred at rt for 15 h. Saturated ammonium chloride solution (3 ml) and 2 N HCl (3 ml) were added to the reaction mixture, and the mixture was extracted with ether. The combined organic layers were washed with water and brine, and dried over anhydous sodium sulfate. The solvent was removed under reduced pressure and the resulting oily substance was purified by preparative TLC (silica gel, hexane:ether=2:1) to give 1-phenyl-1-propanol (181.2 mg, 89%). The alcohol was further purified by bulb-to-bulb distillation for the measurement of the specific rotation ($[\alpha]_D^{20}$ −44.1 (*c* 1.00, $CHCl_3$)). The ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel OD-H (25 cm×0.46 cm i.d.); eluent, 5% 2-propanol in hexane; flow rate, 0.5 ml/min; t_R, 14.9 min for minor peak, 16.5 min for major peak).

3.7. The enantioselective addition of diethylzinc to benzaldehyde catalyzed by the lithium salt of **1c**

To a cyclohexane (1.5 ml) solution of **1c** (52.1 mg, 0.225 mmol) was added a hexane solution (0.14 ml) of butyllithium (0.225 mmol) at 0°C and the reaction mixture was stirred at 0°C for 30 min. A cyclohexane (4.5 ml) solution of benzaldehyde (159.2 mg, 1.5 mmol) and a hexane (2.7 ml) solution of diethylzinc (2.7 mmol) were added to the reaction mixture successively at 0°C. The reaction mixture was stirred at 0°C for 15 h and worked up in the same manner as described above to give 1-phenyl-1-propanol (143.5 mg, 70%). The ee was determined by HPLC analysis using a Daicel Chiralcel OD-H column to be 88% ee.

3.8. The enantioselective addition of diethylzinc to benzaldehydes catalyzed by **5**

To a cyclohexane (6.0 ml) solution of benzaldehyde (159.2 mg, 1.5 mmol) and **5** (48.6 mg, 0.225 mmol) was added a hexane (2.7 ml) solution of diethylzinc (2.7 mmol) at 0°C. The reaction mixture was stirred at rt for 15 h and worked up in the same manner as described earlier, to give 1-phenyl-1-propanol (192.7 mg, 94%). The ee was determined by HPLC analysis using a Daicel Chiralcel OD-H column to be 7% ee.

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