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trans-(1*S*,2*S*)-1-Substituted-2-(*N*,*N*-dialkylamino)-1-indanol derivatives as chiral ligands in the catalytic enantioselective addition of diethylzinc to aldehydes

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Abstract—A series of optically active *trans*-(1*S*,2*S*)-1-substituted-2-(*N*,*N*-dialkylamino)-1-indanol derivatives **1**–**6** were synthesized and applied in the catalytic enantioselective addition of diethylzinc to aldehydes. The enantiomeric purity of the addition products increased considerably with increasing bulk of the substituents both on the nitrogen atom and the hydroxy-bearing carbon atom of the ligands. *sec*-Alcohols were obtained in good yields with enantiomeric excesses up to 93.1%.

1. Introduction

Carbon–carbon bond formation is a fundamental and indispensable method within organic chemistry and the development of enantioselective carbon–carbon bond forming processes is one of the most challenging tasks in the synthesis of enantiomerically enriched organic compounds. In particular, the catalytic enantioselective addition of dialkylzinc reagents to aldehydes has attracted much attention in recent years because of its potential for the efficient preparation of optically active secondary alcohols,[1] which are valuable structural units, being found in many natural products. Additionally, secondary alcohols can serve as useful synthetic intermediates for various other functionalities, e.g. halides, amines, ethers, esters etc.[2] The discovery that certain β-amino alcohols can promote the ethylation of benzaldehyde by diethylzinc[3] initiated a search for efficient chiral auxiliaries for this type of reaction since Oguni's first report in 1984[4] and a myriad of β-amino alcohols have been investigated as catalysts. Among them, derivatives of natural products such as ephedrine,[5] norephedrine,[6] camphor,[7] pinane,[8] and cinchona alkaloids[9] have attracted widespread attention. The catalytic abilities of these natural product derivatives have been probed mostly to study the effects of the substituents on the nitrogen atom[5–8,10] and the hydroxyl-bearing carbon atom of the ligand on the enantioselectivity of the addition reaction.[11] The mechanism of the process has been discussed for tertiary β-amino alcohols and it has been shown that the absolute configuration of the products correlate with the configuration of the hydroxyl-bearing stereocenter of the ligand.[12,13]

Chiral β-amino alcohols are common ligands in asymmetric synthesis as they are readily accessible in enantiomerically pure form in a few steps from natural α-amino acid precursors. Thus, the stereoselective addition of dialkylzinc reagents to aldehydes, catalyzed by chiral β-amino alcohols, has been extensively investigated. The addition of a suitable chiral β-amino alcohol to dialkylzinc compounds converts the relatively unreactive reagent into a reactive complex.[13] In this way, sterically congested β-amino-alcohols, such as DAIB and DPMPM, give excellent enantioselectivities.[1,13]

Amino indanol, which is another kind of sterically congested β-amino alcohol, has been widely applied in the asymmetric reduction of prochiral ketones to secondary alcohols,[14] but has rarely been used as a catalyst in the enantioselective addition of dialkylzinc to alde-

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hydes.[15] Herein, we describe syntheses of new optically active *trans*-(1*S*,2*S*)-1-substituted-2-(*N*,*N*-dialkylamino)-1-indanol derivatives. Some initial results on the catalytic activity of these chiral catalysts in the enantioselective addition of diethylzinc to aldehydes are also reported.

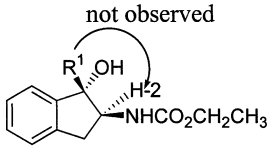
2. Results and discussion

2.1. Synthesis of optically active *trans*-(1*S*,2*S*)-1-substituted-2-(*N*,*N*-dialkylamino)-1-indanol derivatives 1–6

The synthesis of *trans*-(1*S*,2*S*)-1-substituted-2-(*N*,*N*-dialkylamino)-1-indanol derivatives **1–6** are summarized in Scheme 1. The L-phenylalanine was first protected as L-*N*-ethoxycarbonyl-phenylalanine with ethyl chloroformate in quantitative yield. The ethoxycarbonyl derivative was transformed to its acid chloride with PCl_5, followed by Friedel–Crafts cyclization to give (*S*)-2-[(ethoxycarbonyl)amino]-1-indanone **7**.[16] The key intermediate **7** was converted by Grignard reactions to the *trans*-(1*S*,2*S*)-1-substituted-2-(*N*-ethoxycarbonyl)amino-1-indanols **8–10**. Their configurations of the products were determined by two-dimensional NOESY experiments: no NOE interaction between C(2)H and R^1 was observed (Fig. 1), which indicates that C(2)H and R^1 are distanced from each other. Accordingly, the *trans*-(1*S*,2*S*)-configurations were deduced. *trans*-(1*S*,2*S*)-1-Substituted-2-(*N*-ethoxycarbonyl)amino-1-indanols **8–10** were then deprotected with KOH/ethanol solution to give **11–13**, followed by alkylation with iodoethane or 1-iodobutane to produce *trans*-(1*S*,2*S*)-1-substituted-2-(*N*,*N*-dialkylamino)-1-indanol derivatives **1–6**.

2.2. Enantioselective addition of diethylzinc to aldehydes catalyzed by *trans*-(1*S*,2*S*)-1-substituted-2-(*N*,*N*-dialkylamino)-1-indanol derivatives 1–6

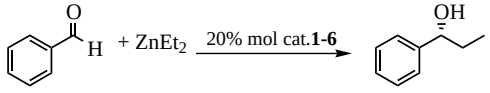
According to the general procedure (see Section 4), the catalysts **1–6** were tested in the enantioselective addition reaction by the addition of 2.0 equiv. of diethylzinc to benzaldehyde in the presence of 0.2 equiv. of the catalyst in toluene/hexane (1/4, v/v) at 0°C to compare their efficiency. The results are given in Table 1. As can be seen, all the reactions proceeded smoothly to give (*R*)-1-phenyl-1-propanol in good yields and with enantiomeric excesses ranging from 78.9 to 93.1%. Furthermore, the enantioselectivities of the reaction were very sensitive to the substituents on the chiral catalysts. Enhancement of the bulk of the substituents on the nitrogen-atom induced an increase in the enantioselectivity (entries 1 versus 4, or 2 versus 5, or 3 versus 6). The enantioselectivity of the alkylation also increased with increasing bulk of the substituents on the hydroxy-bearing carbon atom (entries 1–3 versus 4–6) and the chiral ligand **6**, which has bulky substituents on both the nitrogen atom and the hydroxy-bearing carbon atom, gave the best reactivity and enantioselectivity.[5,6]



8-10

Figure 1.

Table 1. The enantioselective addition of diethylzinc to benzaldehyde catalyzed by chiral *trans*-(1*S*,2*S*)-1-substituted-2-(*N*,*N*-dialkylamino)-1-indanol derivatives **1–6**[a]

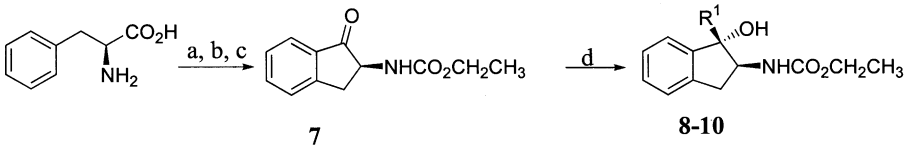


Entry	Catalyst	Yield (%)[b]	E.e. (%) (Config.)[c]
1	**1**	91	81.9 (*R*)
2	**2**	94	78.9 (*R*)
3	**3**	89	84.7 (*R*)
4	**4**	87	88.5 (*R*)
5	**5**	90	88.2 (*R*)
6	**6**	90	93.1 (*R*)

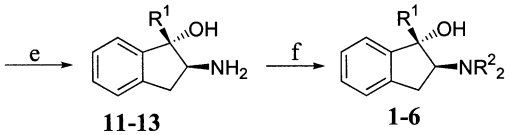
[a] The reactions were carried out in toluene/hexane (v/v 1/4) at 0°C with 20 mol% chiral catalysts, $ZnEt_2$/benzaldehyde = 10.0/5.0 (mmol).

[b] Based on isolated product.

[c] The e.e. values were determined by GC analysis and the configurations were determined by comparison of the specific rotation with that of the known compound.



7 **8-10**



11-13 **1-6**

1 R^1 = Me R^2 = Et
2 R^1 = Et R^2 = Et
3 R^1 = Ph R^2 = Et
4 R^1 = Me R^2 = *n*-Bu
5 R^1 = Et R^2 = *n*-Bu
6 R^1 = Ph R^2 = *n*-Bu

Scheme 1. *Reagents and conditions*: (a) CH_3CH_2OCOCl/MeOH; (b) PCl_5; (c) $AlCl_3$; (d) R^1MgX, ether; (e) KOH/C_2H_5OH; (f) R^2I, K_2CO_3.

In view of the above results, chiral ligand **6** was used as a catalyst in the enantioselective addition of diethylzinc to a family of aldehydes comprising both aromatic and aliphatic aldehydes and the results are shown in Table 2. It can be seen from the results that high enantioselectivities (>80%) were generally obtained for aromatic aldehydes (entries 1–9 and 11, 12) except for 4-pyridinecarboxaldehyde (entry 10), which gave much lower enantioselectivity. For this substrate, the nitrogen atom on the heterocyclic ring and its corresponding addition product, *sec*-alcohol, may promote the ethylation reaction of 4-pyridinecarboxaldehyde with diethylzinc. It then reduces the overall enantioselectivity. This is supported by the observation that (*R*)-1-phenyl-1-propanol underwent autoinduction in the addition of diethylzinc toward benzaldehyde in the presence of a catalytic amount of achiral amine.[17] These phenomena were also observed in the enantioselective addition of diethylzinc to the above substrate when catalyzed by chiral pyridylphenol[18] or brine derivatives.[10d] Moderately enantioselective addition reactions (45.4 ~ 58.2% e.e.) were observed for aliphatic aldehydes (entries 13–16).

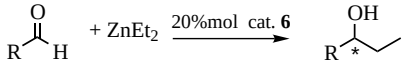
The chiral ligand-mediated addition of dialkylzinc to aldehyde is a well-studied reaction. Although knowledge of the actual active species are unclear, assuming the dinuclear Zn complex proposed in the product-forming transition state (TS) by Noyori,[13] the *anti*-configured 5/4/4-fused tricyclic transition model shown in Fig. 2 is suggested. Zinc monoalkoxide **14**, which is formed from the reaction of $ZnEt_2$ with ligand and does not ethylate benzaldehyde, is converted to the zinc monoalkoxide–diethylzinc complex **15** by diethylzinc. Coordination of the zinc atom with the oxygen or nitrogen atom would increase the nucleophilicity of the ethyl group of $ZnEt_2$ and the ethyl migration from the dizinc complex to benzaldehyde through transition state **16** would give a catalyst/product complex **17**. Regeneration of the catalyst **14** and liberation of the product takes place in a subsequent step.

The *anti*-5/4/4-fused tricyclic transition state **16**-Pro-*S* and **16**-Pro-*R* can be formed from **15** by transfer of the ethyl group on the Zn atom to benzaldehyde both from the *Si*-face and *Re*-face, respectively. In the transition state **16**-Pro-*S*, which leads to (*S*)-1-phenyl-1-propanol, the strong steric interaction between Et and Ph disfavors this structure, and R^1 enforces the repulsion. On the other hand, in the transition state **16**-Pro-*R*, which leads to (*R*)-1-phenyl-1-propanol, the steric interaction between Ph and Et is absent, is the favored structure. Therefore, in all cases, (*R*)-1-phenyl-1-propanol was produced. With the increasing of the bulkiness of R^1 and R^2, they enforce the repulsion among R^1, R^2, Ph, and the ethyl group on the Zn atom in **16**-Pro-*S*, and it gives a higher performance for **16**-Pro-*R* and results in a better stereochemical control. This accounts for the excellent performances of the chiral ligand **6** described above.

3. Conclusions

In conclusion, we have demonstrated that *trans*-(1*S*,2*S*)-1-substituted-2-(*N*,*N*-dialkylamino)-1-indanol derivatives **1**–**6**, which could be easily prepared from L-phenylalanine in several steps, are efficient chiral ligands in the enantioselective addition of diethylzinc to

Table 2. The enantioselective addition of diethylzinc to aldehydes catalyzed by ligand **6**[a]



Entry	Substrate	Yield (%)[b]	E.e. (%) (Config.)[c]
1	Benzaldehyde	90	93.1 (*R*)
2	*o*-Anisaldehyde	88	74.2 (*R*)
3	*p*-Anisaldehyde	91	89.7 (*R*)
4	*o*-Chlorobenzaldehyde	90	90.6 (*R*)
5	*p*-Chlorobenzaldehyde	90	86.2 (*R*)
6	*p*-Tolualdehyde	83	92.3 (*R*)
7	3,4-Dimethoxybenzaldehyde	96	83.0 (*R*)[d]
8	4-(Dimethylamino) benzaldehyde	94	76.4 (*R*)[d]
9	*p*-Morpholinobenzaldehyde	90	87.6 (*R*)[d]
10	4-Pyridinecarboxaldehyde	79	8.2 (*R*)[d]
11	1-Naphthaldehyde	91	86.7 (*R*)[d]
12	2-Naphthaldehyde	95	84.1 (*R*)[d]
13	*trans*-Cinnamaldehyde	93	45.4 (*R*)[d]
14	Dodecylaldehyde	80	55.8 (*R*)[e]
15	Nonylaldehyde	77	50.2 (*R*)[e]
16	Cyclohexanecarboxaldehyde	86	58.2 (*R*)[e]

[a] The reactions were carried out in toluene/hexane (1/4, v/v) at 0°C with 20 mol% chiral ligand **6**, $ZnEt_2$/aldehyde = 10.0/5.0 (mmol).
[b] Based on isolated product.
[c] Unless otherwise specified, the e.e. values were determined by GC analysis and the configurations were determined by comparison of the specific rotation with those of known compounds.
[d] The e.e. values were determined by HPLC.
[e] The e.e. values were determined by GC after acetylation.

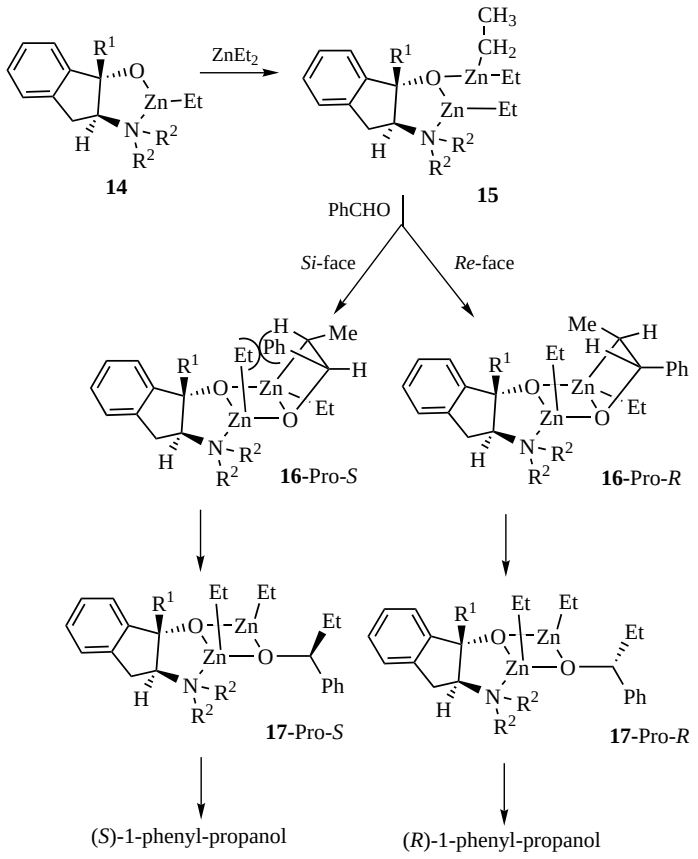


Figure 2.

aldehydes. The effects of the ligand structures on the enantioselectivity were also examined. The predominance of *sec*-alcohol products with *R*-configuration was explained by a mechanism involving the *anti*-5/4/4-fused tricyclic transition state **16**-Pro-*R*. The success of the chiral ligand **6** relied on the greater steric effects between R^1, R^2, Ph, and the ethyl group on zinc. This chiral ligand promoted the ethylation of aldehydes by diethylzinc with good enantioselectivities for a number of aromatic aldehydes and with reasonable enantioselectivities for aliphatic aldehydes. Further applications of these ligands in other catalytic asymmetric reactions are under investigation.

4. Experimental

4.1. General procedure

All reactions were carried out under Ar atmosphere. Melting points were taken on a Kofler melting apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were measured with a Bruker AM-400 NMR spectrometer with TMS as an internal reference. Electron ionization mass spectra were obtained on a Hewlett–Packard HP5988A mass spectrometer. Elemental analyses were performed on a Carlo-Erba-1106 elemental analyzer. Optical rotations were measured on a Jasco J-20C automatic polarimeter. Enantiomeric excess (e.e.) determination was carried out with a Chrompack CP-Chirasil-DEX CB capillary column on Varian CP-3380 GC instrument with FID as detector and nitrogen as carrier gas or with a Chiralcel-OD column on Varian SD-200 HPLC instrument with UV detector and hexane/2-propanol as eluent. All solvents used were dried by standard methods and aldehydes were purified using standard, published methods before use.

4.2. (*S*)-2-[(Ethoxycarbonyl)amino]-1-indanone 7

An ice-cooled solution of L-phenylalanine (0.2 g, 1.21 mmol) in 1N NaOH (10 mL) was treated with solid sodium carbonate (64 mg, 0.604 mmol) and ethyl chloroformate (0.12 mL, 1.26 mmol). Stirring was continued for 0.5 h with cooling and a further 0.5 h without cooling. The mixture was carefully acidified with concentrated HCl to pH 2∼3. The resultant solution was extracted with CH_2Cl_2 and the organic layer was washed with water, dried over anhydrous sodium sulfate, concentrated under reduced pressure to give (*S*)-*N*-(ethyoxycarbonyl)phenylalanine (0.28 g, 98% yield).

To an ice-cooled solution of (*S*)-*N*-(ethyoxycarbonyl)phenylalanine (0.30 g, 1.26 mmol) in ether (10 mL) was added solid PCl_5 (0.28 g, 1.34 mmol). Stirring was continued for 1 h with cooling and a further 0.5 h without cooling. After concentration of the mixture at 30°C, the residue was dissolved in CH_2Cl_2 (10 mL) and rapidly added dropwise to a suspension of $AlCl_3$ (0.54 g, 4.01 mmol) in CH_2Cl_2 (20 mL). Stirring was contin-

ued for 1–2 h after completion of the addition. The mixture was poured into ice-cold dilute HCl with vigorous stirring, which was continued for 1 h. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (acetone:dichloromethane:petroleum ether = 1:2:2) to give a white solid (0.17 g, 61% yield). Mp 131–132°C; $[\alpha]_D^{20} = +12.0$ (*c* 1.21, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): 1.26 (t, 3H, *J* = 6.9 Hz), 3.03 (dd, 1H, *J* = 5.5, 16.6 Hz), 3.70 (dd, 1H, *J* = 8.0, 16.6 Hz), 4.15 (q, 2H, *J* = 6.9 Hz), 4.40 (m, 1H), 5.4 (br, 1H), 7.27–7.87 (m, 4H). EIMS (*m*/*z*): 219 (M^+, 30), 191 (15), 174 (37), 146 (30), 130 (100), 91 (31), 77 (10).

4.3. *trans*-(1*S*,2*S*)-1-Substituted-2-[(*N*-ethoxycarbonyl)amino]-1-indanol 8–10: general procedure

To the appropriate Grignard reagent R^1MX (14 mmol) in ether (10 mL) was added dropwise a solution of **7** (1.0 g, 4.57 mmol) in ether (10 mL) with ice bath cooling. After the addition, the mixture was stirred overnight at rt. When TLC indicated that the reaction was finished, the mixture was quenched with saturated aqueous ammonium chloride solution. The phases were separated and aqueous phase was extracted with ether (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography to give *trans*-(1*S*,2*S*)-1-substituted-2-[(*N*-ethoxycarbonyl)amino]-1-indanol **8**–**10**.

4.3.1. *trans*-(1*S*,2*S*)-1-Methyl-2-[(*N*-ethoxycarbonyl)amino]-1-indanol 8. A colorless liquid was obtained (0.62 g, 57% yield) (ethyl acetate:petroleum ether = 1:4); $[\alpha]_D^{20} = -7.6$ (*c* 0.82, CH_3OH); ^1H NMR (400 MHz, acetone-d_6): 1.19 (t, 3H, *J* = 7.2 Hz), 1.27 (s, 3H), 2.60 (dd, 1H, *J* = 10.0, 15.1 Hz), 3.15 (dd, 1H, *J* = 8.0, 15.1 Hz), 4.10 (q, 2H, *J* = 7.2 Hz), 4.28 (dd, 1H, *J* = 8.0, 10.0 Hz), 5.54 (br, 2H), 7.10–7.70 (m, 4H). EIMS (*m*/*z*): 235 (M^+, 1), 217 (100), 189 (10), 146 (94), 130 (98), 119 (76), 91 (59), 77 (25).

4.3.2. *trans*-(1*S*,2*S*)-1-Ethyl-2-[(*N*-ethoxycarbonyl)amino]-1-indanol 9. A colorless solid was obtained (53% yield) (ethyl acetate:petroleum ether = 1:5). Mp 127–128°C; $[\alpha]_D^{20} = -9.7$ (*c* 0.99, CH_3OH); ^1H NMR (400 MHz, acetone-d_6): 0.87 (t, 3H, *J* = 7.3 Hz), 1.22 (t, 3H, *J* = 7.2 Hz), 1.48 (m, 1H), 1.79 (m, 1H), 2.49 (dd, 1H, *J* = 10.2, 15.6 Hz), 3.02 (dd, 1H, *J* = 8.0, 15.6 Hz), 4.06 (q, 2H, *J* = 7.2 Hz), 4.33 (dd, 1H, *J* = 8.0, 10.2 Hz), 7.17–7.71 (m, 4H). EIMS (*m*/*z*): 249 (M^+, 1) 231 (6), 220 (34), 192 (45), 174 (18), 146 (37), 130 (100), 120 (50), 91 (72).

4.3.3. *trans*-(1*S*,2*S*)-1-Phenyl-2-[(*N*-ethoxycarbonyl)amino]-1-indanol 10. A colorless solid was obtained (54% yield) (ethyl acetate:petroleum ether = 1:5). Mp 90–91°C; $[\alpha]_D^{20} = -122.0$ (*c* 0.81, CH_3OH); ^1H NMR (400 MHz, acetone-d_6): 1.09 (t, 3H, *J* = 7.2 Hz), 2.90 (dd, 1H, *J* = 10.1, 15.3 Hz), 3.26 (dd, 1H, *J* = 8.1, 15.3 Hz), 4.01 (q, 2H, *J* = 7.2 Hz), 4.55 (dd, 1H, *J* = 8.1, 10.1 Hz), 6.08 (br, 2H), 7.05–7.34 (m, 9H). EIMS (*m*/*z*): 297 (M^+, 1), 279 (7), 250 (1), 224 (1), 208 (100), 178 (17), 165 (10), 105 (19), 77 (28).

4.4. *trans*-(1*S*,2*S*)-1-Substituted-2-amino-1-indanol 11–13

To a solution of *trans*-(1*S*,2*S*)-1-substituted-2-[(*N*-ethoxycarbonyl)amino]-1-indanol **8**–**10** (0.85 mmol) in ethanol (5 mL), was added 2N potassium hydroxide solution (5 mL). The mixture was heated under reflux for 4 h under an argon atmosphere and then extracted with chloroform (3×20 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by flash chromatography to give *trans*-(1*S*,2*S*)-1-substituted-2-amino-1-indanol **11**–**13**.

4.4.1. *trans*-(1*S*,2*S*)-1-Methyl-2-amino-1-indanol 11. A white solid was obtained (95% yield) (ethyl acetate:methanol = 3:1). Mp 85–86°C; $[\alpha]_D^{20} = +22.5$ (*c* 0.60, CH_3OH); ^1H NMR (400 MHz, DMSO-d_6): 1.13 (s, 3H) 2.38 (dd, 1H, *J* = 9.6, 15.2 Hz), 2.95 (dd, 1H, *J* = 7.4, 15.2 Hz), 3.31 (dd, 1H, *J* = 7.4, 9.6 Hz), 7.11–7.27 (m, 4H). EIMS (*m*/*z*): 163 (M^+, 20), 145 (14), 119 (100), 103 (20), 91 (27), 77 (17).

4.4.2. *trans*-(1*S*,2*S*)-1-Ethyl-2-amino-1-indanol 12. A white solid was obtained (94% yield) (ethyl acetate:methanol = 3:1). Mp 83–84°C; $[\alpha]_D^{20} = +29.2$ (*c* 0.60, CH_3OH); ^1H NMR (400 MHz, DMSO-d_6): 0.86 (t, 3H, *J* = 7.3 Hz), 1.44 (dt, 1H, *J* = 7.3, 13.8 Hz), 1.66 (dt, 1H, *J* = 7.3, 13.8 Hz), 2.78 (dd, 1H, *J* = 9.9, 15.3 Hz), 3.10 (dd, 1H, *J* = 7.8, 15.3 Hz), 3.59 (dd, 1H, *J* = 7.8, 9.4 Hz), 7.23–7.26 (m, 4H). EIMS (*m*/*z*): 177 (M^+, 18), 148 (31), 131 (41), 119 (100), 91 (32), 77 (21).

4.4.3. *trans*-(1*S*,2*S*)-1-Phenyl-2-amino-1-indanol 13. A white solid was obtained (98% yield) (ethyl acetate:methanol = 3:1). Mp 92–94°C. $[\alpha]_D^{20} = +67.8$ (*c* 0.51, CH_3OH). ^1H NMR (400 MHz, DMSO-d_6): 2.38 (dd, 1H, *J* = 9.4, 15.6 Hz), 3.04 (dd, 1H, *J* = 7.3, 15.6 Hz), 3.58 (dd, 1H, *J* = 7.3, 9.4 Hz), 7.00–7.28 (m, 9H). EIMS (*m*/*z*): 225 (M^+, 4), 195 (100), 178 (18), 152 (7), 130 (15), 105 (11), 77 (27).

4.5. *trans*-(1*S*,2*S*)-1-Substituted-2-(*N*,*N*-dialkylamino)-1-indanol 1–6

To a solution of *trans*-(1*S*,2*S*)-1-substituted-2-amino-1-indanol **1**–**6** (1.27 mmol) and sodium carbonate (0.81 g, 7.6 mmol) in acetonitrile (10 mL) was added 1-iodobutane (0.61 mL, 7.6 mmol). After the reaction mixture was refluxed for 24 h, water (5 mL) was added. Then the reaction mixture was extracted with ethyl acetate (3×15 mL), and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by flash chromatography to give

trans-(1*S*,2*S*)-1-substituted-2-(*N*,*N*-dialkylamino)-1-indanol **1**–**6**.

4.5.1. *trans*-(1*S*,2*S*)-1-Methyl-2-(*N*,*N*-diethylamino)-1-indanol 1. A white solid was obtained (73% yield). Mp 63–64°C; $[\alpha]_D^{20}=+34.6$ (*c* 0.55, CH_3OH); ^1H NMR (400 MHz, DMSO-d_6): 1.00 (t, 6H, $J=7.2$ Hz), 1.27 (s, 3H), 2.67 (dd, 1H, $J=10.2$, 14.9 Hz), 2.76 (m, 2H), 2.94 (m, 3H), 3.24 (dd, 1H, $J=7.4$, 10.2 Hz), 7.12–7.29 (m, 4H); ^{13}C NMR (DMSO-d_6): 10.94, 23.32, 34.98, 43.84, 73.29, 82.92, 123.19, 124.95, 127.35, 127.98, 138.62, 151.24. EIMS (*m*/*z*): 219 (M^+, 1), 190 (1), 86 (100). Anal. calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.58; H, 9.60; N, 6.45%.

4.5.2. *trans*-(1*S*,2*S*)-1-Ethyl-2-(*N*,*N*-diethylamino)-1-indanol 2. A pale yellow liquid was obtained (78% yield); $[\alpha]_D^{20}=+35.8$ (*c* 0.53, CH_3OH); ^1H NMR (400 MHz, DMSO-d_6): 0.86–1.01 (m, 9H), 1.57 (m, 1H), 1.84 (m, 1H), 2.56 (dd, 1H, $J=9.8$, 14.6 Hz), 2.76 (m, 2H), 2.92 (m, 3H), 3.26 (dd, 1H, $J=7.2$, 9.8 Hz), 7.16–7.27 (m, 4H); ^{13}C NMR (DMSO-d_6): 8.01, 10.99, 28.04, 35.07, 44.02, 74.17, 85.14, 124.89, 125.08, 126.70, 128.04, 139.57, 148.87. EIMS (*m*/*z*): 233 (M^+, 1), 204 (1), 174 (1), 159 (1), 131 (3), 86 (100). Anal. calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.30; H, 9.81; N, 6.15%.

4.5.3. *trans*-(1*S*,2*S*)-1-Phenyl-2-(*N*,*N*-diethylamino)-1-indanol 3. A pale yellow liquid was obtained (85% yield); $[\alpha]_D^{20}=-31.6$ (*c* 0.49, CH_3OH); ^1H NMR (400 MHz, DMSO-d_6): 0.76 (t, 6H, $J=6.9$ Hz), 2.34 (m, 2H), 2.57 (m, 2H), 2.86 (dd, 1H, $J=10.8$, 15.4 Hz), 3.03 (dd, 1H, $J=7.2$, 15.4 Hz), 3.70 (dd, 1H, $J=7.2$, 10.8 Hz), 7.13–7.26 (m, 9H); ^{13}C NMR (DMSO-d_6): 12.35, 33.77, 44.43, 76.55, 86.53, 125.04, 125.25, 126.94, 127.78, 127.80, 127.85, 128.48, 140.63, 145.19, 149.83. EIMS (*m*/*z*): 281 (M^+, 2), 252 (2), 86 (100). Anal. calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.21; H, 8.10; N, 5.07%.

4.5.4. *trans*-(1*S*,2*S*)-1-Methyl-2-(*N*,*N*-dibutylamino)-1-indanol 4. A pale yellow liquid was obtained (43% yield); $[\alpha]_D^{20}=+26.9$ (*c* 0.64, CH_3OH); ^1H NMR (400 MHz, DMSO-d_6): 0.91 (t, 6H, $J=7.4$ Hz), 1.27 (m, 7H), 1.44 (m, 4H), 2.67 (m, 2H), 2.80 (m, 3H), 2.93 (dd, 1H, $J=7.2$, 14.9 Hz), 3.28 (dd, 1H, $J=7.2$, 9.0 Hz), 7.12–7.34 (m, 4H); ^{13}C NMR (DMSO-d_6): 14.46, 21.34, 23.32, 29.00, 34.68, 51.38, 74.11, 82.92, 123.21, 125.02, 127.38, 128.03, 138.91, 151.28. EIMS (*m*/*z*): 275 (M^+, 5), 232 (26), 214 (4), 186 (2), 142 (100), 91 (11). Anal. calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.55; H, 10.53; N, 5.19%.

4.5.5. *trans*-(1*S*,2*S*)-1-Ethyl-2-(*N*,*N*-dibutylamino)-1-indanol 5. A pale yield liquid was obtained (44% yield); $[\alpha]_D^{20}=+41.4$ (*c* 0.72, CH_3OH); ^1H NMR (400 MHz, DMSO-d_6): 0.84–0.93 (m, 9H), 1.30 (m, 4H), 1.45–1.59 (m, 5H), 1.88 (m, 1H), 2.66 (m, 2H), 2.81 (m, 3H), 2.94 (dd, 1H, $J=7.3$, 14.9 Hz), 3.31 (dd, 1H, $J=7.3$, 10.1 Hz), 7.14–7.26 (m, 4H); ^{13}C NMR (DMSO-d_6): 8.01, 14.48, 21.35, 27.98, 28.89, 34.90, 51.42, 74.87, 85.11, 124.83, 125.05, 126.67, 127.99, 130.64, 148.86. EIMS (*m*/*z*): 289 (M^+, 2), 246 (9), 142 (100), 91 (9). Anal. calcd for $C_{19}H_{31}NO$: C, 78.84; H, 10.79; N, 4.84. Found: C, 78.69; H, 10.67; N, 4.60%.

4.5.6. *trans*-(1*S*,2*S*)-1-Phenyl-2-(*N*,*N*-dibutylamino)-1-indanol 6. A pale yellow liquid was obtained (53% yield); $[\alpha]_D^{20}=-21.2$ (*c* 0.64, CH_3OH). ^1H NMR (400 MHz, DMSO-d_6): 0.76 (t, 6H, $J=7.3$ Hz), 1.07 (m, 4H), 1.24 (m, 4H), 2.21 (m, 2H), 2.41 (m, 2H), 2.91 (dd, 1H, $J=10.1$, 15.5 Hz), 2.99 (dd, 1H, $J=7.6$ 15.5 Hz), 3.72 (dd, 1H, $J=7.6$, 10.1 Hz), 7.15–7.27 (m, 9H); ^{13}C NMR (DMSO-d_6): 14.37, 21.07, 29.23, 30.48, 51.79, 76.93, 86.20, 125.06, 125.28, 127.00, 127.79, 127.98, 128.47, 140.77, 145.22, 149.73. EIMS (*m*/*z*): 337 (M^+, 2), 319 (1), 294 (4), 264 (2), 209 (5), 142 (100), 77 (8). Anal. calcd for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15. Found: C, 81.77, H, 9.11; N, 4.03%.

4.6. General procedure for asymmetric addition of diethylzinc to aldehydes

To a solution of catalyst **1** (2.0 mmol) in toluene (1 mL) and hexane (4 mL) at 0°C was added a 1.0 M solution of diethylzinc in hexane (10.0 mL, 10.0 mmol). After stirring for 30 min at 0°C, freshly distilled benzaldehyde (5.0 mmol) was added. The reaction mixture was stirred at 0°C for 12 h. After addition of 1N HCl (10 mL), the phases were separated. The water layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. After purification by flash chromatography (ethyl acetate:petroleum ether 1:5), the enantiomeric excess was determined by GC.

References

1. For review, see: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49; (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833; (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994, pp. 255–297.
2. (a) Soai, K.; Watanabe, M.; Koyano, M. *J. Chem. Soc., Chem. Commun.* **1989**, 534; (b) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264; (c) Wilken, J.; Winter, M.; Stahl, I.; Martens, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1067; (d) Okamoto, M.; Tabe, M.; Fujii, T.; Tanaka, T. *Tetrahedron: Asymmetry* **1995**, *6*, 767; (e) Langer, F.; Schwink, L.; Devasagayaaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229; (f) Furstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130; (g) Lutjens, H.; Knochel, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1161; (h) Soai, K.; Hirose, Y.; Niwa, S. *J. Fluorine Chem.* **1992**, *59*, 5; (i) Soai, K.; Hirose, Y.; Sakata, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1734.
3. Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.
4. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823.
5. (a) Chaloner, P. A.; Perera, S. A. R. *Tetrahedron Lett.* **1987**, *28*, 3013; (b) Chaloner, P. A.; Langadianous, E. *Tetrahedron Lett.* **1990**, *31*, 5185; (c) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5233; (d) Corey, E.

J.; Hannon, F. J. *Tetrahedron Lett*. **1987**, *28*, 5237; (e) Soai, K.; Nishi, M.; Ito, Y. *Chem. Lett*. **1987**, 2405; (f) Itsuno, S.; Frechet, J. M. J. *J. Org. Chem*. **1987**, *52*, 4140.
6. Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc., Chem. Commun*. **1987**, 1690.
7. (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc*. **1986**, *108*, 6071; (b) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc*. **1989**, *111*, 4028.
8. Cherng, Y.-J.; Fang, J.-M.; Lu, T.-J. *J. Org. Chem*. **1999**, *64*, 3207.
9. Smaardijk, A. A.; Wynberg, H. *J. Org. Chem*. **1987**, *52*, 135.
10. (a) Kawanami, Y.; Mitsuie, T.; Miki, M.; Sakamoto, T.; Nishitani, K. *Tetrahedron* **2000**, *56*, 175; (b) Trentmann, W.; Mehler, T.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2033; (c) Wilken, J.; Kossenjans, M.; Groger, H.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2007; (d) Dai, W. M.; Zhu, H. J.; Hao, X. J. *Tetrahedron: Asymmetry* **2000**, *11*, 2315; (e) Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem*. **1997**, *62*, 4970.
11. (a) Xu, Q.; Wang, G.; Pan, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 381; (b) Xu, Q.; Wang, H.; Pan, X.; Chan, A. S. C.; Yang, T. K. *Tetrahedron Lett*. **2001**, *42*, 6171.
12. Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc*. **1987**, *109*, 7111.
13. (a) Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605; (b) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128; (c) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc*. **1998**, *120*, 9800.
14. (a) Ghosh, A. K.; Fidanze, S.; Senanayake, C. H. *Synthesis* **1998**, 937; (b) Hong, Y.; Gao, Y.; Nie, X.; Zepp, C. M. *Tetrahedron Lett*. **1994**, *35*, 6631; (c) Hett, R.; Senanayake, C. H.; Wald, S. A. *Tetrahedron Lett*. **1998**, *39*, 1705; (d) Kaptein, B.; Elsenberg, H.; Minnaard, A. J.; Broxterman, Q. B.; Hulshof, L. A.; Koek, J.; Vries, T. R. *Tetrahedron: Asymmetry* **1999**, *10*, 1413; (e) Sibi, M. P.; Cook, G. R.; Liu, P. *Tetrahedron Lett*. **1999**, *40*, 2477; (f) Jones, S.; Atherton, J. C. C. C. *Tetrahedron: Asymmetry* **2000**, *11*, 4543.
15. (a) Simone, B. D.; Savoia, D.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron: Asymmetry* **1995**, *6*, 301; (b) Sola, L.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1559.
16. (a) McClure, D. E.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem*. **1981**, *46*, 2431; (b) McClure, D. E.; Lumma, P. K.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem*. **1983**, *48*, 2675.
17. (a) Li, S. J.; Jiang, Y. Z.; Mi, A. Q.; Yang, G. *J. Chem. Soc., Chem. Commun*. **1993**, 885; (b) Ding, K. L.; Ishii, A.; Mikami, K. *Angew. Chem., Int. Ed. Engl*. **1999**, *38*, 497.
18. Zhang, H. C.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Org. Chem*. **1996**, *61*, 8002.