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Enantioselective addition of diethylzinc to aldehydes catalyzed by chiral amino alcohols. Substituent effect and nonlinear effect

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Abstract—A new series of chiral β-amino alcohols derived from (*S*)-leucine, valine, and phenylalanine have been synthesized and evaluated as chiral catalysts for the enantioselective addition of diethylzinc to aldehydes. The β-amino alcohol (**1c**) possessing a isobutyl substituent and two phenethyl substituents on the carbinol carbon atom was found to be an efficient and optimal ligand to catalyze the diethylzinc addition with high enantioselectivity (up to 97% ee) and good yield. Furthermore, a strong (+)-nonlinear effect (asymmetric amplification) was observed in the enantioselective catalysis, providing high level of enantioselection (93% ee) by use of ligand **1c** in 20% ee.

1. Introduction

In order to synthesize optically active secondary alcohols, the enantioselective additions of dialkylzincs to aldehydes in the presence of catalytic amounts of chiral ligand have been extensively investigated and chiral β-amino alcohols have been shown to be efficient chiral ligands.[1] Among them 3-*exo*-(dimethylamino)isoborneol[2] and (*S*)-prolinol derivatives[3] have been reported to catalyze the diethylzinc addition to aromatic aldehydes with excellent enantioselectivity. For the addition to aliphatic aldehydes only proceeds with moderate enantioselectivity. However, *N*,*N*-di-*n*-butylnorephedrine,[4] 2-piperidino-1,1,2-triphenylethanol,[5] and *N*-phenylfluorenyl β-amino alcohols[6] have been reported to enhance the enantioselectivity for the addition to aliphatic aldehydes. Recently, we also reported that β-amino alcohols derived from (*S*)-leucine and bearing two flexible and larger phenethyl groups, compared to a phenyl and *n*-butyl group, afforded excellent enantioselection[7] and revealed that the substituent (R^2) on the carbinol carbon atom of β-amino alcohols might play an important role in controlling the enantioselection via a five-membered ethylzinc aminoalkoxide complex as shown in Fig. 1. Therefore, we anticipated that further systematic ligand modifications could lead to realizing the stereoselection and developing a rational design of chiral ligands. In this paper, we report the full detail of the influence of the substituent of a new series β-amino alcohols derived from (*S*)-leucine, valine, and phenylalanine and the nonlinear effect in the catalytic asymmetric induction (Scheme 1).

2. Results and discussion

β-Amino alcohols **1a**–**d**, **2a**–**c**, and **3a**–**c** were readily

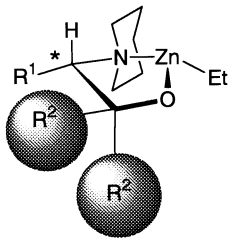
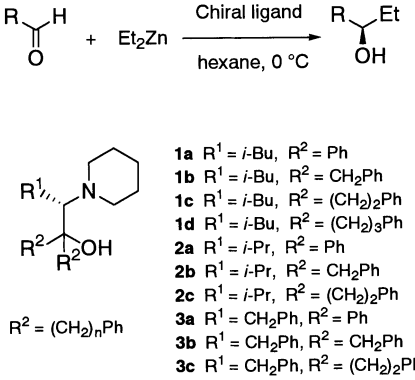


Figure 1.



Scheme 1.

Keywords: catalysis; addition reaction; asymmetric induction; amino alcohols; nonlinear effect.

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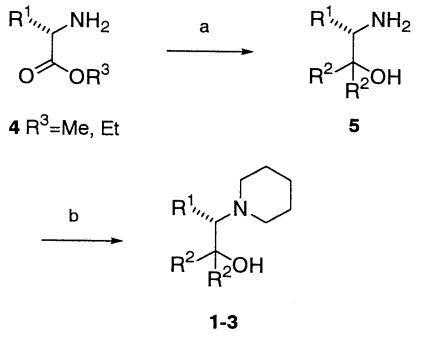

Scheme 2. (a) R^2MgBr, THF (28–47%); (b) $I(CH_2)_5I$, K_2CO_3, CH_3CN, reflux (49–74%).

prepared via a two-step sequence from commercially available (*S*)-leucine ethyl ester hydrochloride, (*S*)-valine methyl ester hydrochloride, and (*S*)-phenylalanine methyl ester hydrochloride, respectively, according to the previously described procedure.[7] Addition of different carbon chain of Grignard reagents to the amino acid esters followed by alkylation with 1,5-diiodopentane and potassium carbonate afforded the corresponding β-amino alcohols without a loss of enantiopurity as shown in Scheme 2.

First, we examined the enantioselective addition of diethylzinc to benzaldehyde and *n*-hexylaldehyde to heptanal, which were used as a model reaction, in the presence of 10 mol% of the chiral amino alcohol ligands **1a–d**, **2a–c**, and **3a–c** in hexane at 0°C. These results are summarized in Table 1.

Comparing the amino alcohol ligands derived from (*S*)-leucine, ligand **1c** with a phenethyl substituent (R^2) was the optimal ligand to provide higher enantioselectivity than that of ligands **1a**, **1b**, and **1d** with a phenyl, benzyl, and longer 3-phenylpropyl group, respectively (entries 1–4). The similar tendencies were observed in the addition to *n*-hexylaldehyde and ligand **1c** showed the highest enantioselectivity (entries 5–8) as shown in Fig. 2. Furthermore,

Table 1. Enantioselective addition of diethylzinc to aldehydes using various ligands **1a–d**, **2a–c**, and **3a–c**

Entry	Ligand	RCHO	Yield (%)	Ee (%)[a]	Config.[b]
1	**1a**	Ph	88	85	*R*
2	**1b**		68	84	*R*
3	**1c**		90	97	*R*
4	**1d**		56	92	*R*
5	**1a**	n-C_6H_{13}	76	78[c]	*R*
6	**1b**		66	84[c]	*R*
7	**1c**		81	88[c]	*R*
8	**1d**		58	76[c]	*R*
9	**2a**	Ph	63	82	*R*
10	**2b**		59	82	*R*
11	**2c**		86	97	*R*
12	**2c**	n-C_6H_{13}	68	86[c]	*R*
13	**3a**	Ph	64	82	*R*
14	**3b**		77	67	*R*
15	**3c**		69	96	*R*
16	**3c**	n-C_6H_{13}	64	84[c]	*R*

[a] Determined by HPLC analysis using DAICEL Chiralcel OB (hexane/*i*-PrOH 98:2).
[b] The absolute configurations of the resulting alcohols were determined to be (*R*) by comparison of the specific rotations (Ref. 3).
[c] Determined by HPLC analysis using DAICEL Chiralcel OD (hexane/*i*-PrOH 800:1) after benzoylation.

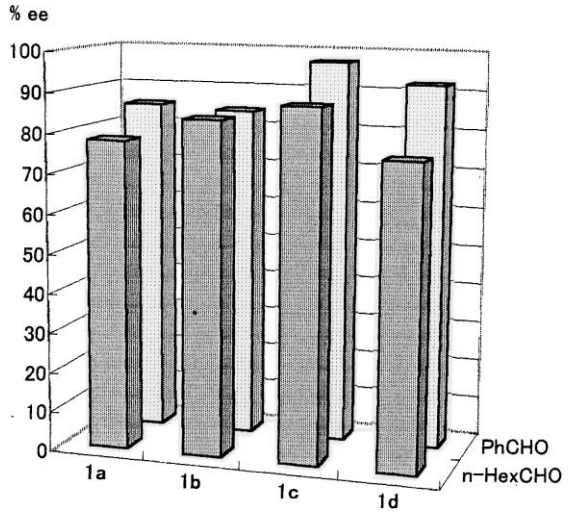

Figure 2. Substituent effect (R^2).

the ligand **2a–c** derived from (*S*)-valine (entries 9–11) and the ligand **3a–c** derived from (*S*)-phenylalanine (entries 13–15) showed the similar substitution effect (Fig. 3). Thus, the chiral ligand **1c** with two flexible phenethyl substituent was found to be the most efficient and optimal ligand, giving (*R*)-1-phenyl-1-propanol with 97% ee and (*R*)-3-nonanol with 88% ee. These results suggest that the influence of amino acid residue (R^1) is negligible and the flexibility of the substituent (R^2) at the carbinol carbon atom could play a critical role in the enantioselection of the addition reaction.

Since Kagan et al. reported nonlinear effect in asymmetric synthesis,[8] it has been established that nonlinear effect provides useful information on the reaction mechanism such as the structure and aggregation of active species involved in asymmetric reaction, especially in enantioselective catalysis.[9] A strong (+)-nonlinear effect (asymmetric amplification) as observed in the addition to aldehydes catalyzed by DAIB[10] and 1-piperidino-3,3-dimethyl-2-butanol (PDB)[11] is particularly valuable for generating products

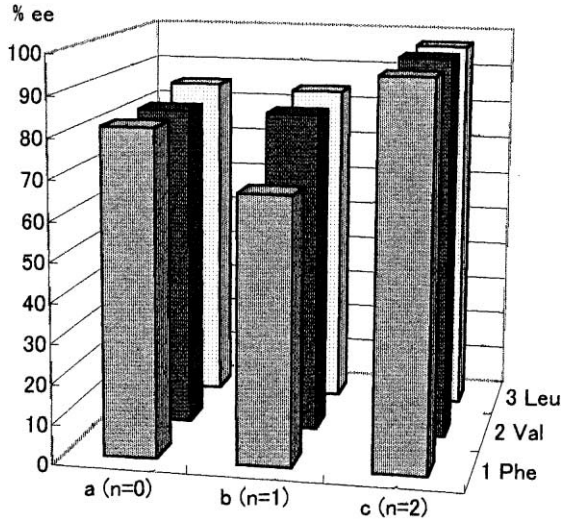

Figure 3. Substituent effect (R^1).

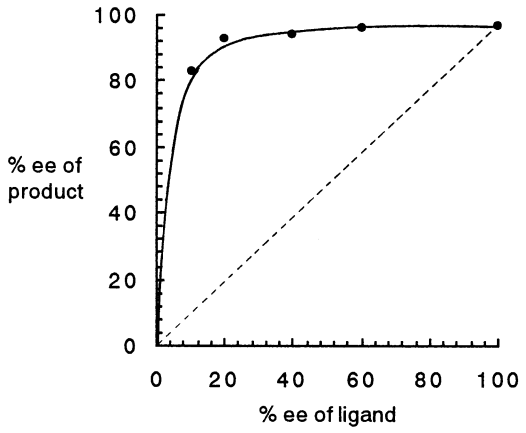

Figure 4. Nonlinear effect.

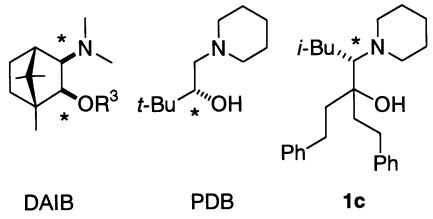

Figure 5.

with high ee from ligands with low ee. Therefore, we investigated the nonlinear effect in this enantioselective catalysis next. The similar asymmetric amplification, (+)-nonlinear effect, was observed in the addition using enatiomerically impure ligands **1c** that was prepared via mixing with (*R*)-**1c** as shown in Fig. 4, for example, providing high level of enantioselection (93% ee) by use of ligand **1c** in 20% ee. This phenomenon could be attributed to the stability of heterochiral (*R*)·(*S*)-dimer as in the mechanism proposed by Noyori et al.[12] Also discussion of the enantioselections are based on the carbinol stereocenter of DAIB and PDB, but ligand **1c** has only one chiral center at amino acid residue as shown in Fig. 5. These facts, therefore, suggest that the steric interaction between the isobutyl group on the chiral center and one of two phenethyl groups should render the achiral carbinol atom of ligand **1c** conformationally chiral center.

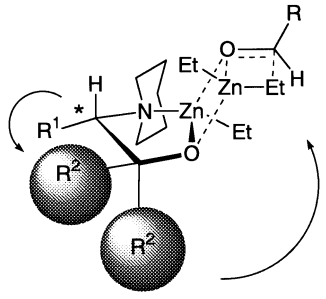

Figure 6. Transition state model with chiral relay system.

Although the actual active species are unclear, the addition reaction catalyzed by chiral amino alcohol ligand **1c** might proceed through the similar transition state model as proposed by Noyori et al. (Fig. 6).[12] This model is partially supported by MM2 minimized conformation of ligand **1c** itself, which clearly shows that one of the phenethyl groups locates in a pseudo-axial position as shown in Fig. 7. Therefore, the aldehyde might be attacked on its *re*-face at the upper side of the dinuclear Zn complex to produce the corresponding (*R*)-secondary alcohol. It is noteworthy that conformationally flexible moiety could serve to relay and amplify the stereochemical information of the relatively remote stereogenic center via the chiral relay system, ensuring efficient stereocontrol of approaching aldehydes and diethylzinc.

3. Conclusion

Systematic study of a new series of chiral β-amino alcohols derived from (*S*)-leucine, valine, and phenylalanine showed that ligand **1c** possessing two phenethyl substituents was an efficient and optimal ligand to catalyze the enantioselective addition of diethylzinc to aromatic and aliphatic aldehydes with high enantioselectivity. Furthermore, (+)-nonlinear effect, asymmetric amplification, was observed in the addition catalyzed by ligand **1c**. These results suggest that the achiral carbinol atom with two phenethyl substituents should be conformationally restricted by the proximity of the chiral amino acid residue and this chiral relay system could be a factor in the efficiency of this ligand. Thus, this ligand design bearing chiral relay system would lead to developing further efficient chiral ligands.

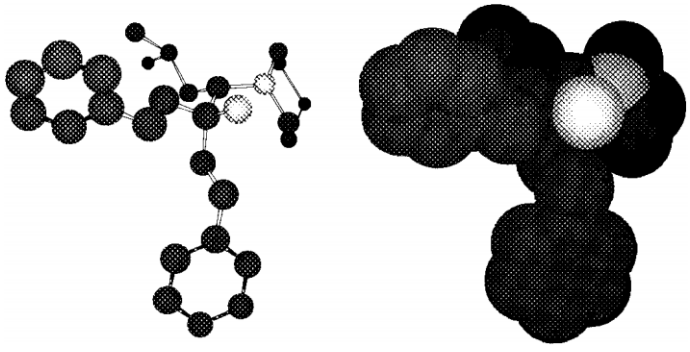

Figure 7. MM2 minimized conformation of ligand **1c**.

4. Experimental

4.1. Data for compounds

IR spectra were determined using a Shimadzu IR-435 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 90 and 23 MHz using a JEOL JNM-EX90 spectrometer, respectively. All NMR spectra were taken in $CDCl_3$ solution with TMS as the internal standard. Mass spectra were recorded on a JEOL JMS-SX102A mass spectrometer. Optical rotations were determined on a Yanagimoto OR-50 polarimeter. The HPLC analysis was carried out using a DAICEL Chiralcel OB or OD column (0.46×25 cm^2) with a Shimadzu LC-6A. THF was distilled from sodium benzophenone ketyl. TLC was carried out on Merck glass plates precoated with silica gel 60F-254 (0.25 mm) and column chromatography was performed using Merck 23–400 mesh silica gel. Diethylzinc was purchased from the Aldrich Chemical Co. (*S*)-Leucine ethyl ester hydrochloride, (*S*)-valine methyl ester hydrochloride, (*S*)-phenylalanine methyl ester hydrochloride, and the other reagents were obtained from Tokyo Kasei Kogyo Co. or Wako Pure Chemical Ind. Chiral β-amino alcohols were prepared according to the previously described procedure for **1a** and **1c**.[7]

4.1.1. (*S*)-8-Methyl-1-phenyl-4-(3-phenylpropyl)-5-piperidino-4-octanol 1d. (*S*)-Leucine ethyl ester hydrochloride (587 mg, 3.0 mmol) was suspended in Et_2O (15 ml) and neutralized with 10% aqueous NaOH solution. The aqueous solution was separated and extracted with Et_2O (3×5 ml) and the ethereal solution was dried over $MgSO_4$. The solution of the resulting amino acid ester in THF (1.5 ml) was slowly added to $Ph(CH_2)_3MgBr$ that was prepared from Mg (292 mg, 12 mmol) and $Ph(CH_2)_3Br$ (1.8 ml, 12 mmol) in THF (7.2 ml) and the mixture was stirred for 18 h at room temperature. An aqueous saturated NH_4Cl solution was added to the reaction mixture and the THF solution was decanted. The aqueous solution was twice washed with ethyl acetate. After evaporation of the combined organic solution, the residue was flash chromatographed (ethyl acetate/MeOH, 6:1) to give the amino alcohol (352 mg, 33%). To the amino alcohol in acetonitrile (10 ml), 1,5-diiodopentane (178 μl, 1.2 mmol) and K_2CO_3 (331 mg, 2.4 mmol) were added and the mixture was refluxed for 19 h. After filtration of the reaction mixture and evaporation, the residue was dissolved with CH_2Cl_2 and dried over $MgSO_4$. The residue was flash chromatographed (hexane/ethyl acetate, 10:1) to give a colorless oil **1d** (325 mg, 77%); $[\alpha]_D^{25}$=+0.2 (*c* 4.35, $CHCl_3$); IR (neat) 3300, 3020, 3000, 2920, 2840, 2800, 1605, 1490, 1450, 1160, 1095, 1030, 984, 745, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 0.91 (d, 6H, *J*=6.3 Hz), 1.08–2.13 (m, 17H), 2.13–2.94 (m, 9H), 4.38 (s, 1H), 6.95–7.48 (m, 10H); ^{13}C NMR ($CDCl_3$) d 142.7, 128.4, 128.2, 125.5, 74.1, 67.6, 36.6, 36.2, 35.9, 35.5, 27.2, 26.6, 25.2, 24.7, 24.3, 21.3. EI HRMS $C_{29}H_{43}NO$ (M^+) 421.3347. Found 421.3349.

4.1.2. (*S*)-2-Benzyl-5-methyl-1-phenyl-3-piperidino-2-hexanol 1b. Yield 33 and 49%: $[\alpha]_D^{25}$=+31.3 (*c* 3.77, $CHCl_3$); IR (neat) 3280, 3080, 3020, 2920, 2850, 2820, 1605, 1490, 1450, 1390, 1160, 1090, 1030, 980, 740, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 0.64 (d, 3H, *J*=6.4 Hz), 0.96 (d, 3H, *J*=6.4 Hz), 1.11–2.03 (m, 9H), 2.14–2.98 (m, 9H), 5.15 (s, 1H), 6.90–7.67 (m, 10H); ^{13}C NMR ($CDCl_3$) d 138.3, 138.1, 130.9, 130.6, 128.2, 127.6, 127.3, 125.7, 74.7, 65.9, 43.7, 41.9, 36.0, 26.3, 24.6, 20.8. EI HRMS $C_{25}H_{35}NO$ (M^+) 365.2721. Found 365.2725.

4.1.3. (*S*)-3-Methyl-1,1-diphenyl-2-piperidino-1-butanol 2a. Yield 34 and 59%: $[\alpha]_D^{25}$=+86.9 (*c* 3.71, $CHCl_3$); IR (neat) 3350, 3050, 3020, 2910, 2840, 1730, 1600, 1490, 1445, 995, 745, 695, 615 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 0.60 (d, 3H, *J*=6.6 Hz), 1.10 (d, 3H, *J*=6.2 Hz), 1.15–1.85 (m,7H), 1.90–2.78 (m,4H), 3.00 (d, 1H, *J*=10.8 Hz), 6.23 (s, 1H), 7.12–7.94 (m, 10H); ^{13}C NMR ($CDCl_3$) d 146.2, 142.9, 128.0, 127.6, 127.5, 126.9, 126.8, 81.8, 78.0, 52.4, 29.2, 27.2, 24.6, 23.5, 23.4. EI HRMS $C_{22}H_{29}NO$ (M^+) 323.2251. Found 323.2257.

4.1.4. (*S*)-2-Benzyl-4-methyl-1-phenyl-3-piperidino-2-pentanol 2b. Yield 32 and 74%: $[\alpha]_D^{25}$=+47.6 (*c* 3.47, $CHCl_3$); IR (neat) 3395, 3080, 3060, 3020, 2920, 2840, 1735, 1595, 1490, 1450, 1235, 1085, 745, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 0.55–1.74 (m, 7H), 1.00 (d, 3H, *J*=6.0 Hz), 1.26 (d, 3H, *J*=5.4 Hz), 1.83–3.08 (m, 9H), 6.30 (S, 1H), 6.97–7.78 (m, 10H); ^{13}C NMR ($CDCl_3$) d 139.1, 138.7, 131.0, 127.6, 127.4, 125.8, 125.5, 73.7, 73.5, 51.9, 44.3, 44.2, 28.3, 27.1, 24.6, 23.6, 23.1. EI HRMS $C_{24}H_{33}NO$ (M^+) 351.2564. Found 35.2569.

4.1.5. (*S*)-5-Methyl-1-phenyl-3-(2-phenylethyl)-4-piperodino-3-hexanol 2c. Yield 47 and 56%: $[\alpha]_D^{25}$=+14.9 (*c* 4.37, $CHCl_3$); IR (neat) 3400, 3080, 3050, 3020, 2930, 2850, 1735, 1600, 1490, 1445, 1385, 1085, 735, 695, 630 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 1.08 (d, 6H, *J*=6.2 Hz), 1.40–3.16 (m, 20H), 5.67 (s, 1H), 6.98–7.55 (m, 10H); ^{13}C NMR ($CDCl_3$) d 143.7, 143.2, 128.4, 128.3, 128.2, 125.5, 125.4, 75.2, 72.7, 52.9, 40.1, 39.8, 30.5, 30.0, 28.3, 27.3, 24.7, 23.9, 22.6. EI HRMS $C_{26}H_{37}NO$ (M^+) 379.2877. Found 379.2881.

4.1.6. (*S*)-1,1,3-Triphenyl-2-piperidino-1-propanol 3a. Yield 29 and 69%: $[\alpha]_D^{25}$=+10.8 (*c* 7.61, $CHCl_3$); IR (neat) 3420, 3060, 3020, 2920, 2840, 1725, 1700, 1655, 1595, 1490, 1445, 1270, 1150, 1015, 725, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 0.98–2.55 (m, 10H), 2.72 (dd, 1H, *J*=11.6, 14.7 Hz), 3.15 (dd, 1H, *J*=2.4, 14.7 Hz), 3.90 (dd, 1H, *J*=2.5, 11.6 Hz), 6.35 (s, 1H), 7.02–7.78 (m, 15H); ^{13}C NMR ($CDCl_3$) d 145.6, 144.4, 140.2, 128.9, 128.3, 128.0, 127.8, 127.5, 127.2, 127.1, 126.6, 126.1, 77.5, 74.1, 52.9, 34.1, 26.9, 24.2. EI HRMS $C_{26}H_{29}NO$ (M^+) 371.2251. Found 371.2252.

4.1.7. (*S*)-2-Benzyl-1,4-diphenyl-3-piperidino-2-butanol 3b. Yield 35 and 70%: mp 101.5°C; $[\alpha]_D^{25}$=+9.8 (*c* 12.61, $CHCl_3$); IR (KBr) 3360, 3120, 3090, 3030, 2940, 2840, 1595, 1490, 1450, 1385, 1085, 1030, 748, 740, 720, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 1.02–1.65 (m, 6H), 2.06–3.08 (m, 11H), 5.05 (s, 1H), 6.91–7.60 (m, 15H); ^{13}C NMR ($CDCl_3$) d 140.0, 139.2, 139.0, 130.9, 130.6, 129.0, 128.0, 127.7, 126.0, 125.9, 74.9, 70.0, 53.2, 44.1, 42.3, 32.2, 27.0, 24.2. EI HR MS $C_{28}H_{33}NO$ (M^+) 431.2462. Found 431.2467.

4.1.8. (*S*)-1,5-Diphenyl-3-(2-phenylethyl)-2-piperidino-3-pentanol 3c. Yield 28 and 61%: $[\alpha]_D^{25}$=+29.7 (*c* 1.45,

$CHCl_3$); IR (neat) 3400, 3040, 3010, 2920, 2840, 1605, 1490, 1450, 1240, 1090, 1030, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) d 1.13–2.33 (m, 10H), 2.33–3.27 (m, 12H), 6.94–7.49 (m, 15H); ^{13}C NMR ($CDCl_3$) d 143.4, 142.9, 140.7, 129.1, 129.0, 128.4, 128.3, 126.2, 126.1, 125.7, 125.6, 73.7, 71.4, 53.5, 44.5, 39.8, 38.5, 32.0, 30.0, 27.1, 24.4. EI HRMS $C_{30}H_{37}NO$ (M^+) 427.2877. Found 427.2881.

4.1.9. Typical procedure for enantioselective addition of diethylzinc to aldehyde: (*R*)-1-phenyl-1-propanol. To a solution of **2c** (38.0 mg, 0.1 mmol, 10 mol%) in hexane (2.2 ml) was added benzaldehyde (101 μl, 1.0 mmol) under an argon atmosphere and the resulting solution was stirred at room temperature for 20 min. Diethylzinc (1.0 M solution in hexane, 2.2 ml, 2.2 mmol) was added to the solution at 0°C and the mixture was stirred for 12 h. After being quenched with aqueous saturated NH_4Cl solution, the mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (hexane/ethyl acetate 4:1) to give (*R*)-1-phenyl-1-propanol (117.7 mg, 86%) and the recovered **2c** (27.1 mg, 71%). The ee was determined to be 97% by HPLC analysis using a DAICEL Chiralcel OB column (hexane/*i*-PrOH 98:2, flow rate: 0.5 ml/min). For 3-nonanol, after 4-nitrobenzoylation, OD column (hexane/*i*-PrOH 800:1, flow rate: 0.5 ml/min).

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