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New Chiral Ligands Derived from (*S*)-Leucine for the Enantioselective Addition of Diethylzinc to Aldehydes

Yasuhiro Kawanami,[a,*] Tomoko Mitsuie,[b] Misuzu Miki,[b] Takanobu Sakamoto[b] and Kazumi Nishitani[b]

[a]*Department of Biochemistry and Food Science, Faculty of Agriculture, Kagawa University, Miki-cho, Kagawa 761-0795, Japan*
[b]*Department of Chemistry, Faculty of Education, Kagawa University, Takamatsu, Kagawa 760-8522, Japan*

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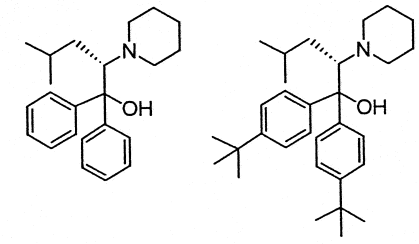
Abstract—A new series of chiral β-amino alcohols derived from (*S*)-leucine has been synthesized. The amino alcohol possessing a piperidine ring and a phenethyl group on the carbinol carbon atom was found to be an efficient ligand to catalyze the enantioselective addition of diethylzinc to aromatic (up to 97% ee) and aliphatic (up to 95% ee) aldehydes.

Introduction

The development of chiral ligands for catalytic asymmetric synthesis has been exceedingly important in modern synthetic chemistry.[1] Among them, chiral β-amino alcohols have been shown to be efficient chiral ligands for a variety of asymmetric reactions, in particular, the enantioselective addition of dialkylzincs to aldehydes since the discovery by Oguni.[2] Excellent enantioselectivity for the addition to aromatic aldehydes has been achieved using 3-*exo*-(dimethylamino)isoborneol[3] and (*S*)-prolinol derivatives,[4] but the addition reaction with aliphatic aldehydes only proceeds with moderate enantioselectivity. However, *N*,*N*-dialkyl-norephedrine[5] and recently, β-amino alcohols derived from (*S*)-valine[6] or (*S*)-tyrosine,[7] have been reported to enhance the enantioselectivity for the addition to aliphatic aldehydes. All these ligands possess an *n*-butyl substituent on the nitrogen and/or the carbinol carbon atom and we anticipated that further ligand modifications could lead to developing a rational design of chiral ligands for the reaction with aliphatic aldehydes. In this paper, we report the studies of the synthesis of new amino alcohols derived from (*S*)-leucine and their use as chiral ligands for the enantioselective addition of diethylzinc to aldehydes.[8]

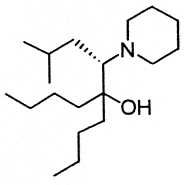
Results and Discussion

The ligands **1a**–**d** were prepared from commercially available (*S*)-leucine ethyl ester hydrochloride as follows: addition of various Grignard reagents to the (*S*)-leucine ethyl ester (34–47%) and alkylation with 1,5-diiodopentane in acetonitrile at reflux in the presence of potassium carbonate (51–73%). In this case, the dialkylation with alkyl halide was unsuccessful and afforded the monoalkylated product in moderate yield.

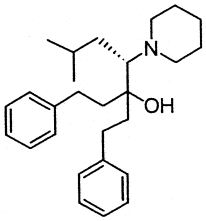


1a

1b



1c



1d

We first examined the enantioselective addition of diethylzinc to benzaldehyde as a test substrate with 10 mol% of the chiral ligands **1a**–**d**. These results are summarized in Table 1.

It should be noted that the ligand **1c** with an *n*-butyl group provided higher enantioselectivity than the ligands **1a** and **1b** with a relatively larger phenyl or 4-*t*-butylphenyl group

Keywords: chiral ligands; enantioselective addition; (*S*)-leucine.
* Corresponding author. E-mail: kawanami@ag.kagawa-u.ac.jp

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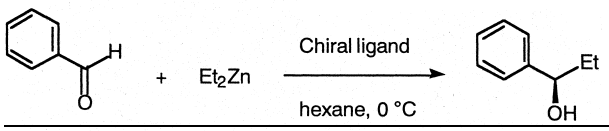
Table 1. Enantioselective addition of diethylzinc to benzaldehyde using various ligands **1a–d**



Entry	Ligand	Yield (%)	Ee (%)[a]
1	**1a**	88	85
2	**1b**	76	80
3	**1c**	86	94
4	**1d**	91	97

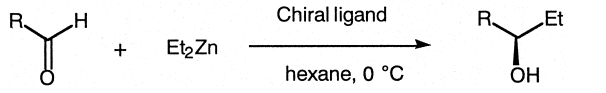
[a] Determined by HPLC analysis using DAICEL Chiralcel OB (hexane/*i*-PrOH 98:2). The absolute configurations of the resulting alcohols were determined to be (*R*) by comparison of the specific rotations (Ref. 5).

(entries 1–3) as well as the amino alcohol derived from (*S*)-valine.[6] Furthermore, the chiral ligand **1d** with a flexible and more bulky phenethyl group[9] was found to be the most efficient ligand. Thus ligand **1d** catalyzed the addition of diethylzinc to benzaldehyde in hexane at 0°C to give (*R*)-1-phenyl-1-propanol with 97% ee in 90% yield. These results suggest that the substituent at the carbinol carbon atom plays a critical role in the enantioselection of the addition reaction.

Next, the enantioselective additions of diethylzinc to various aromatic and aliphatic aldehydes using chiral ligand **1d** were examined and these results are summarized in Table 2. The catalytic diethylzinc addition to an aldehyde possessing an electron-withdrawing group in the *para* position of the aromatic ring proceeded with higher enantioselectivity than the addition to an aldehyde with an electron-donating group (entries 2 and 3), probably due to an electronic effect.[10] The addition reaction with 2-naphthylaldehyde showed high enantioselectivity that was comparable to that of benzaldehyde (entry 4). Most importantly, the addition of diethylzinc to aliphatic straight-chain and branched aldehydes proceeded with good to excellent enantioselectivity (85–95% ee).

Although the actual active species are unclear, assuming the

Table 2. Enantioselective addition of diethylzinc to various aldehydes using ligand **1d**



Entry	Aldehyde/R	Yield (%)	Ee (%)[a]	Configuration[b]
1	Ph	91	97	*R*
2	4-ClPh	76	96	*R*
3	4-MePh	87	89	*R*
4	2-Naphthyl	77	97	*R*
5	*n*-C_6H_{13}	81	88[c]	*R*
6	*n*-C_8H_{17}	88	85[d]	*R*
7	*i*-C_4H_9	64	88[d]	*R*
8	*c*-C_6H_{11}	72	95[d]	*R*

[a] Determined by HPLC analysis using DAICEL Chiralcel OB (hexane/*i*-PrOH 98:2).
[b] Determined by comparison of specific rotations (Refs. 3,5).
[c] Determined by HPLC analysis using DAICEL Chiralpak AD (hexane/*i*-PrOH 200:1) after 4-nitrobenzoylation.
[d] Determined by HPLC analysis using DAICEL Chiralpak OD (hexane/*i*-PrOH 200:1) after benzoylation.

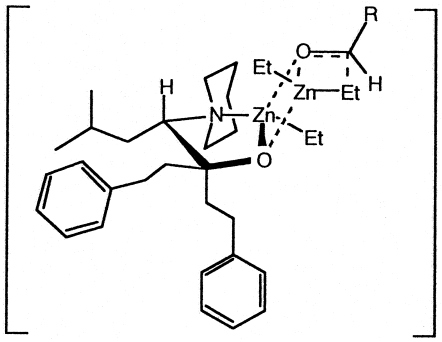


Figure 1. Transition state model.

dinuclear Zn complexes proposed by Noyori,[11] the transition state model shown in Fig. 1 is suggested. The addition reaction catalyzed by chiral amino alcohol ligand **1d** might proceed through the transition state model, in which one of the phenethyl groups should locate in a *pseudo*-axial position and, 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 this chiral ligand design is conceptually in agreement with that of the chiral relay auxiliary,[12] the *N*-protected 5-phenylmorpholin-2-one, where configurationally flexible moieties are employed to relay and amplify the stereochemical information of the relatively remote stereogenic centers via the chiral relay networks, ensuring efficient stereocontrol in the alkylation (1,3-asymmetric induction). Furthermore, the introduction of a flexible and larger phenethyl group, compared to the phenyl and *n*-butyl groups, should cause an efficient steric hindrance with aliphatic aldehydes and, therefore, enhance the enantioselectivity.

In conclusion, we have demonstrated that a new chiral amino alcohol derived from (*S*)-leucine, which possesses a piperidine ring and a phenethyl group, catalyzed the enantioselective addition of diethylzinc to aromatic and aliphatic aldehydes with high enantioselectivity. Thus, this strategy using chiral relay networks would lead to developing further efficient chiral ligands.

Experimental

IR spectra were determined using a Shimadzu IR-435 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 90 MHz 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. Optical rotations were determined on a Yanagimoto OR-50 polarimeter. The HPLC analysis was carried out using a DAICEL Chiralcel OB, OD, or AD 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 230–400 mesh silica gel. Diethylzinc was purchased from the Aldrich Chemical Co. (*S*)-Leucine ethyl ester hydrochloride and the other reagents were obtained from Tokyo Kasei Kogyo Co. or Wako Pure Chemical Ind.

(*S*)-4-Methyl-1,1-diphenyl-2-piperidino-1-pentanol 1a. (*S*)-Leucine ethyl ester hydrochloride (391 mg, 2.0 mmol) was suspended in Et_2O (10 ml) and neutralized with 10% aqueous NaOH solution. The aqueous solution was separated and extracted with Et_2O (2×5 ml) and the ethereal solution was dried over $MgSO_4$. The solution of the resulting amino-acid ester in THF (1 ml) was slowly added to PhMgBr (2M solution in THF, 4 ml, 8.0 mmol) and the mixture was stirred for 12 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 (hexane/ethyl acetate, 1:1) to give the amino alcohol (242 mg, 45%); ^{1}H NMR δ 0.86 (d, 3H, J=6.4 Hz), 0.88 (d, 3H, J=6.2 Hz), 0.95–1.45 (m, 3H), 1.96 (br s, 1H), 3.96 (dd, 1H, J=3.0, 9.1 Hz), 6.95–7.70 (m, 10H). To the amino alcohol in acetonitrile (9 ml), 1,5-diiodopentane (132 μl, 0.9 mmol) and K_2CO_3 (248 mg, 1.8 mmol) were added, and the mixture was refluxed for 24 h. After filtration of the reaction mixture and evaporation, the residue was dissolved in CH_2Cl_2 and dried over $MgSO_4$. The residue was flash chromatographed (hexane/ethyl acetate, 20:1) to give a colorless oil **1a** (221 mg, 73%): $[\alpha]_D^{25}$ −28.0 (c 2.93, $CHCl_3$); IR (neat) 3380, 3070, 3030, 2920, 2860, 1720, 1660, 1495, 1450, 750, 705 cm^{-1}; ^{1}H NMR δ 0.87 (d, 3H, J=6.2 Hz), 1.07 (d, 3H, J=6.4 Hz), 1.17–1.90 (m, 9H), 2.20–2.66 (m, 4H), 3.51 (dd, 1H, J=4.6, 9.2 Hz), 4.90 (s, 1H), 6.95–7.60 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 145.8, 144.7, 128.0, 127.9, 127.7, 127.0, 126.9, 126.5, 77.4, 69.1, 52.8, 37.9, 27.1, 26.3, 24.6, 24.3, 21.1. Anal. Calcd for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15%. Found: C, 81.72; H, 9.29; N, 4.11%.

(*S*)-4-Methyl-1,1-bis(4-*t*-butylphenyl)-2-piperidino-1-pentanol 1b. Prepared according to a previously described procedure, 34 and 51%: $[\alpha]_D^{25}$ −27.1 (c 1.29, $CHCl_3$); IR (neat) 3250, 3080, 2950, 2850, 2800, 1655, 1605, 1508, 1460, 1360, 1265, 1165, 1100, 1015, 820, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.86 (d, 3H, J=6.2 Hz), 1.06 (d, 3H, J=5.9 Hz), 1.14–1.74 (m, 27H), 2.15–2.65 (m, 4H), 3.50 (dd, 1H, J=4.6, 9.2 Hz), 6.20 (br s, 1H), 7.02–7.50 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 149.6, 149.1, 142.9, 141.6, 127.6, 127.4, 124.7, 123.6, 77.0, 69.1, 52.8, 37.8, 34.3, 31.4, 31.3, 31.1, 27.1, 26.4, 24.6, 24.4, 21.1. Anal. Calcd for $C_{31}H_{47}NO$: C, 82.79; H, 10.53; N, 3.11%. Found: C, 82.65; H, 10.64; N, 3.02%.

(*S*)-5-Butyl-2-methyl-4-piperidino-5-nonanol 1c. Prepared according to a previously described procedure, 35 and 61%: $[\alpha]_D^{25}$ +4.80 (c 2.93, $CHCl_3$); IR (neat) 3400, 2920, 2860, 1482, 1380, 1162, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 6H, J=6.7 Hz), 0.96 (d, 6H, J=6.7 Hz), 1.05–2.07 (m, 21H), 2.35–3.04 (m, 5H), 4.40 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 74.2, 67.7, 36.6, 35.6, 36.1, 27.4, 26.7, 25.8, 25.5, 24.9, 24.4, 23.9, 23.6, 21.3. Anal. Calcd for $C_{19}H_{39}NO$: C, 76.70; H, 13.21; N, 4.71%. Found: C, 76.62; H, 13.32; N, 4.62%.

(*S*)-6-Methyl-3-(2-phenylethyl)-1-phenyl-4-piperidino-3-heptanol 1d. Prepared according to a previously described procedure, 47 and 71%: $[\alpha]_D^{25}$ +11.1 (c 1.9, $CHCl_3$); IR (neat) 3360, 3060, 3020, 2920, 1710, 1600, 1495, 1452, 748, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3H, J=6.2 Hz), 1.01 (d, 3H, J=4.8 Hz), 1.10–2.24 (m, 13H), 2.32–3.08 (m, 9H), 4.74 (s, 1H), 6.87–7.46 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 143.5, 143.0, 128.3, 125.5, 125.4, 77.2, 73.5, 67.2, 39.3, 38.1, 35.9, 30.0, 29.8, 27.2, 26.5, 24.6, 24.2. Anal. Calcd for $C_{27}H_{39}NO$: C, 82.39; H, 9.99; N, 3.56%. Found: C, 82.23; H, 9.85; N, 3.44%.

Typical procedure for enantioselective addition of diethylzinc to aldehyde: (*R*)-1-phenyl-1-propanol. To a solution of **1d** (197 mg, 0.5 mmol, 10 mol%) in hexane (10 ml) was added benzaldehyde (0.51 ml, 5 mmol) under an argon atmosphere and the resulting solution was stirred at room temperature. After 20 min, diethylzinc (1.0M solution in hexane, 10 ml, 10 mmol) was added to the mixture at 0°C and 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 (618 mg, 91%) and the recovered **1d** (189 mg, 96%). 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^{-1}). For 1-(4-chlorophenyl)-1-propanol, 1-(4-methylphenyl)-1-propanol and 1-(2-naphthyl)-1-propanol, OB column (hexane/*i*-PrOH 98:2, flow rate: 0.5 ml min^{-1}). For 3-undecanol, 5-methyl-3-hexanol, and 1-cyclohexyl-1-propanol, after benzoylation, OD column (hexane/*i*-PrOH 200:1, flow rate: 0.3 ml min^{-1}). For 3-nonanol, after 4-nitrobenzoylation, AD column (hexane/*i*-PrOH 200:1, flow rate: 1.0 ml min^{-1}).

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