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Enantioselective Addition of Diethylzinc to Aldehydes by Chiral Oxazolidine–Titanium Complex

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Abstract: A series of chiral oxazolidines derived from (1*R*, 2*S*)-cis-1-amino-2-indanol was found to be effective in promoting the asymmetric addition of diethylzinc to aldehydes. Among the ligands developed, it was found that ligand **1b** in the presence of $Ti(O^iPr)_4$ yielded the highest enantioselectivities when it was applied in the catalytic asymmetric addition of diethylzinc to aldehydes (up to 91% *ee*).

Keywords: Asymmetric alkynylation, enantioselectivity oxazolidine, secondary alcohol.

INTRODUCTION

Chiral sec-alcohols are important and versatile building blocks for many natural products and drugs [1-3]. One of the most useful methods for the asymmetric preparation of sec-alcohols is the enantioselective addition of dialkylzinc reagent to aldehydes in the presence of chiral ligands [4]. A wide variety of chiral catalysts, such as amino alcohols [5-10], diamines [11-14], disulfonamides [15-19] and diols [20-27] have been reported. Although so many chiral ligands have been used to catalyze the reaction with good to excellent selectivity, it is still desirable to develop new chiral ligands which are greatly needed to probe how the chiral catalysts act on the reaction and how to design new types of chiral ligands more successfully. (1*R*, 2*S*)-cis-1-amino-2-indanol has a special structure which has attracted much attention. However, among the ligands developed, only a few chiral ligands derived from (1*R*, 2*S*)-cis-1-amino-2-indanol were found to be effective in promoting the asymmetric addition of diethylzinc to aldehydes [28]. In the long run, we aim to synthesize the ligands which are easily prepared in short pathway from readily available starting materials and to apply them in asymmetric transition processes [29-31]. With the interest in oxazolidine catalysts, we have designed and synthesized chiral ligands derived from (1*R*, 2*S*)-cis-1-amino-2-indanol and applied them in the asymmetric alkynylzinc addition reactions [29]. Herein, we reported the enantioselective addition of dialkylzinc reagents to aldehydes in the presence of those ligands.

RESULTS AND DISCUSSION

Ligands **1a-1g** were synthesized *via* the reaction of (1*R*, 2*S*)-cis-1-amino-2-indanol and the aldehydes in one step with quantitative yields. With ligands **1a-1g** (Fig. **1**) in hand, we examined the use of each in the ethylation of benzaldehyde. As the results shown in Figure **2**, we found that ligand **1b** gave the best result with 70% yield and 55% *ee*, respectively. Although ligand **1g** gave the highest *ee*, which may be due to the presence of the chelating group of CN of the ligand, it is not suitable to choose it as the ligand to catalyze the reaction because the product is hard to separate from the ligand. In this case, we chose ligand **1b** for our further studies.

Then the effects of the reaction conditions, such as the choice of solvents, the amount of ligand **1b**, the reaction temperature and the amount of $Ti(O^iPr)_4$ were investigated. The results are shown in Table **1**. At room temperature, the best *ee* was obtained in hexane with 10 mmol % ligand (Table **1**, entry 5). Decreasing the amount of the ligand **1b** to 5 mmol % gave only 52 % *ee* of the product (Table **1**, entry 6) and increasing the amount of ligand to 30 mol % improved the selectivity only slightly (Table **1**, entry 8). Lowering reaction temperatures did not improve the enantioselectivities (Table **1**, entries 9-10). Addition of appropriate $Ti(O^iPr)_4$ to the reaction provided a better effective catalytic system. When the reaction was carried out in hexane at room temperature with a reagent ratio of Et_2Zn– benzaldehyde–ligand–$Ti(O^iPr)_4$ = 4 : 1 : 0.1 : 0.25, the highest *ee* of the product was obtained (Table **1**, entry 12).

Under the optimized conditions (Table **1**, entry 12), the scope of the reactions catalyzed by **1b** was investigated (Scheme **1**). As shown by the results summarized in Table **2**, moderate to good enantioselectivities were obtained for most of the active aromatic aldehydes. Substituents of the aldehydes have important effects on the enantioselectivity. Those containing electron-withdrawing groups at the *para* positions gave better *ee*s than those containing electron-donating ones (Table **2**, entries 1-9). Substituents at the *ortho*- position of aldehydes gave poorer *ee* than benzaldehyde (Table **2**, entries 6-8 and 10). The cyano derivative gave the highest *ee* (91%) in this series which may be due to the presence of the

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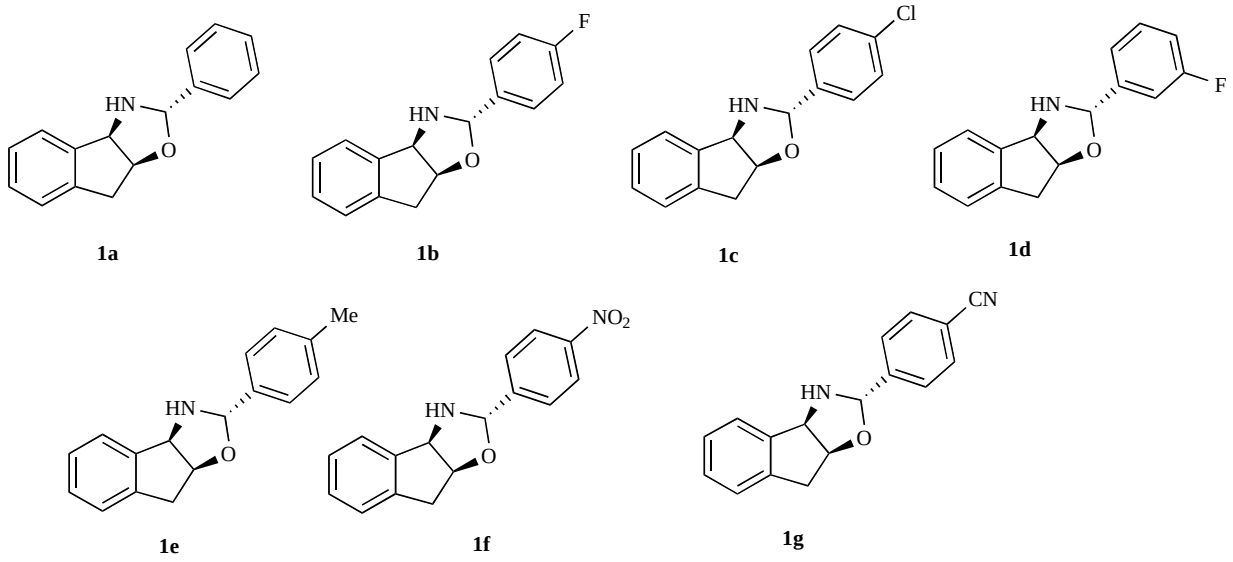


Fig. (1). Ligands evaluated in this paper.

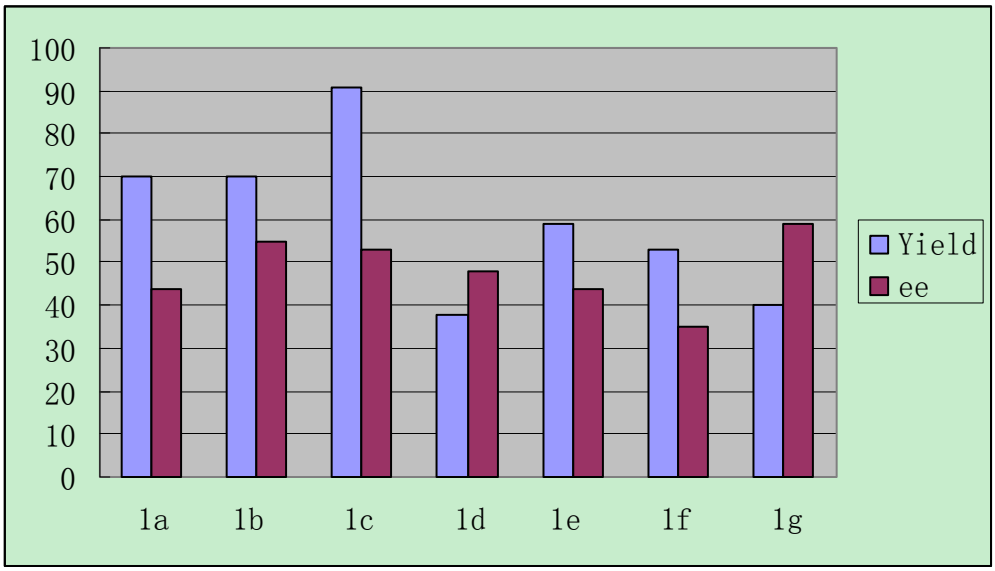


Fig. (2). Screening of ligands.

Table 1. Screening of the Reaction Conditions[a].

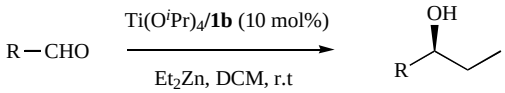
Entry	Ligand (mol%)	$Ti(O^iPr)_4$/Ligand	Solvent	Yield (%)[b]	*ee* (%)[c]
1	10	-	Et_2O	52	24
2	10	-	DCM	16	29
3	10	-	THF	64	31
4	10	-	DMF	18	0
5	10	-	Hexane	60	58
6	5	-	Hexane	38	52
7	20	-	Hexane	51	55
8	30	-	Hexane	52	61

Table 1. contd….

Entry	Ligand (mol%)	$Ti(O^iPr)_4$/Ligand	Solvent	Yield (%)[b]	*ee* (%)[c]
9[d]	30	-	Hexane	27	37
	30	-	Hexane	18	41
11	10	0.125	Hexane	57	59
12	**10**	**0.25**	**Hexane**	**63**	**62**
13	10	1.0	Hexane	58	59
14	10	2.0	Hexane	60	31
15	10	3.0	Hexane	62	11
16	10	4.0	Hexane	54	6
17	10	5.0	Hexane	74	6
18	10	6.0	Hexane	59	4

[a] The reaction conditions: benzaldehyde (0.5 mmol), Et_2Zn (2.0 ml), **1b** (0.05 mmol), Solvent (1.0 ml), room temperature, 24 h.
[b] Isolated yield.
[c] The *ee* was determined by Chiral HPLC: Daicel CHIRALPAD OD-H column (IPA : hexane = 3 : 97), flow: 0.5 mL/min, 30 °C, Retention time: t_{major} = 24.90 min, t_{minor} = 21.35 min and the absolute configuration of the product is *R* [32].
[d] The reaction was carried out at 0 °C.
[e] The reaction was carried out at -25 °C.

chelating group of CN (Table **2**, entry 5). Moderate *ee* (60%) can also be obtained with aliphatic aldehyde (Table **2**, entry 12).



Scheme 1. Scopes of the reaction.

In summary, ligand **1b** which is readily prepared in one step from commercially available starting materials, showed good catalytic activities (63-95%) and enantioselectivities (up to 91%) in the asymmetric addition reactions of diethylzinc to various aldehydes in the presence of $Ti(O^iPr)_4$. The results of this paper would help to reveal the relationship between ligand structure and *ee* values of the products. Further investigation on the applications of these ligands for other asymmetric reactions is underway.

EXPERIMENTAL

All manipulations were carried out under an argon atmosphere in dried and degassed solvents. Diethylzinc was

Table 2. Scopes of the Reaction[a].

Entry	R	Yield (%)[b]	*Ee* (%)[c]
1	4-Cl-C_6H_4	78	63
2	4-Br-C_6H_4	75	67
3	4-I-C_6H_4	71	73
4	4-OMe-C_6H_4	72	17
5	4-CN-C_6H_4	87	91
6	2-Me-3-Me-C_6H_3	75	31
7	2-OMe-3-OMe-C_6H_3	77	27
8	2-OMe-C_6H_4	72	28
9	3-F-C_6H_4	65	60
10	C_6H_5	63	62
11	2-naphthyl	95	67
12	Ph-CH_2-CH_2	64	60

[a] The reaction conditions: aldehydes (0.5 mmol), Et_2Zn (2.0 ml), **1b** (0.05 mmol), Solvent (1.0 ml), $Ti(O^iPr)_4$ (0.0125 mmol), room temperature, 24 h.
[b] Isolated yield after column chromatography.
[c] Determinated by Chiral HPLC: Daicel CHIRALPAD AD-H or OD-H; the absolute configuration of the product is *R* by comparing with the literatures or based on comparison of the elution order of HPLC analysis with those reported analogs [32, 33].

purchased from Aldrich (St. Louis, MO). The reactions were monitored by thin layer chromatography (TLC). NMR spectra were measured in $CDCl_3$ on a Varian-Inova-400 NMR spectrometer with TMS as an internal reference. Optical rotations were measured with a HORIBA SEPA-200 high sensitivity polarimeter. Chiral HPLC analyses were carried out on an Agilent 1100 instrument. Enantiomeric excess (*ee*) determination was carried out using a chiral AD-H column (4.6×250 mm) or OD-H column (4.6×250 mm) (Solvent, hexane/isopropanol) at 25 °C. UV detection, 254 nm. MS were recorded on a Bruker Micro-TOF-QII spectrometer using the ESI method. Melting points were determined using a standard melting point apparatus (XT-5 Type) and uncorrected.

General Experimental Procedure

A solution of ligand **1b** (0.05 mmol) was dissolved in dry hexane (2 ml) under Ar in a schlenk tube. Then diethylzinc (2 mL, 1 M in hexane, 2.0 mmol) and $Ti(O^iPr)_4$ (0.0125 mmol) was added separately *via* a syringe. The reaction was stirred at room temperature for 2 h. Then the aldehyde (0.5 mmol) was added and the reaction mixture was stirred for 24 h. The reaction was quenched with 1 M HCl (5 mL). The mixture was extracted with ethyl acetate (EtOAc) (3 × 15 ml). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel H, EtOAc: Petroleum ether = 1: 6) to give the pure product.

SPECTRAL DATA

Synthesis and the X-Ray crystal structure of ligand **1a** have been reported by us [29]. The other ligands are new compounds. All of the chiral propanol derivatives are known compounds.

Ligand **1a**: White crystal. mp. 69–70 °C; $[\alpha]_D^{25}$ = + 82.8 (*c* 1.02, *abs*. EtOH); dr. 2.89:1 (determined by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58–7.07 (m, 9H), 5.12–5.07 (m, 2H), 4.81 (d, *J* = 4.4 Hz, 1H), 3.24–3.17 (m, 2H), 2.53 (s, 1H); IR (cm^{-1}) : 3280, 1026, 895, 756; MS [ESI] [M^+] found (expected): 237.1165 (237.1154).

Ligand **1b**: White crystal. mp. 95–97 °C; $[\alpha]_D^{25}$ = + 127.5 (*c* 0.51, acetone); dr. 2.44:1 (determined by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.49 (m, 1H), 7.48–7.42 (m, 2H), 7.31–7.27 (m, 2H), 7.25–7.24 (m, 1H), 7.03 (t, *J* = 8.4 Hz, 2H), 5.10–5.08 (m, 2H), 4.95–4.92 (m, 1H), 3.32–3.16 (m, 2H), 2.50 (1s, 1H); IR (cm^{-1}) : 3300, 1604, 1509, 1439, 1221; MS [ESI] [M^+] found (expected): 278.0972 (278.0957).

Ligand **1c**: White crystal. mp. 118–120 °C; $[\alpha]_D^{25}$ = + 89.4 (*c* 2.11, acetone); dr. 3.03:1 (determined by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, *J* = 8.4 Hz, 1H), 7.41–7.38 (m, 2H), 7.35–7.28 (m, 4H), 7.23–7.21 (m, 1H), 5.08–5.07 (m, 2H), 4.93–4.90 (m, 1H), 3.29–3.20 (m, 2H), 2.51 (s, 1H); IR (cm^{-1}) : 3290, 1598, 1436, 1088, 1014; MS [ESI] [M+Na] found (expected): 294.0707 (294.0662).

Ligand **1d**: White solid. mp. 38–40 °C; $[\alpha]_D^{25}$ = + 84.3 (*c* 0.58, acetone); dr. 2.93:1 (determined by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, *J* = 7.8 Hz, 1H), 7.39–7.29 (m, 3H), 7.24–7.12 (m, 3H), 7.03–6.95 (m, 1H), 5.11(s, 1H), 5.08 (d, *J* = 5.6 Hz, 1H), 4.93–4.90 (m, 1H), 3.32–3.20 (m, 2H), 2.53 (s, 1H); IR (cm^{-1}) : 3293, 1689, 1592, 1456, 1384, 1167, 1049; MS [ESI] [M+H] found (expected): 256.2619 (256.1138).

Ligand **1e**: White crystal. mp. 78–80 °C; $[\alpha]_D^{25}$ = + 69.5 (c 1.83, acetone); dr. 3.0:1 (determined by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.30–7.27 (m, 2H), 7.24–7.20 (m, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.09–5.08 (m, 2H), 4.93–4.90 (m, 1H), 3.27–3.24 (m, 2H), 2.40 (s, 1H), 2.33 (s, 3H); IR (cm^{-1}) : 3290, 2946, 2897, 1458, 1447, 1102, 1021; MS [ESI] [M^+] found (expected): 252.1349 (252.1388).

Ligand **1f**: Yellow crystal. mp. 120–122 °C; $[\alpha]_D^{25}$ = + 91.3 (*c* 0.79, acetone); dr. 2.75 : 1 (determined by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.50 (t, *J* = 8.4 Hz,1H), 7.33–7.29 (m, 2H), 7.21–7.14 (m, 1H), 5.20 (s,1H), 5.10 (d, *J* = 5.6 Hz, 1H), 4.98–4.96(m, 1H), 3.34–3.21 (m, 2H), 2.51 (s, 1H); MS [ESI] [M+H] found (expected): 283.1117 (283.1083).

Ligand **1g**: White solid. 119–121 °C; $[\alpha]_D^{25}$ = + 91.3 (*c* 0.71, acetone); dr. 2.78:1 (determined by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.51–7.48 (m, 2H), 7.31–7.29 (m, 2H), 5.16 (s, 1H), 5.08 (d, *J* = 5.6 Hz, 1H), 4.97–4.90 (m, 1H), 3.29–3.20 (m, 2H), 2.49 (s, 1H); IR (cm^{-1}) : 3273, 2229, 1554, 1044; MS [ESI] [M^+] found (expected): 263.1275 (263.1184).

1-(4-chlorophenyl)propan-1-ol [35-38]

Colorless oil, 78% yield. 63% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA: hexane = 1 : 99). Flow: 1.0 mL/min, 25°C, Retention time: t_{major} = 12.27 min, t_{minor} = 14.13 min. H^1 NMR ($CDCl_3$, TMS): δ 7.29 (q, *J* = 8.4 Hz, 4H), 4.58 (t, *J* = 6.4 Hz, 1H), 1.90 (s, 1H), 1.83–1.68 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H).

1-(4-bromophenyl)propan-1-ol [35, 37]

Colorless oil, 75% yield. 67% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA: hexane = 3 : 97). Flow: 0.5 mL/min, 25°C, Retention time: t_{major} = 21.96 min, t_{minor} = 24.13 min. H^1 NMR ($CDCl_3$, TMS): δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 4.46 (t, *J* = 6.4 Hz, 1H), 2.00 (s, 1H), 1.73–1.58 (m, 2H), 0.81 (t, *J* = 7.6 Hz, 3H).

1-(4-iodophenyl)propan-1-ol [32, 38]

Colorless oil, 71% yield. 73% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA: hexane = 3 : 97). Flow: 0.5 mL/min, 25°C, Retention time: t_{major} = 26.97 min. H^1 NMR ($CDCl_3$, TMS): δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0Hz, 2H), 4.57 (t, *J* = 6.4Hz, 1H), 1.80–1.68 (m, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).

1-(4-methoxyphenyl)propan-1-ol [35, 36]

Colorless oil, 72% yield. 17% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA: hexane = 5 : 95). Flow: 0.5 mL/min, 25°C, Retention time: t_{major} = 21.87 min,

t_{minor} = 20.64 min. H^1 NMR ($CDCl_3$, TMS): δ 7.18 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 8.4 Hz, 2H), 4.47 (t, J = 6.4 Hz,1H), 3.73 (s, 3H), 1.80–1.52 (m, 3H), 0.82 (t, J = 7.2 Hz, 3H).

4-(1-hydroxypropyl)benzonitrile [37]

Colorless oil, 87% yield. 91% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA: hexane = 15 : 85). Flow: 0.5 mL/min, 25°C, Retention time: t_{major} = 12.11 min, t_{minor} = 15.62 min. H^1 NMR ($CDCl_3$, TMS): δ 7.63 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 4.69 (t, J = 6.4 Hz,1H), 2.13 (s, 1H), 1.83–1.71 (m, 2H), 0.93 (t, J = 7.6 Hz,1H).

1-(2,3-dimethylphenyl)propan-1-ol [32]

Colorless oil, 75% yield. 31% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA: hexane = 1 : 99). Flow: 1.0 mL/min, 25°C, Retention time: t_{major} = 13.63 min, t_{minor} = 20.19 min. H^1 NMR ($CDCl_3$, TMS): δ 7.32 (d, J = 7.6 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.07(d, J = 7.6 Hz, 1H), 4.91 (t, J = 6.4 Hz), 2.29 (s, 3H), 2.22 (s, 3H), 1.78–1.71(m, 3H), 1.26(s, 3H), 0.98 (t, J = 7.2 Hz).

1-(2,3-dimethoxyphenyl)propan-1-ol [32]

Colorless oil, 77% yield. 27% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA: hexane = 5 : 95). Flow: 0.5 mL/min, 25°C, Retention time: t_{major} = 26.09 min, t_{minor} = 32.57 min. H^1 NMR ($CDCl_3$, TMS): δ 7.04 (t, J = 8.0 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 4.84 (t, J = 6.8 Hz,1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.41 (s, 1H), 1.85–1.72 (m, 2H), 0.95 (t, J = 7.6 Hz, 3H).

1-(2-methoxyphenyl)propan-1-ol [32]

Colorless oil, 72% yield. 28% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA: hexane = 5 : 95). Flow: 0.5 ml/min, 25°C, Retention time: t_{major} = 18.66 min, t_{minor} = 20.63 min. ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 7.6 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H), 6.87 (t, J = 7.4 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.71 (t, J = 6.6 Hz, 1H), 3.76 (s, 3H), 2.54 (s, 1H), 1.75–1.71 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H).

1-(3-fluorophenyl)propan-1-ol [32, 39]

Colorless oil, 65% yield. 60% *ee* determined by HPLC analysis (Chiralcel AD-H column, IPA: hexane = 3 : 97). Flow: 1.0 mL/min, 25°C, Retention time: t_{major} = 11.69 min, t_{minor} = 10.93 min. H^1 NMR ($CDCl_3$, TMS): δ 7.32–7.27 (m, 1H), 7.10–7.05 (m, 2H), 6.95 (dt, J = 2.4 Hz, 8.5 Hz, 1H), 4.60 (t, J = 6.4 Hz,1H), 1.91 (s, 1H), 1.81–1.72 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H).

1-phenylpropan-1-ol [35-37]

Colorless oil, 63% yield. 62% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA: hexane = 3 : 97). Flow: 0.5 mL/min, 25°C, Retention time: t_{major} = 24.90 min, t_{minor} = 21.35 min. H^1 NMR ($CDCl_3$, TMS): δ 7.35–7.27 (m, 5H), 4.59 (t, J = 6.8 Hz,1H), 1.87 (s, 1H), 1.86–1.71 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H).

1-(naphthalen-2-yl)propan-1-ol [35, 36]

White solid, mp 33-35°C, 56% yield. 63% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA: hexane = 10 : 90). Flow: 0.5 mL/min, 25°C, Retention time: t_{major} = 18.49 min, t_{minor} = 21.55 min. H^1 NMR ($CDCl_3$, TMS): δ 7.84–7.82 (m,3H),7.67 (s,1H), 7.48–7.45 (m,3H), 4.76 (t, J = 6.4 Hz,1H), 1.99 (s,1H), 1.94–1.81 (m,2H), 0.94 (t, J = 7.6 Hz, 3H).

1-phenylpentan-3-ol [32, 39]

Colorless oil, 64% yield. 60% *ee* determined by HPLC analysis (Chiralcel AD-H column, IPA: hexane = 3 : 97). Flow: 1.0 mL/min, 25°C, Retention time: t_{major} = 11.69 min, t_{minor} = 10.93 min. H^1 NMR ($CDCl_3$, TMS): δ 7.30–7.25 (m, 2H), 7.21–7.16 (m, 3H), 3.55 (ddd, J = 12.2 Hz, 8.0 Hz, 4.5 Hz, 1H), 2.80 (ddd, J = 14.1 Hz, 9.8 Hz, 5.8 Hz, 1H), 2.67 (ddd, J = 13.8 Hz, 9.7 Hz, 6.7 Hz, 1H), 1.84–1.76 (m, 2H), 1.56–1.41 (m, 3H), 0.94 (t, J = 7.2 Hz, 3H).

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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REFERENCES

[1] Noyori, R. Asymmetric Catalysis in Organic Synthesis Wiley, New York, **1994**.

[2] Soai, K.; Shibata, T. In Comprehensive Asymmetric Catalysis, Jacobsen, E.N.; Pfaltz, A.; Yamamoto, H. Eds., Springer: Berlin, Germany, **1999**, pp. 911-922.

[3] Oguni, N.; Omi, T. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by a small amount of chiral 2-amino-1-alcohols. *Tetrahedron Lett.*, **1984**, *25*, 2823-2824.

[4] Reviews on the asymmetric alkylation, some selected examples: (a) Noyori, R.; Kitamura, M. Enantioselective addition of organometallic reagents to carbonyl compounds: chirality transfer, multiplication, and amplification. *Angew. Chem., Int. Ed. Engl.*, **1991**, *30*, 49-69; (b) Soai, K.; Niwa, S. Enantioselective addition of organozinc reagents to aldehydes. *Chem. Rev.*, **1992**, *92*, 833-856; (c) Pu, L.; Yu, H.B. Enantioselective addition of organozinc reagents to aldehydes. *Chem. Rev.*, **2001**, *101*, 757-824; (d) Knochel, P.; Singer, R.D. Catalytic asymmetric organozinc additions to carbonyl compounds. *Chem. Rev.*, **1993**, *93*, 2117-2188.

[5] Liu, C.L.; Wei, C.Y.; Wang, S.W.; Peng, Y.G. A systematic study of chiral homoprolinols and their derivatives in the catalysis of enantioselective addition of diethylzinc to aldehydes. *Chirality*, **2011**, *10*, 921-928.

[6] Frantz, D.E.; Fassler, R.; Carreira, E.M. Facile enantioselective synthesis of propargylic alcohols by direct addition of terminal alkynes to aldehydes. *J. Am. Chem. Soc.*, **2000**, *122*, 1806-1807.

[7] Schon, M.; Naef, R. New 1-amino-1,2-diphenylethanols as ligands for the enantioselective addition of alkyllithiums to benzaldehyde. *Tetrahedron Asymmetry*, **1999**, *10*, 169-176.

[8] Zhu, H.J.; Jiang, J.X.; Saebo, S.; Pittman, Jr C.U. Chiral ligands derived from Abrine 8. An experimental and theoretical study of free ligand conformational preferences and the addition of diethylzinc to benzaldehyde. *J. Org. Chem.*, **2005**, *70*, 261-267.

[9] Tasgin, D.I.; Unaleroglu, C. Enantioselective addition of diethylzinc to aldehydes catalyzed by β-amino alcohols derived from (1R,2S)-norephedrine. *Applied Organometallic Chemistry*, **2010**, *24*, 33-37.

[10] Dahman, S.; Bräse, S. Planar and central chiral [2.2] paracyclophane- based N,O-ligands as highly active catalysts in the diethylzinc addition to aldehydes. *Chem. Commun.*, **2002**, 26-27.

[11] Conti, S.; Falorni, M.; Giacomelli, G.; Soccolini, F. Chiral ligands containing heteroatoms. 10. 1-(2-pyridyl)alkylamines as chiral catalysts in the addition of diethylzinc to aldehydes: temperature dependence on the enantioselectivity. *Tetrahedron*, **1992**, *48*, 8993-9000.

[12] Niwa, S.; Soai, K. Asymmetric synthesis using chiral piperazines. Part 3. Enantioselective addition of dialkylzincs to aryl aldehydes catalysed by chiral piperazines. *J. Chem. Soc. Perkin Trans.*, **1991**, *1*, 2717-2720.

[13] Pini, D.; Mastantuono, A.; Uccello-Barretta, G.; Iuliano, A.; Salvadori, P. Addition of diethylzinc to aryl aldehydes catalyzed by (1S,3S)-N,N1-bis[benzyl]-1,3-diphenyl-1,3-propanediamine and its dilithium salt: a mechanistic rationale investigation. *Tetrahedron*, **1993**, *49*, 9613-9624.

[14] Rosini, C.; Franzini, L.; Iuliano, A.; Pini, D.; Salvadori, P. Asymmetric alkylation of aromatic aldehydes by diethyl zinc in the presence of (S)-N,N,N′,N′,-tetramethyl-2,2′-diamino-1,1′- binaphthyl. *Tetrahedron Asymmetry*, **1991**, *2*, 363-366.

[15] Paquette, L.A.; Zhou, R.J. Synthesis of enantiopure C2-symmetric VERDI disulfonamides and their application to the catalytic enantioselective addition of diethylzinc to aromatic and aliphatic aldehydes. *J Org Chem.*, **1999**, *64*, 7929-7934.

[16] Yoshioka, M.; Kawakita, T. Ohno, M. Asymmetric induction catalyzed by conjugate bases of chiral proton acids as ligands: Enantioselective addition of dialkylzinc-orthotitanate complex to benzaldehyde with catalytic ability of a remarkable high order. *Tetrahedron Lett.*, **1989**, *30*, 1657-1660.

[17] Cernerud, M.; Skrinning, A.; Bergere, I.; Moberg, C. Bis(ethylsulfonamide)amines *via* nucleophilic ring-opening of chiral aziridines. Application to Ti-mediated addition of diethylzinc to benzaldehyde. *Tetrahedron Asymmetry*, **1997**, *8*, 3437-3441.

[18] Pritchett, S.; Woodmansee, D.H.; Gantzel, P.; Walsh, P.J. Synthesis and crystal structures of bis(sulfonamido) Titanium bis(alkoxide) complexes: Mechanistic implicationsin the bis(sulfonamide) catalyzed asymmetric addition of dialkylzinc reagents to aldehydes. *J. Am. Chem. Soc.* **1998**, *120*, 6423-6424.

[19] Takahashi, H.; Yoshioka, M.; Kobayashi, S. Catalytic enantioselective reactions using C2-symmetric disulfonamides as chiral ligands. *J. Syn. Org. Chem. Jpn*., **1997**, *55*, 714-724.

[20] Zhang, F.Y.; Yip, C.W.; Cao, R.; Chan, A.S.C. Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by Ti(BINOL) complex. *Tetrahedron Asymmetry*, **1997**, *8*, 585-589.

[21] Zhang, F.Y.; Chan, A.S.C. Asymmetric catalytic alkylation of aldehydes with diethylzinc using a chiral binaphthol-titanium complex. *Tetrahedron Lett.*, **1997**, *38*, 6233-6236.

[22] Prasad, K.R.K.; Joshi, N.N. C2-symmetric chiral zinc alkoxides as catalysts for the enantioselective addition of diethylzinc to aryl aldehydes. *Tetrahedron Asymmetry*, **1996**, *7*, 1957-1960.

[23] Rosini, C.; Franzini, L.; Pini, D.; Salvadori, P. Enantioselective alkylation of prochiral aldehydes by diethylzinc promoted by (*S*, *S*)-1, 2-diphenylethan-1, 2-diol. *Tetrahedron Asymmetry*, **1990**, *1*, 587-588.

[24] Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D.P. Asymmetric alkylation of aromatic aldehydes with diethylzinc catalyzed by a fluorous BINOL-Ti complex in an organic and fluorous biphase system. *Tetrahedron Lett.*, **2000**, *41*, 57-60.

[25] Kostova, K.; Genov, M.; Philipova, I.; Dimitrov, V. New bis-steroidal axially chiral diols as ligands for the asymmetric addition of diethylzinc to aldehydes. *Tetrahedron Asymmetry*, **2000**, *11*, 3253-3256.

[26] Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *N*,*N*,*N*′,*N*′-Tetraalkyl-2,2′-dihydroxy-1,1′-binaphthyl -3,3′-dicarboxamides: Novel chiral auxiliaries for asymmetric simmons–smith cyclopropanation of allylic alcohols and for asymmetric diethylzinc addition to aldehydes. *Bull. Chem. Soc. Jpn.*, **1997**, *70*, 207-217.

[27] Omote, M.; Kominato, A.; Sugawara, M.; Sato, K.; Ando, A.; Kumadaki, I. A novel axially dissymmetric ligand with chiral 2, 2, 2-trifluoro-1-hydroxyethyl groups. *Tetrahedron Lett.*, **1999**, *40*, 5583-5585.

[28] Liu, S.L.; Wolf, C. Chiral amplification based on enantioselective dual-phase distribution of a scalemic bisoxazolidine catalyst. *Org. Lett.*, **2008**, *10*, 1831-1834.

[29] Xu, Z.; Mao, J.C.; Zhang, Y.W. Highly enantioselective alkynylation of aldehydes catalyzed by a new oxazolidine–titanium complex. *Org. Biomol. Chem.*, **2008**, 1288-1292.

[30] Xu, Z.; Wu, N.; Ding, Z.H.; Wang, T.; Mao, J.C.; Zhang, Y.W. L-Proline-derived tertiary amino alcohol as a new chiral ligand for enantioselective alkynylation of aldehydes. *Tetrahedron Lett.*, **2009**, *50*, 926-929.

[30] Xu, Z.; Mao, J.C.; Zhang, Y.W.; Guo, J.; Zhu, J.L. Inversion of stereochemistry in the asymmetric transfer hydrogenation of ketones performed in tap water and in open-vessel. *Catalysis Communications*, **2008**, *9*, 618-623.

[31] Xu, Z. ; Mao, J.C.; Zhang, Y.W. Unmodified chiral primary amino alcohol as a new ligand for enantioselective alkynylation of aldehydes. *Catalysis Communications*, **2008**, *10*, 113-117.

[32] Xu, Z. ; Bo, R.C.; Wu, N.; Wan, Y.; Wu, H. L-Proline-Derived Tertiary Amino Alcohols as Chiral Ligands for Enantioselective Addition of Diethylzinc to Aldehydes. *Lett. Org. Chem.*, **2011**, 8, 582-586.

[33] Hui, A.L.; Zhang, J.T.; Fan, J.M.; Wang, Z.R. A new chiral sulfonamide ligand based on tartaric acid: synthesis and application in the enantioselective addition of diethylzinc to aldehydes and ketones. *Tetrahedron: Asymmetry*, **2006**, *17*, 2101-2107.

[34] Huang, W.S.; Hu, Q.S.; Pu, L. From highly enantioselective monomeric catalysts to highly enantioselective polymeric catalysts: application of rigid and sterically regular chiral binaphthyl polymers to the asymmetric synthesis of chiral secondary alcohols. *J. Org. Chem.*, **1999**, *64*, 7940-7956.

[35] Werner, T.; Riahi, A.M.; Schramm, H. Phosphonium salt catalyzed addtion of diethylzinc to aldehydes. *Synthesis*, **2011**, 3482-3490.

[36] Hatano, M.; Miyamoto, T.; Ishihara, K. A highly enantioselective addition of dialkylzincs to aromatic, aliphatic, and heteroaromatic aldehydes is based on conjugate Lewis acid-Lewis base catalysis using bifunctional BINOL ligands. *J. Org. Chem.*, **2006**, *71*, 6474-6484.

[37] Yang, X.F.; Hirose, T.; Zhang, G.Y. Synthesis of novel chiral tridentate aminophenol ligands for enantioselective addition of diethylzinc to aldehydes. *Tetrahedron: Asymmetry*, **2008**, *19*, 1670-1675.

[38] Gou, S.H.; Ye, Z.B.; Chang, J.; Gou, G.J.; Feng, M.M. Modular amino acid amide chiral ligands for enantioselective addition of diethylzinc to aromatic aldehydes. *Appl. Organom. Chem.*, **2011**, *25*, 448-453.

[39] Wu, Z.L.; Wu H.L.; Wu, P.Y.; Uang, B.J. Asymmetric addition of diethylzinc to aldehydes catalyzed by a camphor-derived *β*-amino alcohol. *Tetrahedron Asymmetry*, **2009**, *20*, 1556-1560.