ENANTIOSELECTIVE ADDITION OF DIETHYLZINC TO ALDEHYDES CATALYZED BY ETHYL NIPECOTATE-DERIVED NEW CHIRAL LIGAND

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Abstract- (*R*)-(-)-Diphenyl-(*N*-methylpiperidin-3-yl)methanol (**3**) derived from (±)-ethyl nipecotate catalyzed the enantioselective addition of diethylzinc to various aldehydes in good to moderate optical yield (40 % - 81 %)

1. INTRODUCTION

The addition of diorganozinc reagents to aldehydes[1] using chiral catalyst has been proposed as a convenient method for the preparation of various chiral secondary alcohol since the pioneering work of a highly enantioselective amino alcohol catalyst by Oguni *et al.* in 1984.[2] Among many kinds of them, chiral catalyst prepared from cyclic amino acids such as (*S*)-proline-derived,[3,4] (*S*)-azetidinecarboxylic acid-derived[5] and (*S*)-2-indolinecarboxylic acid-derived chiral catalyst[6] gave excellent chiral induction in addition reaction of organozinc to aromatic benzaldehydes. These catalyst are β-amino alcohols and their roles in chiral induction have been well known. To our knowledge, however, γ-amino alcohols from cyclic nonproteinogenic amino acids have not been used as chiral catalyst and their preparation has not been reported. We want to investigate the different chirality induction between β- and γ-amino alcohols. Therefore, We described the synthesis of chiral catalyst (**3**) and its use as chiral catalyst (**3**) in enantioselective addition of diethylzinc to aldehydes.

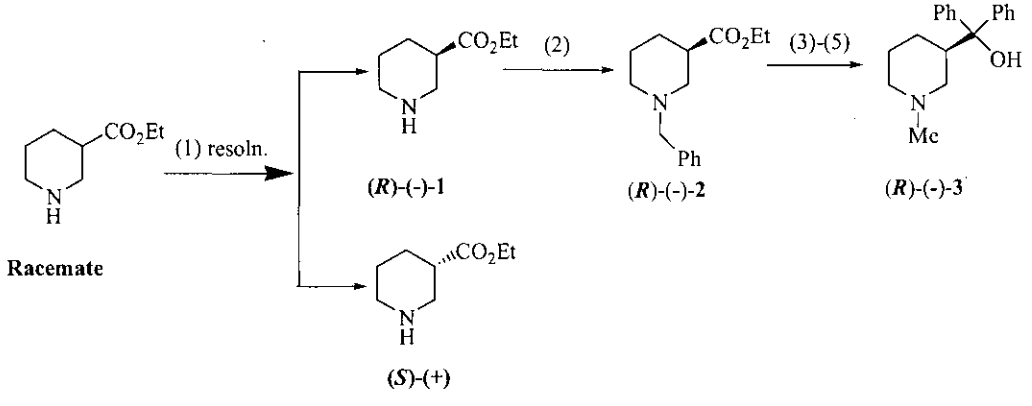
2. RESULTS AND DISCUSSION

We used the (±)-ethyl nipecotate as starting material for the synthesis of cyclic amino alcohol catalyst.

The compound ((*R*)-(-)-**1**) was resolved by the complex formation[7] of (±)-ethyl nipecotate with L-(+)-tartaric acid and it was recrystallized three times using the mixed solvent of ethanol and acetone. After the salt was treated with 3N NaOH, it was extracted with $CHCl_3$. To determine the ee of ester ((*R*)-(-)-**1**), it was transformed to the compound ((*R*)-(-)-**2**) by benzylation with benzylbromide in the presence of triethylamine in CH_2Cl_2 and its ee was determined by HPLC analysis on Chiralcel OD column (ee 95 %). The amino alcohol ((R)-(-)-**3**) was synthesized in good yield as **Scheme 1**.

In order to survey the effect of the new catalyst on organozinc addition reaction, we used the various aldehydes. As can be seen from **Table 1**, all the reactions proceeded smoothly to give the corresponding alcohols in good chemical yield and the optical yield was widely distributed from 40 to 81 % ee in favor of the *S* isomer. These results showed similar trends with ones from the reaction with chirald^R [(2*S*,3*R*)-(+)-4-dimethylamine-1,2-diphenyl-3-methyl-2-butanol],[8] which is γ-amino alcohol and open chain. Compared the catalytic effect of the compound (**3**) with that of chirald^R, the addition reaction of chirald with benzaldehyde gave the ee of 87 % at –10 °C and the ee of 83 % at room temperature, while the those of the compound (**3**) gave the ees of 74 % and 81 % in 0 °C and 25 °C, respectively. The catalytic power of chirald was only a little more effective than those of the compound (**3**). But these ee values are relatively low in comparison with β-amino alcohol such as (*S*)-1-methyl-2-diphenylhydroxymethyl-azetidine[5] or *DPMPM*.[3,4]

The reason is surmised that the rigid zinc complex formation with the compound (*R*-(-)-**3**) is not achieved



(1) Resolution (L-(+) tartaric acid), 3N NaOH, (2) $PhCH_2Br$ / NEt_3 / CH_2Cl_2 / 25 °C,

(3) PhMgCl / THF / 25 °C, (4) Pd / C (10 %) / MeOH, (5) MeI / K_2CO_3 / acetone

Scheme 1. Synthesis of chiral catalyst (3)

because of diverse possibility of conformation of piperidine ring and sterically its weak congestion.

In conclusion, γ-cyclic amino alcohol ((*R*)-(-)-**3**) is less effective than β-amino alcohol in chiral induction of organozinc addition to aldehydes. However, it still produced moderate to good optical yields. We have

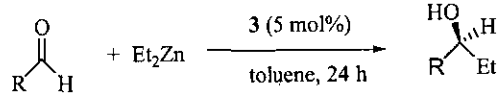
plan to apply this chiral ligand to other organometallic reactions.

3. EXPERIMENTAL

3.1 General

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on Varian Gemini 300 MHz spectrometer with TMS as internal standard. IR spectra were recorded on a MIDAC 101025 FT-IR spectrometer and optical rotation was measured Autopol ® III polarimeter. HPLC analysis were performed on Varian 9010 chromatography system with Varian 9050 UV detector at 254 nm and Chiralcel OD or Chiralcel AD purchased from Daicel Chemical Industries. GC analysis were performed on HP 5890 system on FID

Table 1. Asymmetric addition of diethylzinc to aldehydes



Entry[a]	R in RCHO	temp(°C)	Yield(%)[b]	ee(%)[c]	config.[d]
1	Ph	25	93	74	*S*
2	Ph	0	91	81	*S*
3	4-MeOC$_6$H$_4$	0	90	70	*S*
4	4-MeC$_6$H$_4$	0	92	71	*S*
5	4-ClC$_6$H$_4$	0	80	61	*S*
6	3-ClC$_6$H$_4$	0	82	69	*S*
7	*E*-PhCH=CH	0	94	40	*S*
8	*n*-C$_5$H$_{11}$	0	85	45	*S*

a) aldehyde : [Et$_2$Zn] : [**3**] = 1:2:0.05. b) isolated yield. c) Ee determined by Chiral GC or chiral HPLC analysis[1d,1h] (see experimental part).
d) absolute configurations determined by comparison of reported optical rotations.[9]

detector with Supelco β-Dex™ 110 column purchased from Supelco Inc. Melting point was determined by Thomas Hoover capillary melting point apparatus. Column chromatography was performed on Merck silica gel 60 (230-400 mesh) using appropriate solvents. TLC was carried out using glass sheets precoated with silica gel 60 F_{254} prepared by E. Merck .

3.2 (*R*)-(-)-Diphenyl-(*N*-methylpiperidin-3-yl)methanol (3)

3.2.1 (*R*)-(-)-Ethyl nipecotate (1)

(±)-Ethyl nipecotate (49.1 g, 0.31 mol) and L-(+)-tartaric acid (46.8 g, 0.31 mol) were dissolved in hot

mixed solvent (ethanol, 245 mL ; acetone, 70 mL) and slowly cooled to rt. (*R*)-(-)-Ethyl nipecotate was gained by **Ref. 7** (6.3 g).

$[\alpha]_D^{25}$ -0.95 ° (c 1.2, $CHCl_3$)(lit.,[7] $[\alpha]_D^{21}$ –1.4 ° (c 5, water), lit.,[10] $[\alpha]_D$ -1.8 °); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J=7.14 Hz, 3H), 1.43-1.58 (m, 1H), 1.60-1.68 (m, 3H), 1.94-1.97 (m, 1H), 2.36-2.42 (m, 1H), 2.56-2.65 (m, 1H), 2.74-2.81 (dd, J=9.12 , 9.06 Hz, 1H), 2.86-2.92 (m, 1H), 3.10-3.15 (dd, J=3.57, 3.39 Hz, 1H), 4.11 (q, J=7.14 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.38, 60.22, 48.62, 46.43, 42.55, 27.40, 25.57, 14.22; IR (neat) 3386, 2940, 1732, 1184 cm^{-1}.

3.2.2 Ethyl (*R*)-(-)-*N*-benzylnipecotate (2)

Benzyl bromide (3.82 mL, 32.0 mmol) was added dropwise to a stirred solution of ester ((*R*)-(-)-**1**) (5 g, 32.0 mmol) and triethylamie (13.3 mL, 95.4 mmol) in CH_2Cl_2 (80 mL) at 0 °C for 30 min. The reaction mixture was allowed to 20 °C and stirred for 12 h. The reaction mixture was quenched by saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (100 mL), and the extract was dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by column chromatogrphy (ethyl acetate : *n*-hexane= 1 : 4) to give the liquid (4.95 g, 63 %). The ee determination of compound (2) was performed by HPLC Chiralcel OD (UV detector 254 nm, flow rate 0.5 mL/min, *n*-hexane : 2-propanol = 99 : 1, Retention time of *R* isomer (t_R = 11.93 min), Retention time of *S* isomer (t_S = 13.60), ee 95 %).

$[\alpha]_D^{25}$ –14.0 ° (c 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, J=7.11 Hz, 3H), 1.42-1.50 (m, 1H), 1.67-1.72 (m, 1H), 1.87-1.93 (m, 1H), 1.99-2.05 (m, 1H), 2.17-2.24 (m, 1H), 2.52-2.60 (m, 1H), 2.67-2.73 (m, 1H), 2.90-2.94 (m, 1H), 3.51 (dd, J=13.22, 22.26 Hz, 2H), 4.10 (q, J=7.11 Hz, 2H), 7.22-7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.29, 138.30, 129.09, 128.21, 127.01, 69.30, 60.26, 55.44, 53.62, 41.95, 27.01, 24.57, 14.24; IR (neat) 2942, 1732, 1456, 1180 cm^{-1}; Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.00; H, 8.49; N, 5.63.

3.2.3 (*R*)-(-)-Diphenyl-(*N*-benzylpiperidin-3-yl)methanol

Ester ((*R*)-(-)-**2**) (1.9 g, 7.7 mmol) in THF (30 mL) was added portionwise to phenylmagnesium chloride (38.4 mL, 69.1 mmol, 1.8 M in THF) at 0 °C for 3 h under N_2. The cooling bath was removed and the reaction mixture was stirred overnight at 20 °C. The reaction mixture was poured into cold saturated aqueous NH_4Cl solution and concentrated under reduced pressure. To the residue was added ethyl acetate (100 mL) and the organic layer was separated, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (ethyl acetate : *n*-hexane = 1 : 8) to give the white solid (1.6 g, 61 %).

mp 122-122.5 °C (ethanol); $[\alpha]_D^{25}$ –13.4 ° (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35-1.46 (m, 2H), 1.69-1.73 (m, 1H), 2.01-2.14 (m, 2H), 2.24-2.29 (dd, J=3.30, 3.24 Hz, 1H), 2.68 (s, 1H), 2.83-2.86 (m, 2H), 3.3 (dd, J=12.95 Hz, 17.31 Hz, 2H), 7.01-7.26 (m, 11H), 7.43-7.51 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.93, 147.16, 137.35, 129.23, 128.42, 128.02, 127.30, 126.00, 125.69, 125.57, 81.95, 63.45,

55.97, 54.17, 39.71, 25.01, 23.04; IR (KBr) 3066, 2947, 1472, 766, 696 cm^{-1}; Anal. Calcd for $C_{25}H_{27}NO$: C, 83.99; H, 7.61; N, 3.92. Found: C, 83.70; H, 7.70; N, 3. 95.

3.2.4 (*R*)-(-)-Diphenyl-3-piperidinylmethanol

To a stirred solution of (*R*)-(-)-diphenyl-(*N*-benzylpiperidin-3-yl)methanol (1.5 g, 4.4 mmol) in methanol (80 mL) was added *Pd/C* (10 %, 50 mg). The solution was stirred in hydrogen atmosphere for 24 h and filtered through Celite 545 and evaporated to the white solid (1.1 g, 94 %).

mp 164-165 °C (ethanol); $[\alpha]_D^{25}$ –72.4 ° (c 0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.42-1.47 (m, 1H), 1.55-1.63 (m, 2H), 2.05-2.10 (m, 1H), 2.65-2.79 (m, 2H), 2.85-2.96 (m, 2H), 3.04 (dd, J=4.41, 4.38 Hz, 1H), 7.13-7.32 (m, 6H), 7.51 (d, J=9.65 Hz, 2H), 7.60 (d, J=9.65 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.50, 147.22, 128.17, 126.25, 126.00, 125.68, 81.38, 48.88, 47.04, 40.39, 25.63, 24.17; IR (KBr) 2944, 1486, 1050, 754 cm^{-1}; Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.80; H, 7.83; N, 5.13.

3.2.5 (*R*)-(-)-Diphenyl-(*N*-methylpiperidin-3-yl)methanol (3)

To a suspension containing (*R*)-(-)-diphenyl-3-piperidinylmethanol (0.54 g, 2.0 mmol) in dry acetone (10 mL) and potassium carbonate (0.84 g, 6.1 mmol) was added methyl iodide (0.14 mL, 2.2 mmol) dropwise at 0 °C for 30 min under N_2, and then the solution was stirred for 24 h at 25 °C. The reaction mixture was quenched by saturated aqueous $NaHCO_3$ solution, concentrated under reduced pressure, and the ethyl acetate (50 mL) was added. The organic layer was separated, dried over $MgSO_4$, and evaporated to give the white solid (0.54 g, 95 %).

mp 168-169 °C (ethanol); $[\alpha]_D^{25}$ –63.8 ° (c 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.40-1.43 (m, 2H), 1.49-1.52 (m, 1H), 1.99-2.18 (m, 2H), 2.08 (s, 3H), 2.22-2.35 (m, 1H), 2.55-2.70 (m, 2H), 2.71-2.73 (m, 1H), 7.10-7.27 (m, 6H), 7.49 (d, J=7.68 Hz, 2H), 7.55 (d, J=7.68 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.09, 128.14, 128.01, 126.17, 125.80, 125.52, 81.41, 57.77, 56.21, 46.30, 40.01, 24.34, 23.18; IR (KBr) 3100, 2928, 1448, 1022, 704 cm^{-1}; Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.09; H, 8.11; N, 4.90.

3.3 *General procedure for the enantioselective addition of diethylzinc to various aldehydes*

Diethylzinc (2.0 mmol, 1.1 M in toluene) was added dropwise to a mixture of aldehydes (0.98 mmol) and chiral ligand (2 mL, 5 mol %) in toluene (2 mL) at 0 °C or 25 °C and then the solution was stirred for 24 h at 0 °C or 25 °C. After the reaction was quenched at 0 °C by the addition of 1 N aqueous HCl solution and CH_2Cl_2 (10 mL) was added. The CH_2Cl_2 layer was separated, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and the residue was purified by preparative TLC. The absolute configurations were determined by comparison of reported optical rotations.[9]

3.4 Determination of enantiomeric excess of the corresponding alcohol.[1d,1h]

3.4.1 1-Phenylpropanol

The ee of product was determined 81% (*S*-isomer) by GC, Supelco β-dex 110. The t_R of the R isomer is 14.1 min and t_S of the S isomer is 14.4 min (GC, 105 °C to 200 °C, 1 °C /min, detector, FID 230 °C, injector 200 °C, carrier gas He).

3.4.2 1-(4-Methoxyphenyl)propanol

The ee of product was determined 70 % (*S*-isomer) by HPLC, Chiralcel AD. t_R = 3.56 min, t_S = 7.66 min (HPLC, *n*-hexane : 2-propanol = 90 : 10, 1.0 mL/min, UV detector 254 nm).

3.4.3 1-(4-Methyphenyl)propanol

The ee of product was determined 71 % (*S*-isomer) by GC, Supelco β-dex 110. t_R = 21.8 min, t_S = 22.5 min (GC, 100 °C to 150 °C, 1 °C /min, detector, FID 230 °C, injector 200 °C, carrier gas He).

3.4.4 1-(4-Chlorophenyl)propanol

The ee of product was determined 61 % (*S*-isomer) by GC, Supelco β-dex 110. t_R = 11.3 min, t_S = 11.5 min (GC, 140 °C to 200 °C, 1 °C /min, detector, FID 230 °C, injector 200 °C, carrier gas He).

3.4.5 1-(3-Chlorophenyl)propanol

The ee of product was determined 69 % (*S*-isomer) by GC, Supelco β-dex 110 analyzing the acetate derivative of the 1-(3-chlorophenyl)propanol. t_S = 30.6 min, t_R = 31.1 min (GC, 100 °C to 165 °C, 1 °C /min, detector, FID 230 °C, injector 200 °C, carrier gas He).

3.4.6 *E*-1-Phenyl-1-penten-3-ol

The ee of product was determined 40 % (*S*-isomer) by HPLC, Chiralcel OD. t_R = 7.1 min, t_S = 9.9 min (HPLC, *n*-hexane : 2-propanol = 90 : 10, 1.0 mL/min, UV detector 254 nm).

3.4.7 3-Octanol

The ee of product was determined 45 % (*S*-isomer) by GC, Supelco β-dex 110 analyzing the acetate derivative of the 3-octanol. t_S = 20.9 min, t_R = 21.8 min (GC, 60 °C to 100 °C, 1 °C /min, detector, FID 230 °C, injector 200 °C, carrier gas He).

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