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Synthesis of chiral plane-extended pyridyl alcohols for the enantioselective addition of diethylzinc to aldehydes

Jahyo Kang,[a,*] Ha Young Kim [a] and Joong Hyup Kim [b]

[a] *Department of Chemistry, Sogang University, Seoul 121-742, South Korea*

[b] *Biochemicals Research Center, Korea Institute of Science and Technology, PO Box 131, Cheongryang, Seoul, South Korea*

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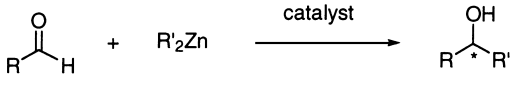
Abstract

Enantiomerically pure pyridyl alcohols, **1** and **2**, were prepared from readily available racemic pyridyl alcohol **3** and applied to the enantioselective addition of diethylzinc to aldehydes resulting in moderately high enantiomeric excess (90%) in the case of benzaldehyde. In this study the first example of an alteration in the configuration of the product upon change of a non-chiral and non-coordinating part of the catalyst was observed.

1. Introduction

During the last decade, the preparation of enantiomerically pure secondary alcohols by asymmetric addition of dialkylzinc to aldehydes in the presence of optically active amino alcohol[1] and thiol[2] catalysts has been studied extensively. Recently, pyridine-derived carbinols[3,4] including C_2-symmetric chiral ligands such as 2,2′-bispyridines and 2,6-disubstituted pyridines have also been used as chiral catalysts in the enantioselective addition of dialkylzinc to aldehydes giving only moderate enantiomeric excess.



Additionally, even though we feel that the amino thiols we developed are presently the ligands of choice for the asymmetric addition of dialkylzinc reagents to α-branched aldehydes giving more than 95% ee in these reactions,[2] they usually give inferior enantioselectivity (~80% ee) for non-α-branched aldehydes. This trend, which is also apparent with other ligands,[1] is clearly related to the mode of coordination of aldehydes to the central metal of the catalyst. So far, tremendous efforts have been made in our laboratories to fill this gap, but without noticeable success to date.[2]

* Corresponding author. E-mail: kangj@ccs.sogang.ac.kr

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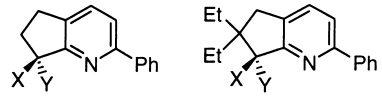
Pursuing the same line of approach, herein the preparation of enantiopure pyridyl alcohol ligands **1** and **2** (Fig. 1) are reported and their effects in the catalytic asymmetric addition of diethylzinc to aromatic aldehyde. The concurrent aim of this study was to elucidate the structural features of β-amino alcohols which can be applied to all kinds of aldehydes regardless of α-substitution.



1 **2**

X=H, Y=OH: *(R)*-**1** X=H, Y=OH: *(R)*-**2**
X=OH, Y=H: *(S)*-**1** X=OH, Y=H: *(S)*-**2**

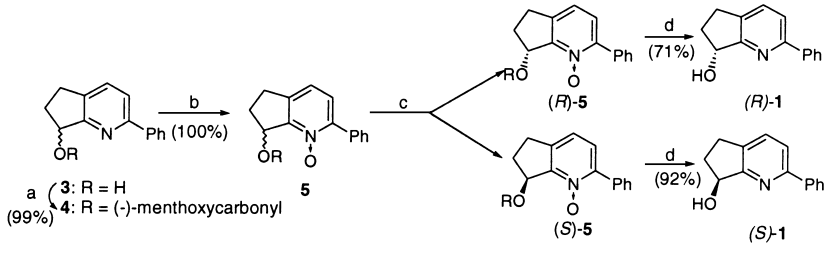
Figure 1.

2. Results and discussion

2.1. Preparation of chiral pyridyl alcohols through diastereomeric resolutions

Mechanistic considerations have led us to employ the 2,3-cyclopenteno group and a 6-phenyl moiety in the pyridine ring of the ligand, which would have the following features: (i) the 2,3-cyclopenteno ring bearing the chiral alcohol moiety could block the conformational freedom of the hydroxy group; and (ii) the phenyl group at the 6-position of the pyridine would bisect perpendicularly the pyridine plane, which could thus direct the mode of coordination of the incoming aldehydes.

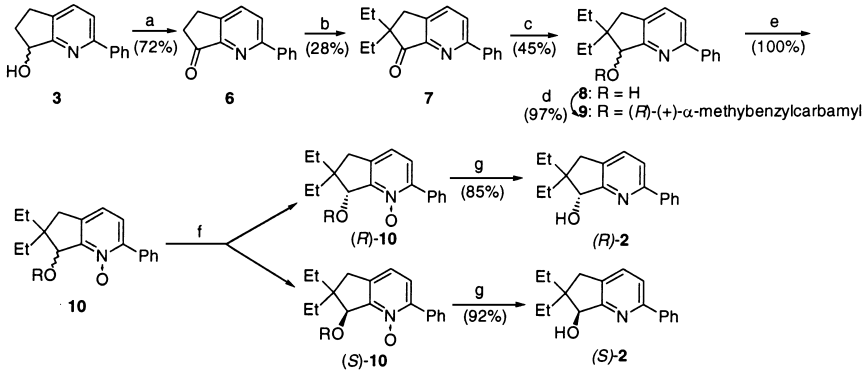
The racemic (±)-7-hydroxy-2-phenyl-6,7-dihydro-5*H*-[1]pyridine **3** which can be readily synthesized from acetophenone by the known procedure[5] was resolved through the formation of diastereomers and fractional crystallization to afford pure enantiomers (Scheme 1). The coupling of the racemic pyridyl alcohol with (−)-menthyl chloroformate (*n*-BuLi, THF, 0°C) gave the corresponding diastereomeric carbonate **4** in 99% yield as a green oil. The oily diastereomers were converted into the corresponding *N*-oxide carbonates **5** with *m*-CPBA in chloroform, which were subsequently fractionally crystallized in a mixture of ether and hexane to give (*S*)-**5** as a white solid. Concentration of the mother liquor provided enantiomerically impure (*R*)-**5** as a liquid. Subsequent deoxygenation of the two *N*-oxides with phosphorus trichloride in chloroform, followed by hydrolysis of the carbonate with potassium hydroxide in aqueous methanol, gave pure enantiomers (*R*)- and (*S*)-**1**, respectively (Scheme 1).



Scheme 1. Synthesis of the pyridyl alcohol **1**. Reaction conditions: (a) *n*-BuLi, (−)-menthyl chloroformate, THF, 0°C → rt; (b) *m*-CPBA, chloroform, rt; (c) fractional crystallization, ether/hexane, rt, 16 h; (d) (i) PCl_3, chloroform, rt; (ii) aq. KOH, 60°C

Besides the alcohol **1** shown above, we also designed the slightly modified pyridyl alcohol **2** (Scheme 2) having *gem*-diethyl groups at the β-position, to investigate the additional effect of an adjacently hindered carbon atom in the catalytic reaction of an oxazazincolidine intermediate. Treatment

of the pyridyl alcohol **3** with pyridinium chlorochromate (PCC) in refluxing dichloromethane for 12 h produced the corresponding ketone **6** in 72% yield, which was further α-dialkylated with two equivalents each of potassium *t*-butoxide and iodoethane to give α,α-diethyl-substituted ketone **7** in 28% yield as a yellow solid. Reduction with LAH in THF at 0°C gave the racemic alcohol **8**. Conversion of the racemic alcohol **8** to the corresponding carbamic diastereomers using (*R*)-(+)-α-methylbenzyl isocyanate and subsequent oxidation with *m*-CPBA afforded the diastereomeric *N*-oxide carbamate **10** in 97% yield for the two steps.



Scheme 2. Synthesis of pyridyl alcohol **2**. Reaction conditions: (a) PCC, CH_2Cl_2, 45°C; (b) *t*-BuOK, EtI, CH_2Cl_2, rt; (c) LAH, THF, rt; (d) (*R*)-(+)-α-methylbenzyl isocyanate, toluene, 100°C; (e) *m*-CPMA, chloroform, rt; (f) fractional crystallization, chloroform/hexane, 0°C, 18 h; (g) (i) PCl_3, rt; (ii) Et_3N, $HSiCl_3$, toluene, 100°C

Fractional crystallization in a chloroform–hexane mixture by standing for 18 h at 0°C separated (*R*)-**10** as a white solid and the remaining mother liquor was concentrated to give (*S*)-**10** as a pale yellow solid. The two enantiomers had different signs of optical rotation. Subsequent deoxygenation of the *N*-oxides with phosphorus trichloride in chloroform and hydrolysis of the carbamates with triethylamine and trichlorosilane in heating toluene at 100°C for 1 h gave the enantiomerically pure diethyl-substituted pyridyl alcohol (*R*)- and (*S*)-**2** in 85% and 92% yields, respectively (Scheme 2).

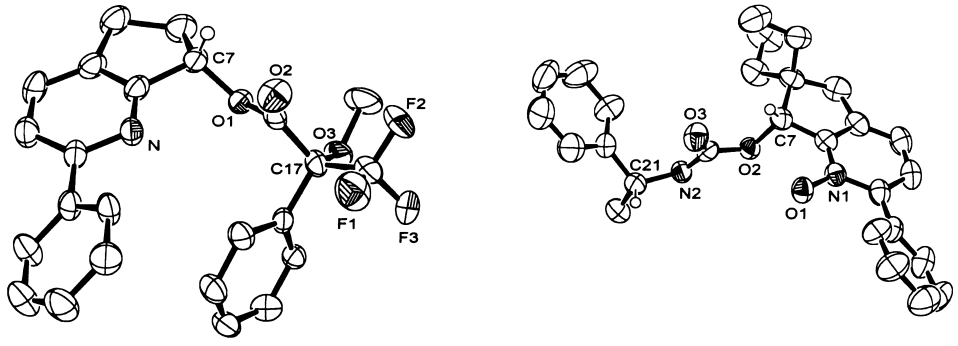
*2.2. Determination of absolute configuration of the chiral pyridyl alcohols **1** and **2***

The absolute configurations of the pyridyl alcohol (*S*)-**1**, derived from the less soluble *N*-oxide carbonates (*S*)-**5**, was determined by X-ray diffraction of the corresponding ester with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), which was prepared from (*R*)-MTPA with (*S*)-**1** in the presence of DCC and DMAP in methylene chloride[6] and subsequently recrystallized from a mixture of ether, chloroform and hexane at room temperature. As shown in Fig. 2 **A**, the absolute configuration at C-7 carbon of the pyridine moiety of the ester is shown to be *S*.

On the other hand, the absolute configuration of the C-7 carbon of the diethylated pyridyl alcohol (*R*)-**2** was determined to be *R*, as judged from the fact that the less soluble *N*-oxide carbamate (*R*)-**10**, a precursor of (*R*)-**2**, was shown to have *R* configuration by X-ray crystallography (Fig. 2 **B**).

*2.3. Asymmetric addition of diethylzinc to aldehydes in the presence of the pyridyl alcohols **1** and **2***

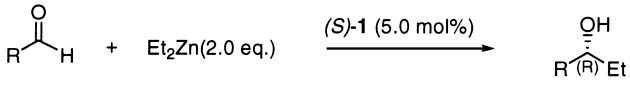
The efficiency of the 2-pyridyl carbinols in the asymmetric addition of diethylzinc to aldehydes was examined. Initially, following the typical reaction conditions of our previous reports with amino thiols,[2]



A **B**

Figure 2. ORTEP depiction of the (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate derived from (*S*)-**1** (**A**), and *N*-[(*R*)-α-methylbenzyl] carbamate (*R*)-**10**, which is a precursor of (*R*)-**2** (**B**)

Table 1
Enantioselective addition of diethylzinc to aldehydes in the presence of catalyst (*S*)-**1**



R in RCHO	Time(h)	Yield(%)[a]	Ee (%)	Configuration
Ph	48	82	90[b,e,f]	*R*
p-Cl-Ph	72	62	54[c,g]	*R*
p-MeO-Ph	72	51	47[c,h]	*R*
(*E*)-PhCH=CH	48	76	9[d,e,i]	*R*

[a] Based on the consumed starting material. Typically, the reaction was stopped after ~50% conversion. [b] Enantiomeric excess was determined by chiral HPLC (Daicel Chiralcel OB). [c] Enantiomeric excess was determined by chiral GC (Chiraldex B-PH). [d] Enantiomeric excess was determined by chiral HPLC (Daicel Chiralcel OD). [e] Eluent 10% IPA/*n*-Hexane; Flow rate 0.5 mL/min. [f] $[\alpha]_D^{25}$ = +41.0 (5.2, $CHCl_3$), [lit.[7] for *S* isomer of 100% ee, $[\alpha]_D^{25}$ = -45.45 (5.2, $CHCl_3$)]. [g] $[\alpha]_D^{25}$ = +15.3 (5.0, C_6H_6), [lit.[8] for *S* isomer of 43% ee, $[\alpha]_D^{22}$ = -10.4 (5.0, C_6H_6)]. [h] $[\alpha]_D^{25}$ = +15.8 (5.0, C_6H_6), [lit.[8,9] for *S* isomer of 51% ee, $[\alpha]_D^{22}$ = -17.2 (5.0, C_6H_6)]. [i] $[\alpha]_D^{25}$ = +0.5 (5.0, $CHCl_3$), [lit.[10] for *S* isomer of 75% ee, $[\alpha]_D^{23}$ = -6.6 (3.2, $CHCl_3$)].

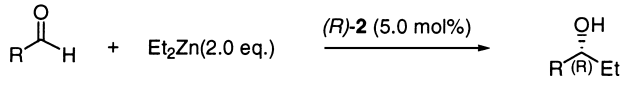
the reaction of 2.0 equivalents of diethylzinc with benzaldehyde in toluene at 0°C was carried out in the presence of 5.0 mol% of the unsubstituted pyridyl alcohol (*S*)-**1**. However, the reaction was exceedingly slow, requiring more than 24 hours. Even after that period, considerable amounts of benzaldehyde remained unreacted, which was recovered by column chromatography. Since the main objective of this study was to elucidate the structural features of β-amino alcohols which can be applied to all kinds of aldehydes regardless of α-substitution, the reaction was stopped at ~50% conversion just to see the degree of enantioselectivity.

Consequently, all reagents were added at 0°C and the reaction mixture was slowly warmed up to room temperature over 24 hours. The enantioselective addition of diethylzinc to benzaldehyde afforded 1-phenyl-1-propanol with the *R* configuration in 90% ee, but *trans*-cinnamaldehyde gave very low 9% ee with the *R* configuration. The asymmetric induction with substituted benzaldehydes such as *p*-chloro- and *p*-methoxybenzaldehyde curiously gave only moderate 54% ee and 47% ee each with the same *R* configurations. The results of the asymmetric reactions are summarized in Table 1.

The *gem*-diethylated ligand (*R*)-**2** gave almost the same enantioselectivity as the unethylated ligand, (*S*)-**1**: the reaction with benzaldehyde afforded the secondary alcohol 87% ee with the *R* configuration, but in the case of *trans*-cinnamaldehyde only 2% ee with the *R* configuration was obtained. Again, the poorly

understood, but still reproducible behavior of substituted benzaldehydes was also observed. Generally, from this study, the resulting enantiomeric excess with (*S*)-**1** is slightly higher than that of (*R*)-**2**. However, most substrates except benzaldehyde were ethylated with only moderate or poor enantioselectivity under the conditions. The results are summarized in Table 2.

Table 2
Enantioselective addition of diethylzinc to aldehydes in the presence of catalyst (*R*)-**2**



R in RCHO	Time(h)	Yield(%)[a]	Ee (%)	Configuration
Ph	48	80	87[b,e,f]	*R*
p-Cl-Ph	72	49	48[c,g]	*R*
p-MeO-Ph	72	71	50[c,h]	*R*
(*E*)-PhCH=CH	48	73	2[d,e,i]	*R*

[a] Based on the consumed starting material. Typically, the reaction was stopped after ~50% conversion. [b] Enantiomeric excess was determined by chiral HPLC (Daicel Chiralcel OB). [c] Enantiomeric excess was determined by chiral GC (Chiraldex B-PH). [d] Enantiomeric excess was determined by chiral HPLC (Daicel Chiralcel OD). [e] Eluent 10% IPA/*n*-Hexane; Flow rate 0.5 mL/min. [f] $[\alpha]_D^{25}$ = +39.7 (5.2, $CHCl_3$), [lit.[7] for *S* isomer of 100% ee, $[\alpha]_D^{25}$ = -45.45 (5.2, $CHCl_3$)]. [g] $[\alpha]_D^{25}$ = +13.7 (5.0, C_6H_6), [lit.[8] for *S* isomer of 43% ee, $[\alpha]_D^{22}$ = -10.4 (5.0, C_6H_6)]. [h] $[\alpha]_D^{25}$ = +16.9 (5.0, C_6H_6), [lit.[8,9] for *S* isomer of 51% ee, $[\alpha]_D^{22}$ = -17.2 (5.0, C_6H_6)]. [i] $[\alpha]_D^{25}$ = +0.1 (5.0, $CHCl_3$), [lit.[10] for *S* isomer of 75% ee, $[\alpha]_D^{23}$ = -6.6 (3.2, $CHCl_3$)].

However, it is rather surprising that the absolute configuration of the major secondary alcohol enantiomers obtained from both of the reactions was predominantly *R*, even though the absolute configurations of the two catalysts (*S*)-**1** and (*R*)-**2** were opposite. This result may represent the first example of alteration of chirality of the product upon change of non-chiral and non-coordinating part of catalyst in asymmetric addition of dialkylzinc to aldehydes, although there are some precedents for reversed chirality of products upon variation of the structure of catalysts (phenyl vs pyridyl;[3c] *tert*-amino-*tert*-alcohol vs *sec*-amino-*tert*-alcohol,[11] where actual coordination sites of dialkylzinc[1] might be different in each case of these examples).

These results may indicate that the modes of the initial coordination of the aldehyde in each ligand system were different. The mechanistic pathway with the pyridyl alcohol (*S*)-**1** could be explained by invoking the usual oxazazincolidine intermediate.[3e] Despite the 1,3-diaxial type interaction between the *pseudo*-axial hydrogen and oxygen, the transition state **11** seems to be more favorable. The apparent opposite results obtained with the diethyl-substituted ligand (*R*)-**2** may presumably be due to the steric interaction of the ethyl group in diethylzinc which resides on the *pseudo*-axial alkoxy oxygen with the *syn* ethyl group in the *gem*-diethyl moiety of the pyridine ligand in **11**. These effects may push the carbinol oxygen away from the ethyl group to assume *pseudo*-equatorial position and also force the ligand to coordinate diethylzinc on α-face, which is represented by **12**. Thus, the *pseudo*-axially positioned ethyl group seems to control the direction of the introduction of alkyl groups to the aldehyde in the oxazazincolidine intermediate (Fig. 3).

In conclusion, new enantiomerically pure pyridyl alcohol ligands were prepared and applied to the enantioselective addition of diethylzinc to aromatic aldehydes resulting in moderate enantioselectivity in the case of benzaldehyde. The introduction of a bulky *gem*-diethyl group at the β-position of the chiral alcohol exerted an opposite effect as compared to the unsubstituted system, which is unusual.

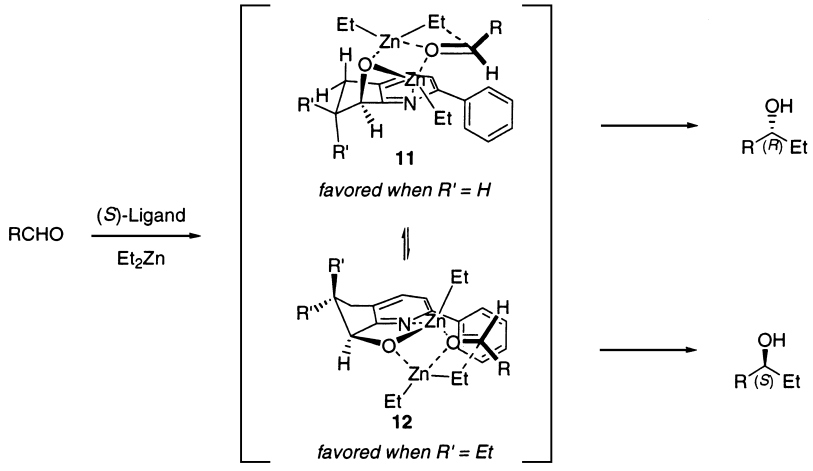


Figure 3.

3. Experimental

All reactions involving organometallic reagents were carried out under an inert atmosphere of nitrogen. Tetrahydrofuran and diethyl ether were freshly distilled from sodium benzophenone ketyl prior to use. Solvents and liquid reagents were transferred using hypodermic syringes. Alkyllithium solutions (Aldrich) were assayed for active alkyl by titration with *N*-methyl benzamide. Flash chromatography was performed on a Tokyo Rikakikai EF-10 with Merck 230–400 mesh silica gel. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and all melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Gemini 300 (300 MHz) spectrometer. NMR spectra were recorded in ppm (δ) relative to tetramethylsilane (δ 0.00) as an internal standard unless stated otherwise and are reported as follows: chemical shift, multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant and integration. Infrared spectra were obtained on a Mattson Galaxy 2000 spectrometer. Mass spectra were taken on a VG Trio 2000 (low resolution) spectrometer and VG 70-VSEQ (high resolution) with an electron beam energy of 70 eV (EI, CI). Elemental analysis was performed with Carlo Erba EA 1180 elemental analyzer. Optical rotations were obtained on a Rudolph Autopol III digital polarimeter. Data are reported as follows: $[\alpha]_D^{22}$ (concentration g/100 mL, solvent). Enantiomeric excesses (% ees) were determined by HPLC analyses using chiral column (Chiralcel, Daicel Chemical Co. Ltd.) and GC analyses using capillary chiral column (Chiraldex, Advanced Separation Technologies Inc.).

*3.1. (±)-2-Phenyl-6,7-dihydro-5*H*-[1]pyridin-7-yl-(−)-menthyl carbonate, **4***

To a solution of 7-hydroxy-2-phenyl-6,7-dihydro-5*H*-[1]pyridine **3** (4.14 g, 19.60 mmol) in dry THF (50.0 mL) was added dropwise 1.60 M *n*-BuLi (12.86 mL, 20.58 mmol) in *n*-hexane on an ice-bath. The pyridine solution was warmed up to rt and stirred for 2 h, after which a diluted solution of (−)-menthyl chloroformate (4.41 mL, 20.58 mmol) in dry THF (20.0 mL) was added dropwise to the lithiated solution through a dropping funnel at 0°C. The solution was slowly warmed up to rt overnight. The reaction mixture was quenched with water (50 mL) and extracted with methylene chloride (50 mL×3). The combined extracts were dried over anhydrous magnesium sulfate and chromatographed on silica gel to yield the menthyl carbonate **4** (7.63 g, 98.9%) as a green oil. TLC (20% EtOAc/*n*-hexane) R_f 0.74; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86–3.14 (m, 22H), 4.65 (m, 1H), 6.14 (m, 1H), 7.37–8.09 (m, 7H); IR

(neat) 2956, 2870, 1738, 1258 cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 210 ($M-C_{11}H_{19}O_2$, 15), 209 ($M-C_{11}H_{20}O_2-1$, 100). Anal. calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56, found: C, 76.21; H, 7.88; N, 3.77; HRMS calcd for $C_{25}H_{31}NO_3$: 393.2304, found: 393.2301.

3.2. (±)-2-Phenyl-6,7-dihydro-5H-[1]pyridin-7-yl-(−)-menthyl carbonate N-oxide, **5**

To a solution of the menthyl carbonate **4** (0.50 g, 1.27 mmol) in chloroform (30.0 mL) was added *m*-CPBA (0.47 g, 1.91 mmol). After stirring for 3 days, the resulting solution was filtered through a Büchner funnel to eliminate solid. The filtrate was washed with water (20 mL×2), dried over anhydrous sodium sulfate and evaporated through a rotary evaporator. The residue was purified by flash column chromatography (25% EtOAc in hexane) to give *N*-oxide compound **5** (0.58 g, 100%) as a yellow solid. TLC (40% EtOAc/*n*-hexane) R_f 0.32; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85–3.31 (m, 22H), 4.55 (m, 1H), 6.52 (m, 1H), 7.29–7.99 (m, 7H); IR (KBr) 2956, 1740, 1388, 1258 cm^{-1}. Anal. calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42, found: C, 73.18; H, 7.55; N, 3.51; HRMS calcd for $C_{25}H_{31}NO_4$: 409.2253, found: 409.2250.

3.3. (R)- and (S)-7-Hydroxy-2-phenyl-6,7-dihydro-5H-[1]pyridine, (R)-**1** and (S)-**1**

Fractional crystallization of the racemic *N*-oxide **5** (3.86 g, 9.43 mmol) in an ether–hexane cosolvent system by standing for 16 h at rt separated the pure hydroxy precursor (*S*)-**5** as a white solid (1.75 g, 4.27 mmol), and the remaining mother liquor was evaporated to give enantiomerically impure (*R*)-**5** as a yellow oil (2.11 g, 5.16 mmol). The white solid was dissolved in chloroform (40.0 mL). To this solution was added dropwise phosphorus trichloride (0.46 mL, 5.13 mmol) and the mixture was stirred for 1 h at rt. The reaction mixture was cautiously quenched with water (20.0 mL) and neutralized with conc. KOH solution at 0°C. The aqueous layer was extracted with chloroform (30 mL×3) and the organic layer was concentrated in a rotary evaporator. The residue was dissolved in methanol (30.0 mL) and was added a solution of KOH (2.40 g, 42.71 mmol) in water (30.0 mL). This solution was heated at 60°C for 3 h and the solvent was distilled off to a half volume. The aqueous layer was extracted with dichloromethane (30.0 mL×3) and dried over anhydrous sodium sulfate. Evaporation and purification by flash column chromatography (20% EtOAc in hexane) produced the pure hydroxy enantiomer (*S*)-**1** (0.83g, 92.1%) as a white solid. TLC (20% EtOAc/*n*-hexane) R_f 0.20; mp 102.5–104°C; $[\alpha]_D^{25}$ +52.7 (c=1, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.97–2.09 (m, 1H), 2.42–2.53 (m, 1H), 2.70–2.81 (m, 1H), 2.92–3.02 (m, 1H), 4.56 (br s, 1H), 5.24 (t, *J*=6.5 Hz, 1H), 7.35–7.56 (m, 5H), 7.89 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.91, 156.52, 139.50, 134.90, 133.74, 128.65, 127.08, 120.05, 103.39, 74.74, 33.08, 27.28; IR (KBr) 3434, 3198, 2966, 1590, 1456, 1314 cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 211 (M^+, 36), 193 ($M-H_2O$, 6), 182 (M−CHO, 100), 155 ($M-C_3H_4O$, 27), 77 (C_6H_5, 14). Anal. calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63, found: C, 79.71; H, 6.23; N, 6.58. The remaining hydroxy enantiomer (*R*)-**1** (0.76 g, 71.2%) was obtained from the yellow oil product (*R*)-**5** in an analogous manner and its spectral data were the same except for the specific rotation and melting point. TLC (20% EtOAc/*n*-hexane) R_f 0.20; mp 103–104°C; $[\alpha]_D^{23}$ −36.5 (c=1, MeOH).

3.4. 7-Oxo-2-phenyl-6,7-dihydro-5H-[1]pyridine, **6**

To a solution of the racemic hydroxy pyridine compound **3** (1.96 g, 9.28 mmol) in dry methylene chloride (30.0 mL) was added pyridinium chlorochromate (2.97 g, 13.49 mmol) and stirred for 10 h at 45°C. The solution was diluted with water (30.0 mL) and filtered to remove emulsions. The filtrate

was extracted with chloroform (25.0 mL×3) and dried over anhydrous sodium sulfate. Purification by a short-pass column on silica gel (40% EtOAc in hexane) yielded the ketone compound **6** (1.40 g, 72.1%) as a yellow solid. TLC (60% EtOAc/*n*-hexane) R_f 0.57; mp 167.5–168°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (t, *J*=5.6 Hz, 2H), 3.17 (t, *J*=5.6 Hz, 2H), 7.44–7.52 (m, 3H), 7.89–7.97 (m, 2H), 8.09 (d, *J*=7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.53, 154.05, 148.31, 138.24, 136.02, 129.56, 128.75, 127.62, 127.42, 35.33, 23.25; IR (KBr) 3056, 2927, 1720 cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 209 (M^+, 100), 179 (M−CO, 35), 77 (C_6H_5, 12). Anal. calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69, found: C, 80.41; H, 5.30; N, 6.66.

*3.5. 6,6-Diethyl-7-oxo-2-phenyl-6,7-dihydro-5*H*-[1]pyridine, **7***

To a solution of the keto-pyridine compound **6** (0.30 g, 1.43 mmol) in dry methylene chloride (10.0 mL) was added potassium *t*-butoxide (0.35 g, 2.94 mmol) at 0°C and stirred for 30 min at rt. A solution of iodoethane (0.24 mL, 2.94 mmol) in dry methylene chloride (2.0 mL) was added dropwise to the above mixture at 0°C. The mixed solution was slowly warmed up to ambient temperature and stirred for 13 h at rt. The resulting solution was combined with water (15.0 mL) and extracted with methylene chloride (15.0 mL×3). The organic layer was washed with brine and dried over anhydrous sodium sulfate. Evaporation and purification by flash column chromatography (5% EtOAc in hexane) provided the diethylated product **7** (0.11 g, 28.4%) as a yellow solid. TLC (20% EtOAc/*n*-hexane) R_f 0.45; mp 123.5–125°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, *J*=7.3 Hz, 6H), 1.68 (q, *J*=7.3 Hz, 4H), 1.77 (q, *J*=7.3 Hz, 4H), 2.98 (s, 2H), 7.43–7.49 (m, 3H), 7.87–7.94 (m, 2H), 8.08 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.89, 135.73, 129.48, 128.72, 127.46, 127.33, 124.80, 124.75, 52.70, 42.98, 34.45, 29.92, 11.38, 8.62; IR (KBr) 2968, 1714 cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 265 (M^+, 15), 237 (M−CO, 85), 222 (M−C_2H_3O, 100), 208 (M−C_3H_5O, 45), 77 (C_6H_5, 12). Anal. calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28, found: C, 81.49; H, 7.11; N, 5.31.

*3.6. (±)-6,6-Diethyl-7-hydroxy-2-phenyl-6,7-dihydro-5*H*-[1]pyridine, **8***

To a vacuum-dried 25 mL two-necked round bottomed flask containing the α,α-disubstituted ketone compound **7** (0.20 g, 0.75 mmol) in dry THF (4.0 mL) in an ice-bath was added LAH (0.05 g, 1.13 mmol) under a nitrogen atmosphere. After removal of the ice-bath, the solution was stirred for 6 h at rt and cautiously quenched with a solution of Rochelle salt (potassium sodium tartrate). After 2 h, the resulting solution was filtered through a Büchner funnel, extracted with dichloromethane (15.0 mL×2) and dried over anhydrous sodium sulfate. Purification by flash column chromatography (5% EtOAc in hexane) gave the racemic alcohol **8** (0.09 g, 44.7%) as a white solid. TLC (20% EtOAc/*n*-hexane) R_f 0.52; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, *J*=7.1 Hz, 3H), 0.88 (t, *J*=7.2 Hz, 3H), 1.46 (q, *J*=7.1 Hz, 2H), 1.67 (q, *J*=7.2 Hz, 2H), 2.65 (dd, *J*=7.2 Hz, *J*=7.2 Hz, 2H), 3.89 (br s, 1H), 4.81 (s, 1H), 7.36–7.53 (m, 5H), 7.91 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.05, 156.20, 139.54, 134.09, 133.65, 133.48, 128.57, 127.20, 126.91, 120.05, 80.47, 49.46, 38.56, 29.34, 23.54, 8.92; IR (KBr) 3180, 3058, 2940, 1588, 1440 cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 267 (M^+, 21), 238 (M−CHO, 31), 169 (M−$C_6H_{10}O$, 100), 77 (C_6H_5, 11). Anal. calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24, found: C, 80.75; H, 7.77; N, 5.11; HPLC resolution Chiralcel OD; eluent 10% IPA/*n*-hexane; flow rate (mL/min) 0.5; retention time (min) 15.4 (+), 16.30 (−).

3.7. (±)-6,6-Diethyl-7-{[N-(R)-methylbenzyl]formamidyl}oxy-2-phenyl-6,7-dihydro-5H-[1]pyridine, **9**

The racemic alcohol **8** (0.66 g, 2.47 mmol) was stirred to complete dissolution in pure toluene (15.0 mL). Subsequently, (*R*)-(+)-α-methylbenzyl isocyanate (1.08 mL, 7.62 mmol) was added dropwise to the above solution and the mixture was heated to 100°C for 8 h. The resulting solution was mixed with water (15.0 mL) and extracted with dichloromethane (10.0 mL×3). The combined extracts were dried over anhydrous sodium sulfate and chromatographed (10% EtOAc in hexane) on silica gel to afford the carbamate **9** (1.02 g, 99.7%) as a green oil. TLC (10% EtOAc/*n*-hexane) R_f 0.29; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79–2.99 (m, 16H), 3.49 (m, 1H), 6.03 (br s, 1H), 7.25–8.02 (m, 12H); IR (neat) 3066, 2957, 1710, 1461, 1242 cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 267 (M−C_9H_9NO, 28), 238 (M−$C_{10}H_{10}NO_2$, 24), 169 (M−$C_{15}H_{19}NO_2$, 100), 77 (C_6H_5, 4). Anal. calcd for $C_{27}H_{30}N_2O_2$: C, 78.23; H, 7.29; N, 6.76, found: C, 78.25; H, 7.60; N, 6.70; HRMS calcd for $C_{27}H_{30}N_2O_2$: 414.2307, found: 414.2309.

3.8. 6,6-Diethyl-7-{[N-(R)-methylbenzyl]formamidyl}oxy-2-phenyl-6,7-dihydro-5H-[1]pyridine N-oxide, (R)-**10** and (S)-**10**

A mixture of carbamate **9** (1.02 g, 2.47 mmol) and *m*-CPBA (1.51 g, 7.42 mmol) in chloroform (20.0 mL) was stirred for 20 h at rt. The reaction mixture was filtered and purified by flash column chromatography (20% EtOAc–50% EtOAc in hexane) to afford the carbamic *N*-oxide **10** (1.03 g, 96.7%) as a yellow solid. Fractional crystallization in chloroform–hexane cosolvent system by standing 18 h at 0°C separated the less soluble (*R*)-**10** (0.45 g) as a white solid. The mother liquor was concentrated to give (*S*)-**10** (0.54 g) a pale yellow solid. (−)-Carbamate (*R*)-**10**: TLC (40% EtOAc/*n*-hexane) R_f 0.42; mp 197–198°C; $[\alpha]_D^{22}$ −57.4 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66–2.92 (m, 16H), 4.78 (s, 1H), 6.21 (br s, 1H), 7.03–7.94 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.93, 150.76, 147.46, 145.67, 141.93, 132.13, 130.06, 129.77, 127.81, 126.56, 126.00, 123.00, 122.91, 51.18, 50.89, 48.54, 41.75, 41.58, 27.19, 23.05, 22.56, 8.59; IR (KBr) 3208, 2966, 1716, 1266 cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 283 (M−C_9H_9NO, 5), 267 (M−C_6NO_2, 43), 169 (M−$C_{15}H_{19}NO_3$, 100), 77 ($C_{16}H_5$, 10). Anal. calcd for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02; N, 6.51, found: C, 75.44; H, 7.23; N, 6.44; HRMS calcd for $C_{27}H_{30}N_2O_3$: 430.2256, found: 430.2255. (+)-Carbamate (*S*)-**10**: TLC (40% EtOAc/*n*-hexane) R_f 0.42; mp 120–122°C; $[\alpha]_D^{22}$ +90.1 (c=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59–2.82 (m, 16H), 4.74 (s, 1H), 6.05 (br s, 1H), 6.99–7.89 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.26, 150.11, 147.71, 143.52, 141.32, 132.34, 130.20, 130.13, 127.97, 127.47, 126.16, 126.15, 122.80, 50.88, 50.55, 48.36, 41.78, 41.58, 27.67, 23.19, 22.67, 8.13.

3.9. (R)- and (S)-6,6-Diethyl-7-hydroxy-2-phenyl-6,7-dihydro-5H-[1]pyridine, (R)-**2** and (S)-**2**

To a solution of the (−)-carbamate (*R*)-**10** (0.40 g, 0.93 mmol) in chloroform (15.0 mL) was added dropwise phosphorus trichloride (0.1 mL, 1.11 mmol) at rt. The mixture was stirred for 1 h at rt and cautiously quenched with water (10.0 mL) and neutralized with conc. KOH solution at 0°C. The solution was extracted with chloroform (15.0 mL×3), and then the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was dissolved in toluene (10.0 mL) and triethylamine (1.02 mL, 7.26 mmol) was added. Trichlorosilane (0.55 mL, 5.44 mmol) was added to the reaction mixture, which was heated in an oil bath for 1 h at 100°C and quenched with a small amount of water. The resulting suspension was slowly poured into 10% KOH solution (15.0 mL) and stirred for 30 min. The aqueous solution was extracted with dichloromethane (20.0 mL×3), and dried over anhydrous sodium sulfate. Purification by flash column chromatography (10% EtOAc

in hexane) produced the pure hydroxy enantiomer (*R*)-**2** (0.21 g, 84.5%) as a white solid. TLC (20% EtOAc/*n*-hexane) R_f 0.52; mp 98–100°C; $[\alpha]_D^{25}$ −40.0 (c=1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, *J*=7.1 Hz, 3H), 0.88 (t, *J*=7.2 Hz, 3H), 1.46 (q, *J*=7.1 Hz, 2H), 1.67 (q, *J*=7.2 Hz, 2H), 2.65 (dd, *J*=7.2 Hz, *J*=7.2 Hz, 2H), 3.80 (br s, 1H), 4.81 (s, 1H), 7.36–7.53 (m, 5H), 7.91 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.05, 156.20, 139.54, 134.09, 133.65, 133.48, 128.57, 127.20, 126.91, 120.05, 80.47, 49.46, 38.56, 29.34, 23.54, 8.92; IR (KBr) 3180, 3058, 2940, 1588, 1440 cm^{-1}; MS (EI, 70 eV) m/e (relative intensity) 267 (M^+, 21), 238 (M−CHO, 31), 169 (M−$C_6H_{10}O$, 100), 77 (C_6H_5, 11). Anal. calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24, found: C, 80.90; H, 7.84; N, 5.26; HPLC resolution Chiralcel OD; eluent 10% IPA/*n*-hexane; flow rate (mL/min) 0.5; retention time (min) 16.22 (−). The hydroxy enantiomer (*S*)-**2** (0.26 g, 83.7%) was obtained from the carbamic *N*-oxide (*S*)-**10** (0.50 g) in an analogous manner and its spectral data were the same except the specific rotation and melting point. TLC (20% EtOAc/*n*-hexane) R_f 0.52; mp 110–111°C; $[\alpha]_D^{25}$ +29.4 (c=1, $CHCl_3$). Anal. calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24, found: C, 80.87; H, 7.91; N, 5.17; HPLC resolution chiralcel OD; eluent 10% IPA/*n*-hexane; flow rate (mL/min) 0.5; retention time (min) 15.34 (+).

3.10. A typical procedure for the enantioselective addition of diethylzinc to aldehydes in the presence of chiral pyridyl alcohols

To a solution of an aldehyde (1.00 mmol) and the chiral pyridyl carbinol (0.05 mmol) in toluene (4.0 mmol) was added diethylzinc (1 M in *n*-hexane, 2.0 mmol) at 0°C. The mixture was slowly warmed up to ambient temperature over 24 h and quenched with 1 M HCl solution at 0°C. The aqueous phase was extracted with dichloromethane, and the combined extracts were dried over anhydrous sodium sulfate and evaporated through a rotary evaporator. The residue was purified by flash column chromatography on silica gel (EtOAc in hexane). The secondary alcohols were identified by comparing the ^1H NMR, IR spectra and retention time of GC or HPLC resolution with those of standard samples.[2]

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