Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 2, pp. 549-558, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00039-9

Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Pyridineoxazolinealcohols

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Abstract: Chiral 2-pyridylcarbinols carrying chiral oxazolyl substituents in the 6-position of the pyridine ring catalyze the enantioselective addition of diethylzinc to aromatic aldehydes. The absolute configuration of the product alcohol is determined by the configuration at the stereogenic center bearing the alcohol group, the effect of the oxazoline ring being to increase the stereoselectivity. Attempts to use methyl ether derivatives of the same ligands in the rhodium-catalyzed hydrosilylation of acetophenone did not result in any observed enantioselectivity.

Introduction

Chiral metal catalysts are important tools for the synthesis of enantiopure organic compounds. Therefore, in order to obtain novel catalytic systems exhibiting high reactivity and enantioselectivity, the design and preparation of new chiral ligands for metal ions is essential.[1]

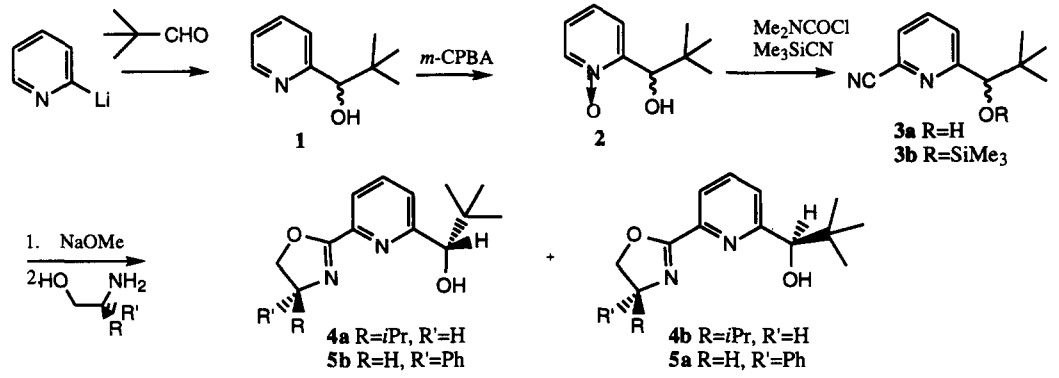
Chiral ligands containing nitrogen atoms as donors are presently attracting much attention, since such ligands are often more easily accessible in enantiomerically pure form and often have higher stability than their phosphorus counterparts.[2] Among such ligands, pyridine derivatives with chiral substituents have been shown to result in high selectivity when employed in a variety of catalytic reactions.[3] Pyridine and bipyridine, substituted with oxazoline rings derived from chiral aminoalcohols, have been successfully used in the rhodium catalyzed hydrosilylation of ketones,[4] whereas chiral pyridylcarbinols and bipyridylcarbinols have been shown to result in high facial diastereoselectivity when used as catalysts in the addition of diethylzinc to aldehydes.[5,6]

It was recently demonstrated that a tridentate ligand, obtained by modification of 2,2-dimethyl-1-(2-pyridyl)propanol via reaction with 1,1-diarylepoxides, was superior to the parent compound, resulting in higher enantioselectivity as well as higher yield.[7] In contrast, it was found that the presence of a chiral alcohol or ether substituent in the 6-position of the pyridine ring did not result in increased selectivity.[7] We have now found that the introduction of a chiral oxazoline ring in that position has a major influence on the reaction. Increased selectivity was observed, the amount depending on the relative configuration of the two stereogenic centers in the ligands.

Results and Discussion

Preparation of ligands. Ligands **4** and **5**, containing isopropyl and phenyl substituents, respectively, in the oxazoline ring, were prepared starting from 2-bromopyridine, which was lithiated and reacted with pivalaldehyde to afford racemic alcohol **1** (Scheme 1). The alcohol was transformed into a mixture of nitriles **3a** and **3b**, containing free and silylated alcohol groups, respectively, in two steps via *N*-oxide **2**, using a standard literature procedure.[8] Reaction of the racemic mixture of nitriles **3a** and **3b** with methoxide followed by the appropriate chiral aminoalcohol yielded diastereomeric oxazolines. Thus, use of (*S*)-valinol afforded a diastereomeric mixture of **4a** and **4b**, whereas **5a** and **5b** were obtained using (*R*)-2-phenylglycinol. Finally, the diastereomers of **4** and **5** were separated by liquid chromatography on silica gel.

Scheme 1



Initial preparation of enantiopure 2,2-dimethyl-1-(2-pyridyl)propanol avoids the chromatographic separation of the two diastereomers. However, the preparation of the pure alcohol also involves chromatographic separation[7] or crystallization[9] of diastereomeric derivatives. Since separation of the diastereomeric oxazolines is straightforward, the route described here is preferred in the present case, but exchange of the *t*-butyl group for a methyl group, using acetaldehyde in place of pivalaldehyde in the initial step of the reaction sequence, afforded products which we were not able to separate. Therefore, when 1-(2-pyridyl)ethanol is used as a starting alcohol, the enantiopure compound, obtained by asymmetric reduction[9] or lipase catalyzed transesterification,[10] should be chosen.

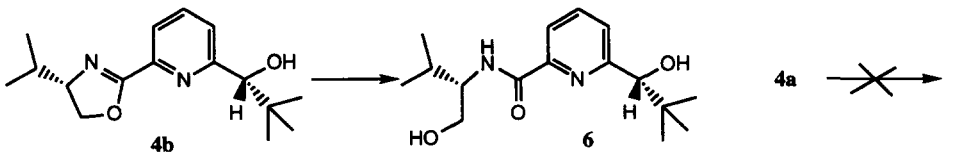
Attempts to introduce the two substituents on the pyridine ring in reverse order, via reaction of 2-bromo-6-oxazolylpyridines with butyllithium were also made. This route was initially considered to be more attractive, since the oxazoline moiety, where the chirality originates from easily available aminoalcohols, could be expected to influence the stereochemistry of the second stereogenic center. However, in this case the desired product was not observed, probably due to competing alkylation of the pyridine ring.[11] This side reaction was also observed

when butyllithium was exchanged for *t* -butyllithium.

Determination of absolute configuration. In order to allow for the determination of the absolute configuration of the diastereomeric ligands, the α-methoxy-α-trifluoromethylphenylacetate (MTPA) esters of **5a** and **5b** were prepared.[12] When (*R*)-(+)-MTPA was used for the preparation of the ester, the ^{1}H NMR spectrum of the first eluted isomer showed a signal from the *t*-butyl group at higher field than that of the epimer. According to the empirically derived correlation of configuration and chemical shifts,[13] this suggests that the stereogenic center bearing the hydroxy group has the *R* absolute configuration in the first eluted isomer, and thus, that this compound is the (*R,R*) isomer **5a**. Since the difference in chemical shift was quite small (0.02 ppm), the (*R*)-*O*-methylmandelic acid derivatives were also prepared.[14] The chemical shifts observed for the *t*-butyl groups of the two diastereomers were in accordance with the above assignment, with the signal from the ester derived from **5a** appearing 0.13 ppm downfield. Similarly, it was assumed that the isomer of **4** having the same absolute configuration (*S,S*) at both stereogenic centers was the first eluted one, and therefore was **4a**.

During the chromatographic separation of **4a** and **4b**, slow hydrolysis occurred on the column to yield an amide (**6**, Scheme 2). To our surprise, the hydrolysis was highly selective, affecting only **4b**. Repeated chromatography resulted in complete hydrolysis of this isomer, while **4a** was recovered unchanged.

Scheme 2

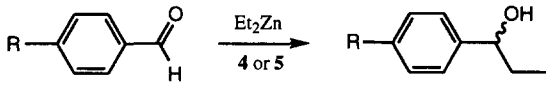


The assignments made by NMR spectroscopy are reasonable considering also the conformation of the compounds and their elution order in the chromatographic separation. We have recently demonstrated by theoretical calculations that due to a stereoelectronic effect, in its most stable conformation, 2-(hydroxymethyl)pyridine has a NCCO torsional angle of approximately 180°, and this is close to the angle usually observed for compounds of this type.[15] It is therefore assumed that in the preferred conformation, the free ligands have all four heteroatoms in one plane, with a transoid arrangment of the diaza system in order to reduce electron repulsion, as exemplified for ligand **4b** in Scheme 2. The two bulky groups of compounds **4b** and **5b** are therefore assumed to be situated on the same side of the plane defined by the two rings, and therefore these isomers are expected to be more strongly absorbed on the silica gel, thus eluting more slowly than their epimers. This also explains the higher tendency of **4b** to undergo hydrolysis during the chromatographic separation from **4a**.

Addition of diethylzinc to aldehydes. Ligands **4** and **5** were tested as catalysts in the addition of diethylzinc to benzaldehyde and *p*-chlorobenzaldehyde (Scheme 3). The results show that the presence of the oxazoline ring and the relative configuration at the two stereogenic centers of the ligand have a profound influence on the stereoselectivity of the reaction. In the presence of ligand **4a**, benzaldehyde (**7a**) reacted with

diethylzinc to yield (*S*)-(-)-1-phenylpropanol ((-)-**8**) with 81% ee (85% yield, Table 1). Ligand **4b** afforded considerably lower selectivity, yielding (*R*)-(-)-1-phenylpropanol ((+)-**8**) with 40% ee (68% yield). The phenyl group of ligand **5a** had an even more advantageous effect on the reaction, giving the product ((+)-**8**) in 88% ee in high yield (95%). That a product with opposite configuration is formed is expected, since the absolute configuration of the two stereogenic centers of the ligands are different in **4a** and **5a**. In analogy with the different results obtained using ligands **4a** and **4b**, the diastereomer with (*S,R*)-configuration, **5b**, resulted in both lower selectivity (71% ee) and lower yield (84%) than **5a**.

Scheme 3



7a, R=H
7b, R=Cl

8a, R=H
8b, R=Cl

It is interesting to compare the results presented here with those obtained using (*S*)-**1** or (*R*)-**1** as catalyst. However, in this case highly varying selectivity has been observed under slightly different reaction conditions, with ee:s ranging from 22 to 79% ee.[7] Under the conditions we used in this investigation, a mere 26% ee was observed when (*R*)-**1** was employed, clearly showing that the oxazoline ring has a beneficial influence on the reaction. The present ligands also show somewhat higher selectivity than bidentate ligands having oxazolines tethered to alcohols.[16]

The addition of diethylzinc to *p*-chlorobenzaldehyde (**7b**) using **4a** or **5a** resulted in slightly lower enantioselectivity (76 and 81% ee, respectively) and considerably lower yield (40 and 83%, respectively) than the addition to benzaldehyde (Table 1).

Table 1. Asymmetric addition of diethylzinc to aldehydes catalyzed by chiral pyridylcarbinols

Ligand	Substrate	ee (%)	yield (%)	abs conf
4a	**7a**	81	85	*S*
4a	**7b***	76	40	*S*
4b	**7a**	40	68	*R*
5a	**7a**	88	95	*R*
5a	**7b***	81	83	*R*
5b	**7a**	71	84	*S*
(*R*)-1	**7a**	26	24	*R*

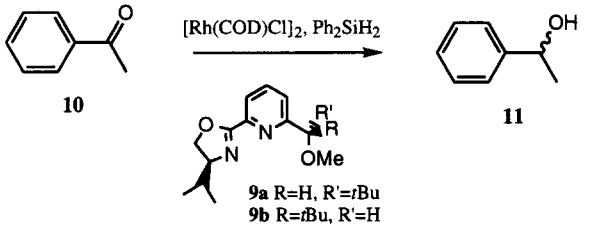
Reaction conditions: 2 mmol aldehyde, 4 mmol Et_2Zn, 0.1 mmol ligand, 4 ml hexane, 4 ml toluene, 0 °C, 24 h. *: room temperature.

It should be noted that the sense of the enantioselectivity is determined by the configuration of the stereogenic center bearing the hydroxy group. The effect excerted by the oxazoline ring is therefore to amplify the effect of that stereogenic center.

Formation of an ethylzinc alkoxide complex, with the metal ion in a tetrahedral environment, has been shown to precede the catalytic reaction. With bidentate 2-(2,2-dimethyl-1-hydroxypropyl)-6-phenylpyridine, diethylzinc gives a dimeric complex with the metal ion coordinating to the oxygen of the second ligand molecule, as demonstrated by X-ray crystallography. In the present case, the oxazoline nitrogen is appropriately situated to replace the coordination of a second ether oxygen, resulting in a monomeric complex. By comparison with the spectra obtained from the complex between diethylzinc and 2-(2,2-dimethyl-1-hydroxypropyl)pyridine, it was possible to assign the signals, but we could not conclude from these results or from IR measurements whether a monomeric or dimeric complex was obtained.

Rh-catalyzed hydrosilylation. Another method to obtain chiral alcohols stereoselectively, is by rhodium catalyzed reduction of ketones using a hydrosilane. Since chiral 2-oxazolylpyridines have been shown to result in high enantioselectivity when employed as ligands for rhodium in this process,[4] it was of interest to study the effect of a second stereogenic center in the ligand. Therefore, ligands **4a** or **4b** were methylated using sodium hydride and methyl iodide to yield **9a** and **9b**, respectively. Hydrosilylation of acetophenone (**10**) using diphenylsilane and a catalytic amount of $[Rh(COD)Cl]_2$ and **9a** or **9a** was investigated. With both ligands, only racemic alcohol **11** was observed. The reason for this may be that the ligands are too bulky to allow for coordination of Rh(I) and that the product is formed by a route not involving the chiral ligand.

Scheme 4



Experimental section

THF was distilled from benzophenone ketyl. CH_2Cl_2 and hexane were distilled and stored over molecular sieves. Acetophenone, distilled from P_2O_5, and Ph_2SiH_2, distilled from CaH_2, were stored under nitrogen. Reagents and dry toluene were obtained from Aldrich. For column chromatography, Merck Kieselgel 60H was used. ^1H and ^{13}C NMR spectra were recorded using a Bruker ACF-250 (250 and 62.9 MHz, respectively) or AM-400 (400 and 100.6 MHz, respectively) spectrometer in $CDCl_3$ with TMS as internal standard, where not otherwise stated. Enantiomeric excesses were determined using gas chromatograph Varian 3300 equipped with a chiral column (Chrompack Cp-cyclodextrin-B-2,3,6-M-19, 50 m, 0.25 mm i.d., 0.25 μm film). Assignment of

absolute configuration of the product alcohols was done by optical rotation measurements (Perkin Elmer 241 Polarimeter) and comparison with literature data. Melting points were determined with Melting Point Büchi 510.

(±)-2,2-Dimethyl-1-(2'-pyridyl)propanol (1). To a solution of 2-bromopyridine (5.5 g, 34 mmol) in THF (50 ml) at -78 °C under nitrogen atmosphere was added BuLi (14.5 ml, 34.8 mmol, 2.4 M in hexane) over a period of 30 min. The mixture became brown with time. After being stirred for 0.5 h, pivalaldehyde (2.9 g, 34.8 mmol) was added dropwise to the mixture (becoming dark green) and the mixture was stirred for an additional 2 h at -78 °C followed by 0.5 h at room temperature. The reaction was then quenched with 50 ml saturated aqueous ammonium chloride. The solvent was removed under reduced pressure and the remaining aqueous layer was extracted with 3x30 ml CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, dichloromethane removed under reduced pressure, and the resulting brown oil was purified by Kugelrohr distillation (85 °C, 0.06 mmHg) to yield a slightly yellow oil which solidified (4.4 g, 77 %). Mp 55 °C. ^{1}H NMR (250 MHz) 0.90 (s, 9H, $C(CH_3)_3$), 4.31 (s, 1H, OH), 4.33 (s, 1H, **CH**OH), 7.13 -7.24 (m, 2H, aromatic), 7.62 (td, J = 7.5 and 2.5 Hz, 1H, aromatic), 8.53 (dd, J = 7.5 and 2.5 Hz, 1H, aromatic).

(±)-2,2-Dimethyl-1-(2'-pyridyl)propanol-*N*-oxide (2). To a solution of **1** (2.5 g, 15.2 mmol) in 50 ml dry CH_2Cl_2 at 0 °C was added *m*-CPBA (4.25g 80 %, 19.8 mmol) in portions. After stirring the reaction mixture for 3 days at room temperature, an additional amount of CH_2Cl_2 (50 ml) was added, and the reaction was terminated by bubbling NH_3 (g) through the reaction mixture. The white ammonium salt formed was filtered off and the filtrate dried over $MgSO_4$. Evaporation of the solvent and thorough drying gave 2.5 g (89 %) of the desired *N*-oxide. Mp 139 °C. ^{1}H NMR (250 MHz) 1.01 (s, 9H, $C(CH_3)_3$), 4.60 (d, J = 7.51 Hz, 1H, OH), 7.20 - 7.29 (m, 3H, aromatic), 8.15 (d, J = 6.5 Hz, 1H, aromatic).

(±)-2,2-Dimethyl-1-(6'-cyano-2'-pyridyl)propanol (3a). To a solution of **2** (2.33g, 12.8 mmol) in CH_2Cl_2 (40 ml) were added dropwise *N,N*-dimethylcarbamoyl chloride (1.18 ml, 12.8 mmol) and, after 2.5 h, trimethylsilyl cyanide (2.04 ml, 15.4 mmol). The mixture was stirred overnight at room temperature followed by 8 h at reflux, then allowed to cool to room temperature, whereafter 1 eq each of *N,N*-dimethylcarbamoyl chloride and trimethylsilyl cyanide were added. After one more night of stirring at reflux, the reaction was terminated by the addition of 30 ml of saturated aqueous Na_2CO_3. The phases were separated and the aquous layer was extracted with 3x30 ml CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$. Evaporation *in vacuo* gave a yellow liquid which was purified by flash chromatography on silica gel (14 x 4 cm column, hexane:AcOEt 2:3) to give the expected product **3a** (1.76 g, 72 %) together with the corresponding silylated alcohol (±)-2,2-dimethyl-1-(6'-cyano-2'-pyridyl)-1-((trimethylsilyl)oxy)propane (**3b**, 0.54 g, 16%), both as white crystals. **3a**: Mp 59 °C. ^{1}H NMR (250 MHz) 0.91 (s, 9H, $C(CH_3)_3$), 3.59 (d, J = 8 Hz, 1H, aromatic), 4.41 (d, J = 7.6 Hz, 1H, **CH**OH), 7.46 (d, J = 8 Hz, 1H, aromatic), 7.62 (d, J = 8 Hz, 1H, aromatic), 7.80 (t, J = 8 Hz, 1H, aromatic), 7.80 (t, J = 8 Hz, 1H, aromatic). **3b**: Mp 74 °C. ^{1}H NMR (250 MHz) 0.01 (s, 9H, $3CH_3$), 0.86 (s, 9H, $C(CH_3)_3$), 4.47 (s, 1H, CH), 7.56 (dd, J = 7.5 and 1.5 Hz, 1H, aromatic), 7.68 (dd, J = 7.5 and 1.5 Hz, 1H, aromatic), 7.78 (t, J = 7.5 Hz, 1H, aromatic).

***(3'S,1"S)*-2-(3'-isopropyl)oxazolyl-6-(1"-hydroxy-2,2-dimethyl)propylpyridine (4a) and *(3'S,1"R)*-2-(3'-isopropyl)oxazolyl-6-(1"-hydroxy-2,2-dimethyl)propylpyridine (4b).**

Imidate: To a solution of **3a** (1.1 g, 5.7 mmol) or **3b** (1.5 g, 5.7 mmol) in 15 ml methanol was added sodium methoxide (31 mg, 0.57 mmol). The mixture was stirred for one day at room temperature and the solvent removed under reduced pressure to give the expected product as a white oil, which was used without further purification. ^{1}H NMR (400 MHz) 0.92 (s, 9H, $C(CH_3)_3$), 3.48 (s, 1H, OH), 4.01 (s, 3H, OCH_3), 4.42 (s, 1H, CHOH), 7.29-7.32 (m, 1H, aromatic), 7.75-7.77 (m, 2H, aromatic).

To the above imidate (1.4 g, 6.17 mmol) in CH_2Cl_2 (40 ml) was added a solution of (*S*)-valinol (0.64 g, 6.17 mmol) in CH_2Cl_2 (10 ml). After adding a few drops of conc H_2SO_4, the mixture was stirred at reflux for 2 days and then 30 ml of saturated aqueous Na_2CO_3 was added. The phases were separated and the aquous layer was extracted with 3x30 ml CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a white solid which consisted of a mixture of **4a** and **4b**. Separation of the two diastereoisomers was performed by flash chromatography on silica gel (15 x 4 cm column, hexane:AcOEt 1:4 (400 ml) and hexane:AcOEt 1:9 (300 ml)) to yield 0.53 g of compound **4a** (63%) and 0.31 g of compound **4b** (37%) in a total yield of 50%. During the chromatographic separation, slow hydrolysis of **4b** occurred on the column to yield the corresponding amide (**6**). **4a**: Mp 90.5 °C. $[\alpha]_D^{20}$ = -37.5 (c = 1.01, CH_2Cl_2). ^{1}H NMR (250 MHz) 0.78 (d, *J* = 6.8 Hz, 3H, CH_3), 0.90 (s, 9H, $C(CH_3)_3$), 0.93 (d, *J* = 6.8 Hz, 3H, CH_3), 1.71-1.85 (octet, *J* = 6.5 Hz, 1H, isopropyl CH), 4.05-4.17 (m, 2H, CH_2O), 4.34-4.40 (m, 1H, CHN), 4.46 (d, *J* = 6.9 Hz, 1H, CHOH), 4.62 (d, *J* = 6.9 Hz, 1H, OH), 7.34 (dd, *J* = 7.7 and 1 Hz, 1H, aromatic), 7.63 (t, *J* = 7.7 Hz, 1H, aromatic), 7.67 (dd, *J* = 7.7 and 1 Hz, 1H, aromatic). ^{13}C NMR (100.6 MHz) 17.80 (CH_3), 18.98 (CH_3), 26.02 (3 CH_3, *t*Bu), 32.51 (CH, isopropyl), 36.21 ($C(CH_3)_3$), 70.44 (CH_2), 72.47 (CHN), 80.9 (CHOH), 122.55 (CH aromatic), 124.56 (CH aromatic), 135.96 (CH aromatic), 145.09 (C aromatic), 161.09 (C=N), 162.8 (C aromatic). Found C 69.9; H 8.60; N 10.18. Calcd. for $C_{16}H_{24}N_2O_2$ (276.4) C 69.53; H 8.75; N 10.14. **4b**: Mp 98.5 °C. $[\alpha]_D^{20}$ = -75.5 (c = 1.01, CH_2Cl_2). ^{1}H NMR (250 MHz) 0.85 (d, *J* = 6.76 Hz, 3H, CH_3), 0.89 (s, 9H, $C(CH_3)_3$), 0.95 (d, *J* = 6.76 Hz, 3H, CH_3), 1.7-1.91 (o, *J* = 6.76 Hz, 1H, isopropyl CH), 3.9-4.15 (m, 2H, CH_2O), 4.34-4.41 (m, 1H, CHN), 4.44 (d, *J* = 7.2 Hz, 1H, CHOH), 4.94 (d, *J* = 7.2 Hz, 1H, OH), 7.3 (dd, *J* = 7.83 and 0.97 Hz, 1H, aromatic), 7.62 (t, *J* = 7.83 Hz, 1H, aromatic), 7.84 (dd, *J* = 7.83, and 0.97 Hz, 1H, aromatic). ^{13}C NMR (62.9 MHz) 17.92 (CH_3), 18.83 (CH_3), 25.94 (3 CH_3, *t*Bu), 32.57 (CH, isopropyl), 36.16 ($C(CH_3)_3$), 70.52 (CH_2), 72.25 (CHN), 80.85 (CHOH), 122.37 (CH aromatic), 124.68 (CH aromatic), 135.89 (CH aromatic), 144.84 (C aromatic), 144.84 (C aromatic), 161.02 (C=N), 162.78 (C aromatic). Found C 69.74; H 8.53; N 10.05. Calcd. for $C_{16}H_{24}N_2O_2$ (276.4) C 69.53; H 8.75; N 10.14. **6**: Mp 133.5 °C. $[\alpha]_D^{20}$ = -7.9 (c = 0.68, $CHCl_3$). ^{1}H NMR (250 MHz) 0.93 (s, 9H, $C(CH_3)_3$), 0.99 (d, *J* = 7.26 Hz, 3H, CH_3), 1.98-2.17 (m, 1H, isopropyl CH), 3.05 (t, *J* = 5.3 Hz, CH_2OH), 3.25 (d, *J* = 6.53 Hz, 1H, CHOH), 3.77 - 3.97 (m, 3H, CH_2OH, CHNH), 4.45 (d, *J* = 6.53 Hz, 1H, CHOH), 7.44 (d, *J* = 7.76 Hz, 1H, aromatic), 7.82 (t, *J* = 7.76 Hz, 1H, aromatic), 8.08 (d, *J* = 7.76 Hz, 1H, aromatic), 8.15 (d, *J* = 7.51 Hz, 1H, NH). ^{13}C NMR (62.9 MHz) 18.51 (CH_3), 19.7 (CH_3), 25.77 (3 CH_3, *t*Bu), 29.16 (CH, isopropyl), 36.12 ($C(CH_3)_3$), 57.74 (CH_2), 64.38 (CHNH), 81.05 (CHOH), 121.13 (CH aromatic), 125.31 (CH aromatic), 137.29 (CH aromatic), 148.08 (C aromatic), 159.72 (C=O), 165.12 (C aromatic).

***(3'R,1"R)*-2-(3'-phenyl)oxazolyl-6-(1"-hydroxy-2,2-dimethyl)propylpyridine (5a) and**

***(3'R,1"S)*-2-(3'-phenyl)oxazolyl-6-(1"-hydroxy-2,2-dimethyl)propylpyridine (5b).** Compounds **5a** (0.39 g, 61%) and **5b** (0.246 g, 39%) were prepared according to the procedure described for **4a** and **4b** in a total yield of 60% starting from the above imidate (1.1 g, 4.81 mmol) and *R*-2-phenylglycinol (0.66 g, 4.81 mmol). **5a**: Mp 112 °C. $[\alpha]_D^{20}$ = +40.4 (c = 0.86, CH_2Cl_2). ^1H NMR (250 MHz) 0.95 (s, 9H, $C(CH_3)_3$), 4.04 (d, *J* = 7.28 Hz, 1H, OH), 4.37 (t, *J* = 8.51 Hz, 1H, CHN), 4.48 (d, *J* = 7.28 Hz, 1H, C**H**OH), 4.88 (dd, *J* = 10.26 and 8.76 Hz, 1H, C**H**HO), 5.45 (dd, *J* = 10.26 and 8.76 Hz, 1H, CH**H**O), 7.29-7.39 (m, 6H, 5 phenyl and 1 pyridyl), 7.75 (t, *J* = 7.76 Hz, 1H, aromatic H), 8.07 (d, *J* = 7.76 Hz, 1H, aromatic). ^{13}C NMR (62.9 MHz) 25.94 (3 CH_3, *t*Bu), 36.3 ($\mathbf{C}(CH_3)_3$), 70.23 (CH_2), 75.32 (CHN), 80.7 (CHOH), 123.05 (CH, pyridine), 124.72 (CH, pyridine), 126.78 (2 CH, phenyl), 127.73 (CH, phenyl), 128.79 (2 CH, phenyl), 136.1 (CH, pyridine), 141.92 (C, phenyl), 145.1 (C, pyridine), 160.57 (C=N), 164 (C, pyridine). Found C 72.49; H 7.12; N 9.15. Calcd. for $C_{19}H_{22}N_2O_2$ (310.4) C 73.52; H 7.14; N 9.02 **5b**: Mp 106 °C. $[\alpha]_D^{20}$ = +75.6 (c = 0.90, CH_2Cl_2). ^1H NMR (250 MHz) 0.94 (s, 9H, $C(CH_3)_3$), 4.12 (d, *J* = 7.26 Hz, 1H, OH), 4.35 (t, *J* = 8.76 Hz, 1H, CHN), 4.47 (d, *J* = 7.26 Hz, C**H**OH), 4.89 (dd, *J* = 10.26 and 8.76 Hz, 1H, C**H**HO), 5.44 (dd, *J* = 10.26 and 8.76 Hz, 1H, CH**H**O), 7.29-7.38 (m, 6H, 5 phenyl and 1 pyridyl), 7.74 (t, *J* = 7.76 Hz, 1H, aromatic), 8.07 (d, *J* = 7.76 Hz, 1H, aromatic). ^{13}C NMR (62.9 MHz) 25.95 (3 CH_3, *t*Bu), 36.24 ($\mathbf{C}(CH_3)_3$), 70 (CH_2), 75.35 (CHN), 80.77 (CHOH), 122.84 (CH, pyridine), 124.9 (CH, pyridine), 126.7 (2 CH, phenyl), 127.73 (CH, phenyl), 128.79 (2 CH, phenyl), 136.06 (CH , pyridine), 141.81 (C, phenyl), 144.66 (C, pyridine), 160.92 (C=N), 164.13 (C, pyridine). Found C 72.55; H 7.19; N 9.10. Calcd. for $C_{19}H_{22}N_2O_2$ (310.4) C 73.52; H 7.14; N 9.02.

***(3'S,1"S)*-2-(3'-isopropyl)oxazolyl-6-(1"-methoxy-2,2-dimethyl)propylpyridine (9a).** To a solution of **4a** (100 mg, 0.36 mmol) in 4 ml THF were added NaH (15.9 mg, 60 %, 0.4 mmol) and, after stirring the mixture for 1 h, iodomethane (56.5 mg, 0.4 mmol) dropwise. The mixture was stirred for an additional 4 h at room temperature and the solvent was removed by evaporation *in vacuo* giving a light yellow oil which was purified by flash chromatography on silica gel (7 x 2.5 cm column, hexane:AcOEt 4:1) to yield **9a** as a white solid (87 mg, 83 %). Mp 87 °C. $[\alpha]_D^{20}$ = +138.8 (c = 0.38, CH_2Cl_2). ^1H NMR (250 MHz) 0.90 (s, 9H, $CC(CH_3)_3$), 1.02 (d, *J* = 6.5 Hz, 3H, CH_3), 1.05 (d, *J* = 6.5 Hz, 3H, CH_3), 1.8-2 (m, 1H, isopropyl CH), 3.23 (s, 3H, OCH_3), 4.13-4.26 (m, 3H, CH_2O, C**H**OCH_3), 4.46-4.52 (m, 1H, CHN), 7.49 (dd, *J* = 7.8 and 1 Hz, aromatic), 7.74 (t, *J* = 7.8 Hz, aromatic), 7.98 (dd, *J* = 7.8 and 1 Hz, aromatic).

***(3'S,1"R)*-2-(3'-isopropyl)oxazolyl-6-(1"-methoxy-2,2-dimethyl)propylpyridine (9b).** Compound **9b** was prepared as a white solid (40 mg, 40%) by the procedure described for the synthesis of **9a**, starting from **4b** (100 mg, 0.36 mmol). Mp 98 °C. $[\alpha]_D^{20}$ = +25.5 (c = 0.24, CH_2Cl_2). ^1H NMR (250 MHz) 0.90 (s, 9H, $C(CH_3)_3$), 0.93 (d, *J* = 6.7 Hz, 3H, CH_3), 1.05 (d, *J* = 6.7 Hz, 3H, CH_3), 1.85-2 (m, 1H, isopropyl CH), 4.08 - 4.26 (m, 3H, CH_2O, C**H**OCH_3), 4.47-4.54 (m, 1H, CHN), 7.48 (dd, *J* = 7.85 and 1.1 Hz, 1H, aromati), 7.75 (t, *J* = 7.85 Hz, 1H, aromatic), 8.01 (dd, *J* = 7.85 and 1.1 Hz, 1H, aromatic).

General procedure for the addition of diethylzinc to the aromatic aldehydes using catalysts 4a, 4b, 5a and 5b. Freshly distilled benzaldehyde (**7a**, 212 mg, 2.0 mmol) or *p*-chlorobenzaldehyde (**7b**, 281 mg, 2.0 mmol), the appropriate catalyst ((**4a** or **4b**, 27.63 mg, 0.1 mmol) or (**5a** or **5b**, 31.05 mg, 0.1 mmol)) and 4 ml hexane (when diethylzinc in toluene was used) or 4 ml toluene (when

diethylzinc in hexane was used) were placed in a dried flask which had been purged with nitrogen. After stirring for 0.5 h at 0 °C, diethylzinc (4 ml, 1 M in toluene or hexane, 4 mmol) was added. After 24 h at 0 °C or at ambient temperature (see Table 1), the reaction was quenched with hydrochloric acid (1 M, 10 ml) and the mixture was extracted with 3x20 ml CH_2Cl_2. The CH_2Cl_2 extract was dried ($MgSO_4$) and concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (10 x 2 cm column, hexane:AcOEt 4:1) to give the corresponding alcohol as a pale yellow oil. (+)- or (-)-1-phenyl propanol (**8a**): ^1H NMR (250 MHz) 0.92 (t, J = 7.36 Hz, 3H, CH_3), 1.68 -1.91 (m, 2H, CH_2), 2.08 (s, 1H, OH), 4.58 (t, J = 6.6 Hz, 1H, CHOH), 7.26-7.37 (m, 5H, aromatic). (+)- or (-)-1-(4-chlorophenyl)propanol (**8b**): ^1H NMR (400 MHz) 0.90 (t, J = 7.4 Hz, 3H, CH_3), 1.68-1.89 (m, 2H, CH_2), 1.88 (s, 1H, OH), 4.58 (t, J = 6.5 Hz, 1H, CHOH), 7.26-7.32 (m, 4H, aromatic).

Zinc complex of 4a. The complex was prepared as described by Bolm *et al.* from **4a** (0.095 mmol, 26.5 mg) and diethylzinc (95 µl, 1 M in hexane, 0.095 mmol).[9] The yellow complex obtained was analyzed by ^1H and ^{13}C NMR spectroscopy. ^1H NMR (400 MHz, C_6D_6) 0.77 (d, J = 6.4 Hz, 3H, CH_3), 0.82-0.89 (m, 2H, CH_2), 1.04 (d, J = 6.4 Hz, 3H, CH_3), 1.06 (s, 9H, $C(CH_3)_3$), 1.67-1.78 (m, 1H, isopropyl CH), 1.93 (t, J = 8 Hz, 3H, CH_3), 3.88-3.98 (m, 2H, CH_2O), 4.11-4.17 (m, 1H, CHN), 4.7 (s, 1H, CHO), 6.48 (dd, J = 7.6 and 0.8 Hz, 1H, aromatic), 6.56 (t, J = 7.6 Hz, 1H, aromatic), 7.38 (dd, J = 7.6 and 0.8 Hz, 1H, aromatic). ^{13}C NMR (400 MHz, C_6D_6) 1.15 (CH_2), 14.50 (CH_3), 18.88 (CH_3), 19.9 (CH_3), 27.34 (3 CH_3, *t*Bu), 33.34 (CH, isopropyl), 38.32 ($C(CH_3)_3$), 71.02 (CH_2), 73.98 (CHN), 84.8 (CHO), 121.84 (CH aromatic), 125.30 (CH aromatic), 136.01 (CH aromatic), 144.16 (C aromatic), 161.47 (C=N), 167.75 (C aromatic).

Zinc complex synthesized from racemic 1. This complex was prepared by the above procedure from **1** (0.15 mmol, 24.8 mg) and diethylzinc (150 µl 1 M in hexane, 0.15 mmol), affording a white complex which was analyzed by ^1H NMR and ^{13}C NMR spectroscopy. ^1H NMR (400 MHz, C_6D_6) 0.8-0.9 (m, 2H, CH_2), 0.97 (s, 9H, $C(CH_3)_3$), 1.64 (t, J = 8.4 Hz, 3H, CH_3), 4.97 (s, 1H, CHO), 6.38-6.41 (m, 1H, aromatic), 6.8-6.9 (m, 2H, aromatic), 8.07-8.09 (m, 1H, aromatic). ^{13}C NMR (100.6 MHz, C_6D_6) -2.69 (CH_2), 14.30 (CH_3), 26.92 (3 CH_3, *t*Bu), 37.82 ($C(CH_3)_3$), 85.12 (CHO), 122.57 (CH aromatic), 136.84 (CH aromatic), 147.16 (CH aromatic), 165.76 (C aromatic).

Acknowledgements: This work was supported by the Swedish Natural Science Research Council and by the Swedish Research Council for Engineering Sciences.

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(*Received in UK* 30 *November* 1994)