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Chiral Ligands Containing Heteroatoms. 8.[1] 2-[(2S)-2-Pyrrolidinyl]pyridine as a Novel Catalyst in the Enantioselective Addition of Diethylzinc to Aldehydes

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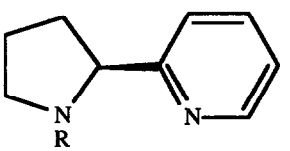
Abstract: The title compound has been demonstrated to be an effective enantioselective catalyst in the addition of diethylzinc to aldehydes: optically active secondary alcohols in up to 100% ee were obtained in high yields. The temperature dependence of the stereodynamic course of the reaction was examined and the nature of the possible catalytic complex was discussed on the basis of NMR data too.

The design of asymmetric reactions that proceed with high enantioselectivity is an important goal in chemical synthesis. One of the most studied processes in the field of the carbon-carbon bond forming reactions is the enantioselective addition of organometallic reagents to carbonyl substrates using chiral ligands.[2-6] In particular, increasing interest is recently devoted to the study of enantioselective addition of dialkylzinc to aldehydes:[7-12] as a result, several catalytic systems are now available from chiral amino alcohols.[13-15] We wish to report herein a new type of chiral catalyst for the dialkylzinc-aldehyde addition, based on chiral 2-[(2*S*)-2-pyrrolidinyl]pyridines (**1-3**),[16] as the first example of the use of amino pyridines. In particular, the catalyst derived from **1**, which can be recovered unchanged after reaction, is highly effective in achieving enantiocontrol with various aldehydes.



1 R = H
2 R = CH_3
3 R = Li

The pyridines **1-2** were prepared starting from natural (*S*)-proline following a recently published procedure.[16] The enantiomeric excess of **1** was determined *via* GLC analysis of the corresponding "Mosher amide" and confirmed by a ^{19}F-NMR spectrum: an ee of about 96% was so established for the prepared compounds.[16]

Enantioselective additions of diethyl zinc to aldehydes in the presence of catalytic amounts (3 mol%) of **1-3** were carried out in hexane/ether at various temperature (50°, 20° or -10°C). The data obtained using chiral pyridine **1** are summarized in Table 1.

Table 1. Asymmetric Addition of Diethylzinc to Aldehydes Using Ligand 1[a]

run	aldehyde	temp. °C	time h	optically active carbinol: conv.[b] %	optically active carbinol: $[\alpha]^{25}_D$, deg. (c, solvent)	optically active carbinol: enantioselectivity[c] %
1	benzaldehyde	20	20	100	-25.75 (neat)	93(*S*)
2	benzaldehyde	-10	18	93	-44.24 (4, $CHCl_3$)	100(*S*)
3	*p*-anisaldehyde	20	16	87	-31.26 (4, benzene)	94(*S*)
4	*p*-anisaldehyde	-10	20	60	-32.25 (3, benzene)	98(*S*)
5	*p*-chlorobenzaldehyde	-10	16	90	-25.00 (5, benzene)	100(*S*)
6	*p*-tolualdehyde	-10	6	77	-34.87 (4, benzene)	92(*S*)
7	*o*-tolualdehyde	-10	16	96	-57.51 (4, benzene)	100(*S*)[d]
8	3-phenylpropanal	50	6	87	+15.59 (4, EtOH)	60(*S*)
9	3-phenylpropanal	20	6	89	+15.22 (3, EtOH)	59(*S*)
10	3-phenylpropanal	-10	40	61	+7.56 (2, EtOH)	29(*S*)
11	(*E*)-3-phenylpropenal	-10	18	98	+5.48 (3, $CHCl_3$)	91(*R*)
12	3-phenylpropynal	-10	18	91	-4.50 (3, Et_2O)	24(*S*)
13	heptanal	20	16	89	+5.44 (4, $CHCl_3$)	67(*S*)
14	heptanal	-10	40	56	+3.23 (3, $CHCl_3$)	40(*S*)
15	cyclohexylcarboxyaldehyde	-10	16	77	-6.37 (3, hexane)	90(*S*)
16	furfural	-10	8	93	-5.82 (4, $CHCl_3$)	33(*S*)
17	ferrocenylcarboxaldehyde	-10	20	50	+51.94 (2, benzene)	54(*S*)[d]

[a]) Reaction carried out in hexane/ether with a molar ratio Et_2Zn/aldehyde/ligand = 2/1/0.06. [b]) GLC yields of the crude products. [c]) Verified both by GLC and ^{19}F NMR of the (+)MPTA esters and corrected for the minimum optical purity of **1**. [d]) Configuration tentatively assigned.

In all the examined cases, the corresponding ethyl carbinols were obtained in good chemical yields, within 6-40 h, as sole products detected. Only at 50°C, in the addition of 3-phenylpropanal (run 8), a small amount (<5%) of the corresponding reduction carbinol was formed. All the carbinols recovered exhibit *S* absolute configuration and, contrary to what has been observed by other authors,[17] only with (*E*)-3-phenylpropenal (run 11) an alcohol having *R* absolute configuration was recovered. The enantioselectivity ranges from low (run 12) to very high (runs 1-7). In particular, all substituted benzaldehydes gave optically active carbinols with asymmetric induction values higher than 90%, the effect of the *para*-substituent in the aldehyde on enantioselectivity being not significant. An increase of ee, up to 100%, was obtained by using *o*-tolualdehyde (run 7) instead of *p*-tolualdehyde (run 6), indicating a steric influence of the *ortho*-substituent on the ee. Steric effects seem to be at the origin of the reduced values of ee obtained using aliphatic aldehydes. In fact, in the cases reported, the optical yields were lower than 70% when 3-phenylpropanal or heptanal were reacted, raising up to 90% in the case of a substrate having a bulky α-substituent, such as the cyclohexylcarboxaldehyde (run 15) or conformationally rigid, as (*E*)-cinnamaldehyde (run 11). In this last respect, it is interesting to note that on passing to 3-phenylpropynal,

which has a reduced steric bulk, the enantioselectivity dropped down (run 12). When the substrates used were the furfural (run 16) or ferrocenylcarboxaldehyde (run 17) the reaction was not quite enantioselective.

Surprisingly, the data obtained show that, in some cases, the steric course of the reaction depends critically upon the reaction temperature. In fact, with benzaldehyde (runs 1-2) and *p*-anisaldehyde (runs 3-4), a lowering of the reaction temperature corresponded to a slight increment of the ee, chemical yields being only slightly affected. On the contrary, when 3-phenylpropanal (runs 9-10) and heptanal (runs 13-14) were involved, a lowering of the reaction temperature from 20°C to -10°C resulted in decreasing of the ees and of the chemical yields:[18] it is however important to note that there was no significant variation in the optical and chemical yield of the product by raising the reaction temperature from 20°C to 50°C (run 9 should be compared with run 8). On these data, it is to suppose that the nature of the substrate (aromatic or aliphatic) is significant for determining the steric course of the reaction at different temperatures.

Table 2. Asymmetric Addition of Dialkylzinc compounds to benzaldehyde[a]

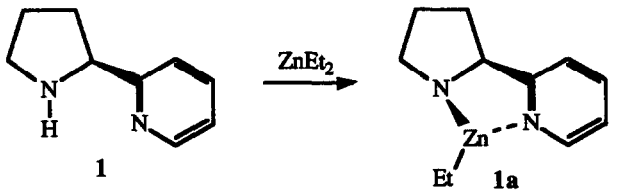
				optically active carbinol		
run	dialkylzinc	chiral ligand	time h	conv.[b] %	$[\alpha]^{25}_D$, deg. (c, solvent)	enantioselectivity[c] %
1	$ZnEt_2$	**1**	20	100	-25.75 (neat)	93(*S*)
18	$Zn(C{\equiv}CBu^n)_2$	**1**	15	87	-4.40 (5, $CHCl_3$)	16(*S*)
19	$ZnEt_2$	**2**	20	100	-1.71(neat)	6(*R*)
20	$ZnEt_2$	**3**	6	95	+0.26(6,$CHCl_3$)	<1(*S*)

a) Reaction carried out in hexane/ether at 20°C with a molar ratio R_2Zn/benzaldehyde/ligand = 2/1/0.06. *b*) GLC yields of the crude products. *c*) Verified both by GLC and ^{19}F NMR of the (+)MPTA esters and corrected for the minimum optical purity of the ligands.

According to reports by other authors,[7] also with the ligand **1**, by using $Zn(C{\equiv}CBu^n)_2$ (run 18, Table 2) instead of $ZnEt_2$ (run 1) for the alkylation of the benzaldehyde, the reaction showed low selectivity, close to that observed in the ethylation of 3-phenylpropynal (run 12). The Table 2 reports also some data obtained by changing the nature of the ligand employed. When 2-[(2*S*)-1-methyl-2-pyrrolidinyl]pyridine (**2**) or the **1**-lithium salt (**3**) was employed for the reaction of diethylzinc with benzaldehyde, the optical yield of the alcohol was negligible in both cases. This effect is quite opposite to that which we have observed using 1-(2-pyridylmethyl)pyrrolidines[15] as chiral catalysts. In fact, these last aminoalcohols exhibit a lower enantioface discrimination capability than the corresponding lithium salts.[15] The data of Table 2 indicate that the presence of a hydrogen atom on the nitrogen atom of the pyrrolidine ring is essential for enantioselection and suggest the formation of a stoichiometric complex **1a** (Scheme I) between the dialkylzinc and the ligand, so providing an effective chiral environment for the reaction.

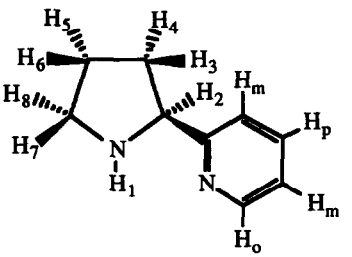
This hypothesis is furtherly supported by the 300 MHz ^1H NMR analysis of the **1**/$ZnEt_2$ complex. The chemical shift values observed for pure **1** and for the **1**/$ZnEt_2$ complex in C_6D_6 as solvent are summarized in Table 3.

Scheme I



The examination of the data shows that, on adding of diethylzinc, the signal at 2.43 ppm, due to the hydrogen bound to the pyrrolidine nitrogen atom, disappeared, that demonstrating the formation of a Zn-N bond. All the signals were significantly shifted upfield, with the exception of those relative to H_p and H_{7-8}: moreover, no further shift of signals was observed when the molar ratio Et_2Zn/ligand was greater than 1. These data seem to be in agreement with the formation of an adduct in which the zinc atom, covalently bound to the pyrrolidine nitrogen atom, is coordinated to the pyridine nitrogen atom by way of a faint interaction.

Table 3. ^1H NMR chemical shifts of 1 and 1/$ZnEt_2$ complex[a]



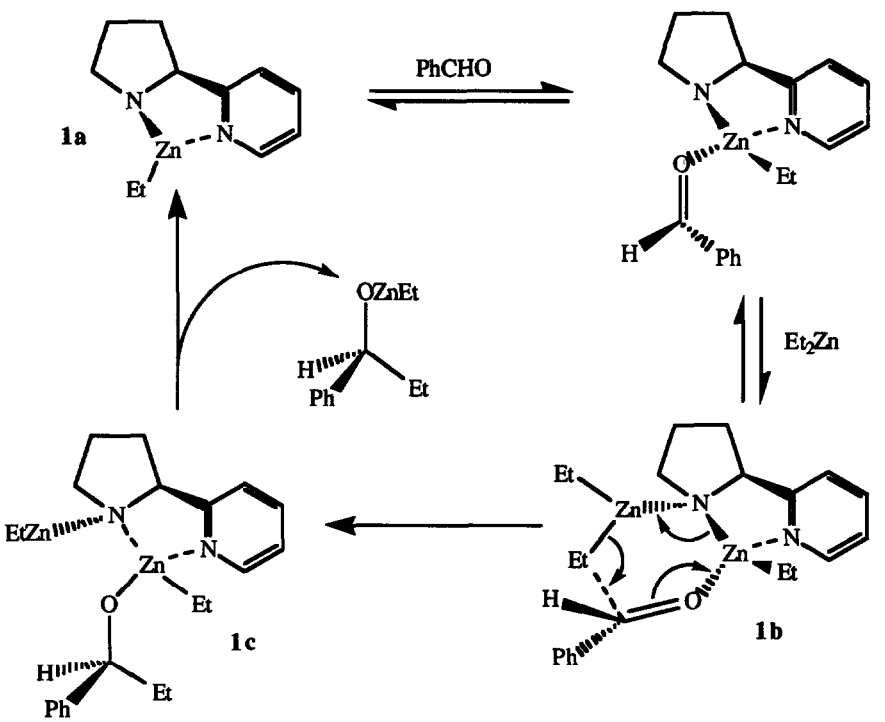
H	1 δ (ppm)	1/$ZnEt_2$ complex δ (ppm)	Δδ
H_o	8.45	7.69	-0.76
H_m	7.18	6.22	-0.96
H_m	7.12	6.15	-0.97
H_p	6.65	6.60	-0.05
H_1	2.43	-	-
H_2	4.18	4.05	-0.13
H_3	2.05	1.61	-0.44
H_4	1.74	1.27	-0.47
H_5+H_6	1.56	0.85	-0.71
H_7	3.00	3.96	+0.96
H_8	2.78	3.53	+0.75

[a]) NMR spectra obtained in C_6D_6 using a 300 MHz spectrometer with a molar ratio 1/$ZnEt_2$ = 1

Taking into account the ^1H NMR and the stereochemical data and on the basis of literature,[8] it is possible to suggest the catalytic cycle shown in Scheme II for the enantioselective reaction. The starting step should be the coordination of the carbonyl oxygen atom to the zinc atom of the adduct **1a** to form a complex which cannot ethylate benzaldehyde but should form slowly benzyl alcohol.[15] Another $ZnEt_2$ molecule is required to afford the

new adduct **1b**, responsible for the alkylation reaction. The transfer of an ethyl group to the carbonyl carbon atom *via* a six-membered transition state should originate the intermediate **1c** that regenerates the catalytic chiral complex **1a** through elimination of the optically active zinc alkoxide. Evidence that the conversion of **1b** to **1c** is the determining step appears to be provided by the experimental observation of the rates of the reaction of benzaldehyde and its *para*-derivatives, the relative reactivities at -10°C being *p*-tolualdehyde > *p*-chlorobenzaldehyde ≥ benzaldehyde > *p*-anisaldehyde.

Scheme II



Examination of molecular models and subsequent calculation show that the transition state, leading to the wrong enantiomer, is not sterically favored because of repulsion between the large group on the aldehyde and the pyrrolidine ring of the complex. However, the assembly **1b** should exist in two different diastereomeric forms involved in a thermodynamic equilibrium: this equilibrium might be in principle responsible of the different steric behavior of aromatic and aliphatic aldehydes with temperature. In this respect, it may be significant that the poorer optical yields occur when the reaction rate decreases noticeably.

Experimental Section

Boiling points are uncorrected. ^1H (300 MHz) and ^{19}F (282 MHz) NMR Fourier transform spectra were performed on a Varian VXR-300 spectrometer with TMS as internal standard. The optical rotations were measured by a Perkin-Elmer 142 automatic polarimeter in a 1 dm tube. Gas chromatographic analyses of the reaction products and diastereoseparations of the (+)MPTA derivatives were performed by a Perkin-Elmer 8600 chromatograph using N_2 as carrier gas on a 15 m DBWAX widebore capillary column (J&W). Optical purity was determined also by direct comparison of optical rotation, which, when possible, was carefully done with the synthetic and authentic resolved materials. All reactions were carried out under argon atmosphere: all reagents and solvents employed were reagent grade materials purified by standard methods and redistilled before use. All the aldehydes employed were obtained by purification of commercial products. As chiral starting materials the following ligands were employed: 2-[(2*S*)-2-pyrrolidinyl]pyridine (**1**),[15] b. p. 60°C/0.5 mbar, $[\alpha]^{25}_D$ -78.63 ($CHCl_3$), 2-[(2S)-1-methyl-2-pyrrolidinyl]pyridine (**2**),[15] b. p. 90°C/5 mbar, $[\alpha]^{25}_D$ -95.61 ($CHCl_3$).

Asymmetric Addition of Dialkylzinc to Aldehydes. The following procedures are representative of all the experiments in the same conditions.

Run 1. - A solution of the ligand **1** (55 mg, 0.37 mmol) in ether (5 mL) was cooled at 0 °C. Diethylzinc (1 M, 12.4 mL, 12.4 mmol) in hexane was added over a period of 5 min. The mixture was stirred at room temperature for 20 min, added with benzaldehyde (0.6 mL, 0.647 g, 6.1 mmol) then stirred for additional 20 h. The reaction mixture was quenched with 10% H_2SO_4 (10 mL) then was extracted with ether and the organic layer was washed with 10% H_2SO_4, saturated $NaHCO_3$ and dried (Na_2SO_4). The residue was distilled and purified by flash chromatography to afford pure (GLC) (-)(*S*)-1-phenylpropanol having $[\alpha]^{25}_D$ - 25.75 (neat).

Run 2. - A solution of the ligand **1** (55 mg, 0.37 mmol) in ether (5 mL) was cooled at 0 °C. Diethylzinc (1 M, 12.4 mL, 12.4 mmol) in hexane was added over a period of 5 min. The mixture was stirred at room temperature for 20 min, cooled at -10°C and added with benzaldehyde (0.6 mL, 0.647 g, 6.1 mmol) then stirred for additional 18 h. The reaction mixture was quenched with 10% H_2SO_4 (10 mL) then was extracted with ether and the organic layer was washed with 10% H_2SO_4, saturated $NaHCO_3$ and dried (Na_2SO_4). The residue was distilled and purified by flash chromatography to afford pure (GLC) (-)(*S*)-1-phenylpropanol (75% yield) having $[\alpha]^{25}_D$ - 44.24 (*c* 4, $CHCl_3$).

Run 8. - A solution of the ligand **1** (55 mg, 0.37 mmol) in ether (5 mL) was cooled at 0 °C. Diethylzinc (1 M, 12.4 mL, 12.4 mmol) in hexane was added over a period of 5 min. The mixture was stirred at room temperature for 20 min, heated at 50°C and added with 3-phenylpropanal (0.82 mL, 0.8 g, 6 mmol) then stirred for additional 6 h. The reaction mixture was quenched with 10% H_2SO_4 (10 mL) then was extracted with ether and the organic layer was washed with 10% H_2SO_4, saturated $NaHCO_3$ and dried (Na_2SO_4). The residue was distilled and purified by flash chromatography to afford pure (GLC) (+)(*S*)-1-phenylpentan-3-ol (69% yield) having $[\alpha]^{25}_D$ + 15.59 (*c* 4, EtOH).

Run 18. - Diethylzinc (1 M, 12.4 mL, 12.4 mmol) in hexane was added over a period of 5 min with 1-hexyne (2.9 mL, 2.07 g, 25 mmol) and the resulting mixture was heated at 70°C for 3 h. Then the reaction mixture was cooled at 0°C and a solution of the ligand **1** (55 mg, 0.37 mmol) in ether (5 mL) was added. The mixture was stirred at room temperature for 20 min, added with benzaldehyde (0.6 mL, 0.647 g, 6.1 mmol) then stirred for additional 15 h. The reaction mixture was quenched with 10% H_2SO_4 (10 mL) then was extracted with ether and the organic layer was washed with 10% H_2SO_4, saturated $NaHCO_3$ and dried (Na_2SO_4). The residue was distilled and purified by flash chromatography to afford pure (GLC) (-)-1-phenylhept-2-yn-1-ol having $[\alpha]^{25}_D$ -4.40 (*c* 5, $CHCl_3$).

Run 19. - A solution of the ligand **2** (60 mg, 0.37 mmol) in ether (5 mL) was cooled at 0 °C. Diethylzinc (1 M, 12.4 mL, 12.4 mmol) in hexane was added over a period of 5 min. The mixture was stirred at room temperature for 20 min, added with benzaldehyde (0.6 mL, 0.647 g, 6.1 mmol) then stirred for additional 20 h. The reaction mixture was quenched with 10% H_2SO_4 (10 mL) then was extracted with ether and the organic layer was washed with 10% H_2SO_4, saturated $NaHCO_3$ and dried (Na_2SO_4). The residue was distilled and purified by flash chromatography to afford pure (GLC) (-)(*S*)-1-phenylpropanol having $[\alpha]^{25}_D$ -1.71 (neat).

Run 20. - A solution of the ligand **1** (70 mg, 0.45 mmol) in ether (5 mL) was cooled at 0 °C added with butyl lithium (1.6 M, 0.35 mL, 0.56 mmol) in hexane and stirred at room temperature for 5 min. Then diethylzinc (1 M, 12.4 mL, 12.4 mmol) in hexane was added over a period of 5 min. The mixture was stirred at room temperature for 20 min, added with benzaldehyde (0.6 mL, 0.647 g, 6.1 mmol) then stirred for additional 6 h. The reaction mixture was quenched with 10% H_2SO_4 (10 mL) then was extracted with ether and the organic layer was washed with 10% H_2SO_4, saturated $NaHCO_3$ and dried (Na_2SO_4). The residue was distilled and purified by flash chromatography to afford pure (GLC) (-)(*S*)-1-phenylpropanol having $[\alpha]^{25}_D$ - 25.75 (neat).

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18. A quite similar effect of temperature has been observed also by Soai (see ref. 7) in the enantioselective ethylation of 3-phenylpropynal.