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Chiral Ligands Containing Heteroatoms. 10.[1] 1-(2-Pyridyl)alkylamines as Chiral Catalysts in the Addition of Diethylzinc to Aldehydes: Temperature Dependence on the Enantioselectivity.

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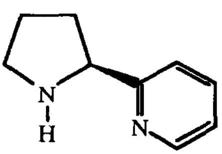
Abstract: Chiral amino pyridines derived from α-aminoacids were demonstrated to be enantioselective catalysts in the addition of diethylzinc to aldehydes: optically active secondary alcohols in up to 98% ee were obtained in high yields. The temperature dependence of the stereochemical course of the reaction was found to be strictly related to the alkyl structure of the chiral catalyst. The nature of the possible catalytic complex and the origin of temperature effect was thus discussed on the basis of NMR data too.

A catalytic enantioselective process is now recognised as one of the most important problems in organic synthesis.[2] It is known that chiral amines and amino alcohols, mainly β-amino alcohols as ligands, may accelerate and direct the stereochemical outcome of the asymmetric alkylation of aldehydes by zinc dialkyls, sometimes achieving high stereoselectivity.[3] Recently, in our laboratory, we found that also amino pyridines act as chiral catalysts in the enantioselective addition of diethylzinc to aldehydes. In fact, we have prepared and used 2-[(2*S*)-2-pyrrolidinyl]pyridine (**1**): ees up to 100% were observed.[4] On this basis, we have extended the investigation to other optically active amino pyridines **2-7**, which have a greater conformational mobility than **1**.



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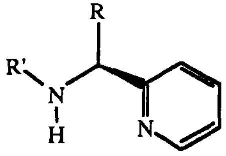


2 $R = R' = CH_3$
3 $R = Pr^i, R' = CH_3$
4 $R = Bu^i, R' = CH_3$
5 $R = Bu^i, R' = H$
6 $R = Bu^s, R' = CH_3$
7 $R = CH_2Ph, R' = CH_3$

We wish to report herein the data obtained using amines **2**-**7** as chiral catalysts for the dialkylzinc-aldehyde addition and, in particular, a study on the temperature dependence of the stereodynamic course of the reaction.

The pyridines **2**-**7** were prepared starting from natural *L*-α-aminoacids following a recently published procedure.[1] The enantiomeric excess of the products **2**-**7** was determined through GLC analysis of the corresponding "Mosher amides" and confirmed by a ^{19}F-NMR spectrum: an ee of about 94% was so established for the compounds **2**-**4**, **6** and **7**; for amine **5** an ee of about 90% was found.[1]

Enantioselective additions of diethylzinc to aldehydes in the presence of catalytic amounts (3 mol%) of **2**-**7** were carried out in hexane/ether at various temperatures (35°, 20° or -10°C). The data obtained using chiral pyridines **1**-**7** are summarised in Table 1. In most of the examined cases, the ethyl carbinols were obtained in good chemical yields, within 12-24 h. Independently by the reaction temperature, the ethyl carbinol is the main product detected; the reduction alcohol is formed only in small amounts (2-3%). All the carbinols recovered exhibit *S* absolute configuration. The enantioselectivity ranges from low to very high: it is noteworthy that, apart from ligand **1**, ligands **3** and **6** are the most efficient among those examined. A comparison with the data obtained with ligand **1**,[4] let us suppose however that a more constrained ligand, like **1**, should be essential as catalyst for achieving high stereoselectivity. The examination of the data also indicates that there was no difference in the stereochemical trend of the reaction using the ligand **4**, bearing only a hydrogen atom on the amino nitrogen atom, and ligand **5**, which is not *N*-alkylated.

All the data obtained showed that the stereochemical outcome of the reaction depended critically upon both the reaction temperature and the chiral ligand employed. Surprisingly, whereas in the most of cases a lowering of the temperature corresponded to an enhancement of the ee, using ligand **3** a lowering of the reaction temperature resulted in a marked decrease of the enantioselectivity[5] (*e.g.* runs 5-7, Table 1), at least in the range investigated.

It is noteworthy that the activation free energy differences ($\Delta\Delta G^{\ddagger}$)[6] among the competing transition states were generally small: however, values higher than 1 Kcal/mole were often revealed. The results reported in the Table 1 show that the lowering of reaction temperature resulted in an increase in the absolute value of the free energy differences $\Delta\Delta G^{\ddagger}$ in all the cases, except when the ligand **3** was employed. In particular in the case of alkylation of benzaldehyde there was a decrease of $\Delta\Delta G^{\ddagger}$.

On the basis of our previous suggestions, the transfer of the ethyl group from the zinc atom to the carbonyl carbon atom should occur through six-membered cyclic transition states.[4,7] According to what is commonly accepted for kinetically controlled asymmetric transformations, the enantioselectivity of the process should only depend on the free energy differences among the competing transition states. A study of the temperature dependence of the reaction stereoselectivity should allow an evaluation of the enthalpy and entropy term contributions and hence the factors leading to a preferential diastereomeric transition state.

The differences in the values of the activation parameters (at 20°C) for the alkylation of aldehydes by diethylzinc, using ligands **2**-**7** as catalysts, are listed in Table 2.

The data reported show that the free energy differences $\Delta\Delta G^{\ddagger}$ are relatively high in the case of the alkylation of benzaldehyde and quite low when an aliphatic aldehyde, such as 3-phenylpropanal, is used as substrate.

Table 1. Asymmetric Addition of Diethylzinc to Aldehydes Using Ligands 1-7[a]

run	aldehyde	ligand	temp. °C	time h	conv.[b] %	optically active carbinol		$\Delta\Delta G^{\ddagger}$[d] Kcal/mole
						$[\alpha]^{25}_{D}$, deg. (c, solvent)	enantio-selectivity[c], %	
1[e]	benzaldehyde	1	20	20	100	-25.75 (neat)	93(*S*)	-1.93
2[e]	benzaldehyde		-10	18	93	-44.24 (4, $CHCl_3$)	100(*S*)	-
3	benzaldehyde	2	20	12	98	-27.51 (4, $CHCl_3$)	64(*S*)	-0.88
4	benzaldehyde		-10	20	94	-31.41 (2, $CHCl_3$)	73(*S*)	-0.97
5	benzaldehyde	3	35	20	87	-38.94 (2, $CHCl_3$)	91(*S*)	-1.87
6	benzaldehyde		20	20	88	-35.19 (4, $CHCl_3$)	82(*S*)	-1.34
7	benzaldehyde		-10	22	92	-17.56 (4, $CHCl_3$)	41(*S*)	-0.45
8	*o*-tolualdehyde		35	20	98	-36.43 (2, benzene)	65(*S*)[f]	-0.95
9	3-phenylpropanal		35	20	77	+7.44 (2, EtOH)	30(*S*)	-0.38
10	3-phenylpropanal		20	20	51	+5.78 (3, EtOH)	23(*S*)	-0.27
11	3-phenylpropanal		-10	20	70	+0.98 (1, EtOH)	4(*S*)	-0.04
12	3-phenylpropynal		35	20	98	-3.29 (2, Et_2O)	18(*S*)	-0.22
13	heptanal		35	24	89	+1.06 (2, $CHCl_3$)	12(*S*)	-0.15
14	benzaldehyde	4	35	20	92	20.19 (4, $CHCl_3$)	47(*S*)	-0.62
15	benzaldehyde		20	16	87	-23.10 (3, $CHCl_3$)	54(*S*)	-0.70
16	benzaldehyde		-10	20	92	-30.63 (3, $CHCl_3$)	72(*S*)	-0.95
17	benzaldehyde	5	20	18	89	-22.08 (2, $CHCl_3$)	54(*S*)	-0.70
18	benzaldehyde		-10	20	75	-31.86 (2, $CHCl_3$)	78(*S*)	-1.09
19	benzaldehyde	6	35	20	93	-25.76 (2, $CHCl_3$)	63(*S*)	-0.91
20	benzaldehyde		20	12	95	-36.45 (3, $CHCl_3$)	85(*S*)	-1.46
21	benzaldehyde		-10	19	97	-41.76 (3, $CHCl_3$)	98(*S*)	-2.40
22	*o*-tolualdehyde		-10	20	76	-23.07 (1, benzene)	44(*S*)[f]	-0.49
23	3-phenylpropanal		-10	48	42	+3.81 (4, EtOH)	15(*S*)	-0.16
24	heptanal		-10	20	38	+1.74 (2, $CHCl_3$)	20(*S*)	-0.21
25	benzaldehyde	7	20	18	52	-31.92 (4, $CHCl_3$)	75(*S*)	-1.13
26	benzaldehyde		-10	20	89	-38.70 (2, $CHCl_3$)	90(*S*)	-1.54

[a] Reactions 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 the ligand employed. [d] Calculated from $\Delta\Delta G^{\ddagger} = -RT\ln K_S/K_R = -RT\ln[S]/[R] = -RT\ln(1+a)/(1-a)$, where a = enantioselectivity. The accuracy of the data is within ± 5%. [e] See ref. 4. [f] Configuration tentatively assigned.

As regard to the other parameters, the examination of the $\Delta\Delta H^{\ddagger}$ values indicates that in the most of the cases the enthalpy favours the formation of the (*S*) 1-phenyl-1-propanol, while in the alkylation catalyzed by ligand **3** the "wrong" enantiomer is preferred. On the other hand, the sign of the entropy factors shows that the

(*R*) carbinol is generally favoured. Only in the case of the ligand **3**, both sign and value of the entropy term contribution indicate that the reactants have lost a greater number of degrees of freedom in the transition states leading to (*R*) carbinol than in those leading to the other enantiomer: in these cases, above -30°C the entropy term overcomes the $\Delta\Delta H^{\ddagger}$ value: thus, (*S*) carbinol is formed.

Table 2. Activation Parameter Differences[a] at 20°C between the Competing States of the Alkylation of Aldehydes with Diethylzinc using Ligands 2-7

ligand	aldehyde	$\Delta\Delta G^{\ddagger}$ Kcal/mole	$\Delta\Delta H^{\ddagger}$ Kcal/mole	$\Delta\Delta S^{\ddagger}$ e.u.
2	benzaldehyde	-0.88	-1.76	-3.0
3	benzaldehyde	-1.34	+7.45	+30.0
	3-phenylpropanal	-0.27	+1.99	+7.7
4	benzaldehyde	-0.70	-3.82	-10.6
5	benzaldehyde			
6	benzaldehyde	-1.46	-10.63	-31.3
7	benzaldehyde	-1.13	-5.14	-13.7

[a] $\Delta\Delta X^{\ddagger} = \Delta X_S^{\ddagger} - \Delta X_R^{\ddagger}$.

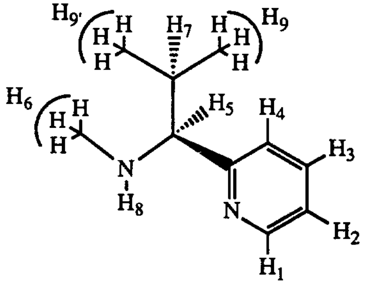
The entropy term contributions are, in the absolute value, higher in the case of the use of ligands **3**, and **6**, which have α-branched alkyl substituents, than using ligands **2**, **4**, **5** and **7**, where R is CH_3, $CH_2CH(CH_3)_2$ or CH_2Ph respectively. However, the $\Delta\Delta S^{\ddagger}$ value decreases drastically on passing from alkylation of benzaldehyde to that of 3-phenylpropanal.

Taking into account our previous suggestions,[4,7] the mechanism of the reaction should involve the formation of a stoichioimetric complex between the dialkylzinc and the ligand because of the formation of a Zn-N bond and of the co-ordination of the pyridine nitrogen atom, so providing an effective chiral environment for the reaction.

This hypothesis is supported by the ^1H NMR spectrum of a C_6D_6 solution of ligand **3** and a stoichioimetric amount of diethylzinc (Table 3). The examination of the data shows that, on adding of diethylzinc, the signal at 1.87 ppm, due to the hydrogen bound to the amino nitrogen atom, disappears, thus confirming the formation of the Zn-N bond. Moreover, all the signals are shifted upfield, and in particular those related to the H_4 proton, to the H_5 proton on the chiral centre and to the doublets of H_9, $H_{9'}$ protons (1.09, 0.86 ppm, $J_{HH} = 7$ Hz) of the isopropyl group of the ligand. These data agree with the fact that in the complex the zinc atom, covalently bound to the amino nitrogen atom, is co-ordinated to the pyridine nitrogen atom by way of a faint, even not negligible, interaction.

The adding of a stoichioimetric amount of benzaldehyde does not cause any occurrence of the reaction between the complex and the benzaldehyde itself, according to what previously noted.[4,7] Only slight further shifts of the resonances of the protons of the benzaldehyde are observed upon the addition. Moreover, a closer look to the ^1H NMR of the benzaldehyde/ligand/diethylzinc spectrum shows that the H_9 protons of one of the methyl group (0.76 ppm, J_{HH} = 7 Hz, 13 Hz) give a definite double doublet, indicating their magnetic inequivalency. In 3/ZnEt$_2$ complex only doublets are observed for H$_9$ and H$_{9'}$ protons.

Table 3. ^{1}H NMR Chemical Shifts of 3, 3/ZnEt$_2$ Complex and 3/ZnEt$_2$/PhCHO Adduct[a]



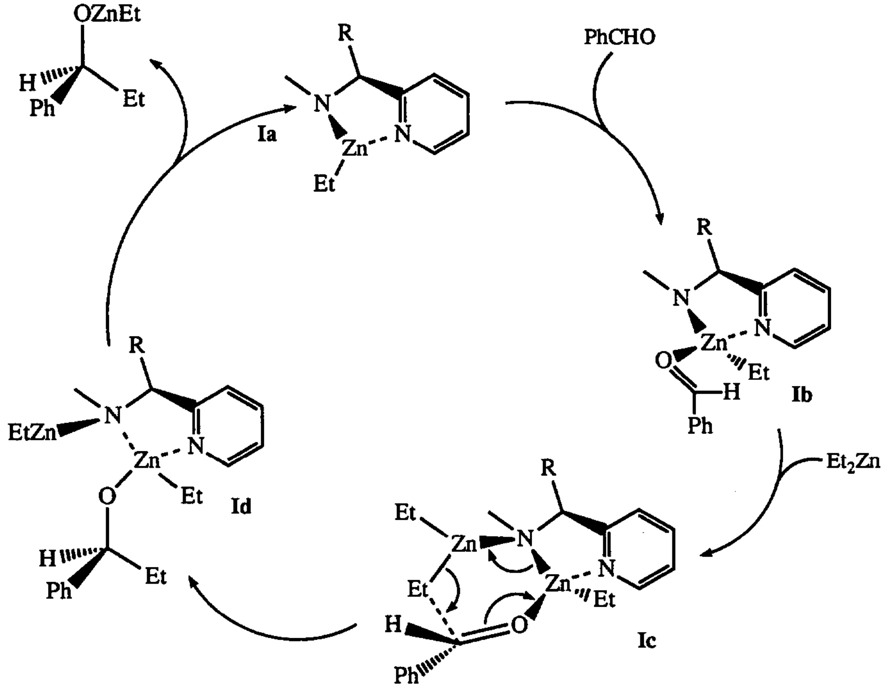
H	3 δ (ppm)	3/ZnEt$_2$ complex[b] δ (ppm)	3/ZnEt$_2$/PhCHO adduct[c] δ (ppm)
H$_1$	8.52	8.30(-0.22)	8.30(0.00)
H$_3$	7.13	6.90(-0.23)	6.92(+0.02)
H$_2$	6.67	6.54(-0.13)	6.51
H$_4$	6.96	6.46(-0.50)	
H$_5$	3.30	2.70(-0.60)	2.76(+0.06)
H$_6$	2.20	2.00(-0.20)	1.95(-0.05)
H$_7$	2.06	n.d.	n.d.
H$_8$	1.87	-	-
H$_9$	1.09[d]	0.73(-0.36)[d]	0.76(+0.03)[e]
H$_{9'}$	0.86[d]	0.40(-0.46)[d]	0.45(+0.05)[d]
ZnCH$_2$	-	0.50[f]	0.50[f](0.00)
ZnCH$_2$CH$_3$	-	1.79[g]	1.79[g](0.00)
PhCHO	-	-	9.65
C$_6$H$_5$CHO	-	-	7.53, 7.15-6.96

[a]) NMR spectra obtained in C$_6$D$_6$ using a 300 MHz spectrometer with a molar ratio 3/ZnEt$_2$/PhCHO= 1/1/1. [b]) Numbers in parentheses refer to Δδ between column 1 and 2. [c]) Numbers in parentheses refer to Δδ between column 2 and 3. [d]) Doublet, J_{HH} = 7 Hz. [e]) Double doublet, J_{HH} = 7 Hz, 13 Hz. [f]) Quartet. [g]) Triplet.

In our opinion, this is a clear evidence of a tight co-ordination of the aldehyde with the zinc complex to form a stable adduct. The structure derived should be extremely constrained and this can explain the particular trend of the stereochemistry of these reactions. In addition, on the basis of literature MO computations,[8] which reported significant bond-length differences between Lewis acid complexes of aliphatic and aromatic aldehydes, it may be assumed that the stronger and more stereospecific co-ordination of the latter to the zinc catalyst should result in a higher enantioselectivity for the alkylation of aromatic than of aliphatic aldehydes.

Taking into account the ^1H NMR and the stereochemical data, it is possible to suggest the catalytic cycle[9] shown in Scheme I for the enantioselective reaction. The starting step should be the co-ordination of the carbonyl oxygen atom to the zinc atom of the adduct **Ia** to form the adduct **Ib** that does not ethylate benzaldehyde even if should form slowly benzyl alcohol.[7]

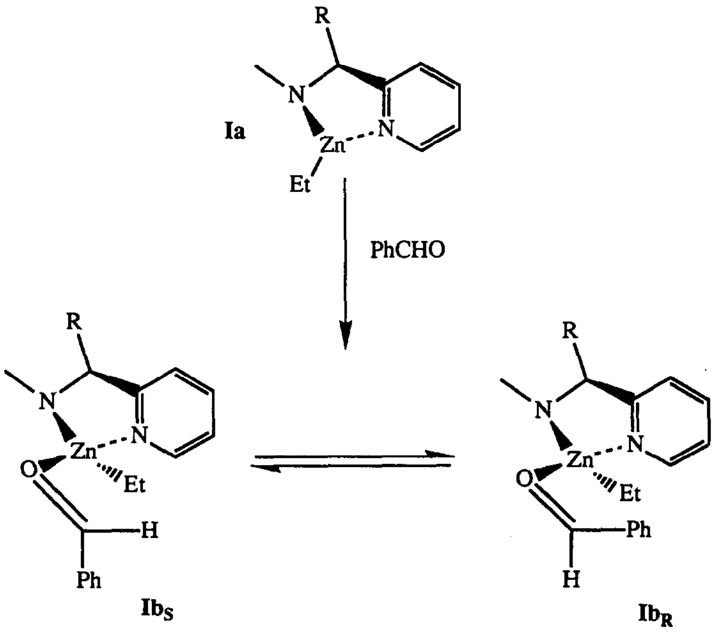
Scheme I



Another $ZnEt_2$ molecule is required to afford the assembly **Ic**, responsible for the alkylation reaction.[4,9] The transfer of an ethyl group to the carbonyl carbon atom by way of a six-membered transition state should originate the intermediate **Id** that regenerates the catalytic chiral complex **Ia** through elimination of the optically active zinc alkoxide. It appears evident that the conversion of **Ic** to **Id** is the determining step.[4]

Some other considerations have to be made. In the formation of the adduct **Ib** the aldehyde may approach the zinc complex **Ia** either from the *Si*-face or from the *Re*-face (Scheme II). Examination of molecular models and preliminary force-field calculation indicate that in the majority of the cases the aldehyde is to be prevalently coordinated to the *Si*-face so that the next insertion of $ZnEt_2$ to form assembly **Ic** leads to the (*S*) carbinol. However, in the case of the ligand **3**, both molecular and force-field models suggest that in the adduct **Ib** the presence of the two methyl groups on the carbon atom in the α-position with respect to the chiral centre seems to force the aldehyde to approach the zinc complex from the opposite *Re*-side. The ^1H NMR data of the zinc complex-benzaldehyde adduct related to the methyl protons of the isopropyl group of the ligands seem to support this hypothesis. When ligand **6**, which bears two chiral centres, is used, the models suggest that the ethyl group present on the β-chiral carbon atom affects the formation and stability of the two possible adducts, strongly favouring the intermediate **Ib$_S$**. On these considerations, the relatively high, although opposite, entropy term contributions observed when ligand **3** and **6** were used (Table 2) might be so explained. However, examination of molecular models and preliminary force-field models of the transition states **Ic** shows that in all the cases the diastereomeric adduct, leading to the (*R*) enantiomer, is not sterically favoured because of repulsion between the large group on the aldehyde and the Zn-containing ring of the complex.

Scheme II



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 an 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 He as carrier gas on a 15 m DB-1, DB-5 or DBWAX wide bore capillary columns (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 at least in duplicate for all temperature conditions 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: (*S*)-*N*-methyl-1-(2-pyridyl)ethylamine (**2**), b. p. 92°C/18 Torr, $[\alpha]^{25}_D$ -78.90 (CCl_4);[1] (*S*)-*N*-methyl-1-(2-pyridyl)-2-methylpropylamine (**3**), b. p. 51°C/0.06 Torr, $[\alpha]^{25}_D$ -55.81 ($CHCl_3$);[1] (*S*)-*N*-methyl-1-(2-pyridyl)-3-methyl-butylamine

(**4**), b. p. 52°C/0.05 Torr, $[\alpha]^{25}_D$ -35.50 ($CHCl_3$);[1] (*S*)-1-(2-pyridyl)-3-methylbutylamine (**5**), b. p. 145°C/0.1 Torr, $[\alpha]^{25}_D$ -8.40 ($CHCl_3$);[1] (1*S*, 2*S*)-*N*-methyl-1-(2-pyridyl)-2-methylbutylamine (**6**), b. p. 70°C/0.02 Torr, $[\alpha]^{25}_D$ -49.64 ($CHCl_3$);[1] (*S*)-*N*-methyl-1-(2-pyridyl)-2-phenylethylamine (**7**), b. p. 98°C/0.04 Torr, $[\alpha]^{25}_D$ +16.00 ($CHCl_3$).[1]

Asymmetric Addition of Dialkylzinc to Aldehydes. General procedure - A solution of the ligand (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, then thermostated at the suitable temperature (-10°, 20° or 35°C) and added with aldehyde (6.1 mmol). Stirring was prolonged for additional 12-24 h (sometimes the reaction course was followed by GLC). The reaction mixture was quenched with 10% H_2SO_4 (10 mL) then extracted with ether and the organic layer 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) ethyl carbinol.

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