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Addition of Diethylzinc to Aryl Aldehydes Catalyzed by (1S,3S)-N,N^{I}-bis[Benzyl]-1,3-Diphenyl-1,3-Propanediamine and its Dilithium Salt: a Mechanistic Rationale Investigation.

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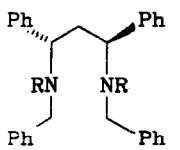
Abstract: N,N^{I}-bis-benzyl substituted 1,3-diamine **1a**, synthesized in high optical purity, and the corresponding dilithium salt **1b** are used, for the first time, as chiral catalysts in the addition of $ZnEt_2$ to aromatic aldehydes. Both **1a** and **1b** are able to promote the reaction but the products obtained exhibited low enantiomeric excesses. By ^{1}H NMR and UV-CD investigation, experimental evidences about the structure of some reaction intermediates have been gained: reaction pathway consistent with spectroscopic data, chemical and stereochemical results could be postulated.

Enantioselective addition of diethylzinc to aryl aldehydes, in the presence of catalytic amount of a chiral ligand, has been extensively studied over the years: asymmetric β-amino alcohols, which appeared very efficient promoters to achieve very good chemical and optical yield, have been the most employed chiral auxiliaries[1]. Rarely chiral C_2-symmetric diamines have been used; to the best of our knowledge up to date only three examples are reported, two utilize substituted piperazine[2] and one a 2,2^{I}-diamino-1,1^{I}-binaphthyl derivative[3]. We report here a study on the use of C_2 symmetry six-membered chelating ligands (1S, 3S)-N,N^{I}-bis-[benzyl]-1,3-diphenyl-1,3-propanediamine, **1a**, and its dilithium salt **1b**,



a : R = H

b : R = Li

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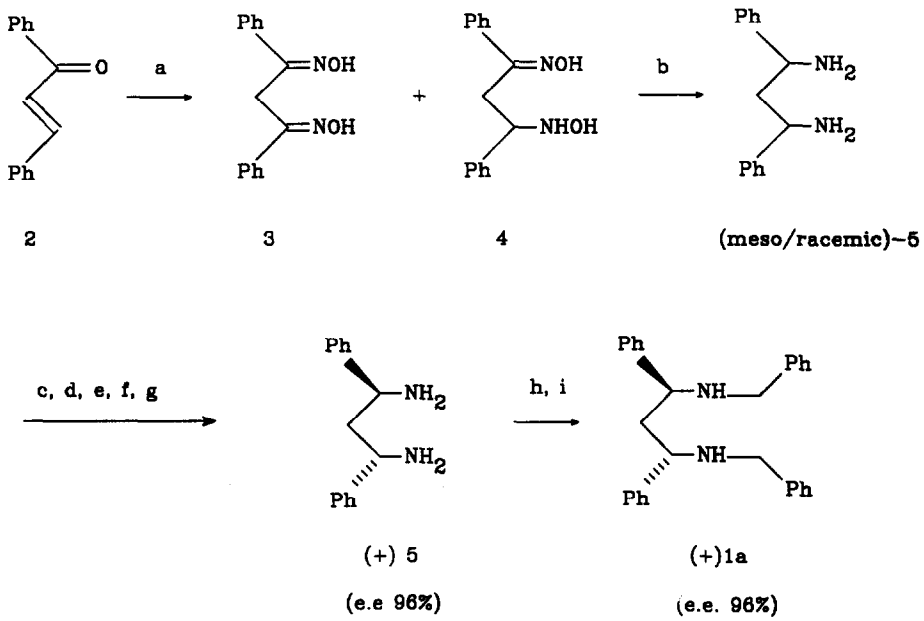
in the addition of $ZnEt_2$ to aryl aldehydes. Such ligands are able to accelerate this reaction, but the products obtained show very low enantiomeric excesses. The low enantioselectivity observed has been rationalized on the basis of ^{1}H NMR and UV-CD data, which provided experimental evidences about the nature of some intermediates involved in the ethylation of aromatic aldehydes.

Results and Discussion.

Synthesis of the chiral ligands. The chiral diamine **1a** was obtained, with high enantiomeric excess, derivatizing (+)-(1S, 3S)-1,3-diphenylpropane-1,3-diamine, (+) (1S,3S)-**5**, prepared modifying (Scheme 1) the original method reported by Arakawa[4]. Our procedure allows to remarkably enhance the total yield of **5**, mixture meso/racemic diastereoisomers (from 61% up to 97%, with respect to the starting ketone **2**), and to follow a simpler experimental route.

Scheme 1



(a) $NH_2OH \cdot HCl$, KOH aq. (80% w/v), EtOH 95%, 50°C (75%); (b) Ni/Al alloy (42/58), NaOH 2N, EtOH 95%, room temperature (95%); (c) HCl anhydrous, Et_2O; (d) EtOH, HCl (37%) (reflux), separation of the filtrate, evaporation of the solvents and addition of acetone (80% of the theoretical yield); (e) KOH aq.; (f) MeOH, Et_2O, (+)-O-dibenzoyltartaric acid; (g) KOH aq.; (h) benzaldehyde, toluene, molecular sieves, 60°C (93%); (i) MeOH, $NaBH_4$, 65°C (98%).

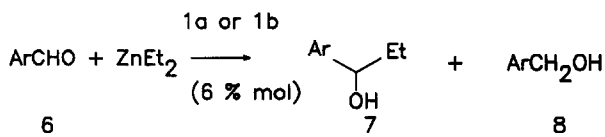
Arakawa, to obtain the diamine **5** (meso and racemic mixture), employed metallic sodium in ethanol as reducing agent. This system is able to reduce the oxime group but not the hydroxyamine one. Therefore it was necessary to separate the mixture **3** + **4** into the components and only the dioxime **3** was used for the successive step, discarding the compound **4**. By contrast our procedure utilizes both the components of the mixture, submitting them, without any separation, to the action of Ni/Al alloy in alkaline ethanol-water solution. In such conditions the mixture of the oxime **3** and the hydroxyamine **4** is quantitatively reduced to **5**, as a mixture of meso and racemic diastereoisomers, and hence also the total yield in separated racemic **5** is appreciably increased. Moreover we have isolated the chiral diamine (+) **5** from its less soluble diastereoisomeric di-O-benzoyltartrate salt and we have determined the enantiomeric purity analyzing its dicarbamate derivative[5] by

HPLC, equipped with a UV detector using a chiral column (Chiralcel OD; 250 mm; 254 nm UV detector; eluent 20% propan-2-ol in hexane; flow rate 0.5 ml/min).
For a sample of diamine (+)**5**, having $[\alpha]_D^{20}$ +17.02 (c= 1.975, $CHCl_3$), the e.e. was evaluated as 96%.

On the basis of Arakawa's report[4] we assumed that the absolute configuration of the chiral centres of the dextrogire enantiomer **5** is (S, S). By reaction with benzaldehyde, (1S, 3S)-**5** gives the correponding dialdimine which is quantitatively reduced, in stereospecific manner, to (+)(1S, 3S)-N,N[1]-bis-substituted diamine **1a**. The derivative **1b** was prepared in situ, by reacting **1a** with 2 mol equivalent of butyllithium just before the addition of $ZnEt_2$ and then of the aldehyde.

Alkylation of the aromatic aldehydes. Both diamine **1a** and dilithium salt **1b** were used, in catalytic amount (6% in mol), for promoting the addition of $ZnEt_2$ to various aromatic aldehydes (Scheme 2)

Scheme 2



The results are shown in Table. The outcomes of the reaction are very similar by using **1a** or **1b** as catalysts, but with the latter the conversion into the products is higher. The aldehyde substrates give rise to the alkylated derivative **7** (major product) beside the reduction product **8** (minor product) with the exception of p-methoxybenzaldehyde which is not reactive (entries 6 and 14, Table), being quantitatively recovered. By contrast, the addition of $ZnEt_2$ to p-trifluoromethylbenzaldehyde (entry 7, Table) with the catalyst **1a** is a chemoselective process giving only the addition compound **7** in high chemical yield.

As far as the optical yield is regarded, the addition product **7** was obtained either in the racemic form or with a low enantiomeric excess ($\leq$ 20%), which increases (up to 35%) by lowering the temperature (entry 8, Table).

These results indicate that : a) the acyclic secondary diamine **1a** can promote the addition of $ZnEt_2$ to aromatic aldehydes, b) the corresponding dilithium amide **1b** is even a better catalyst for the reaction, c) the nature and the position of the groups on the substrate aromatic ring affects to some extent the outcome of the reaction, d) the chiral ligand has a weak stereocontrol in the reaction pathway, giving no or low enantiomeric excess in the product **7**.

Much to our surprise for the low enantiomeric excesses found with respect to those obtained with β-amino alcohols[1], we felt it was necessary to gain some insights into the plausible mechanism operating when this type of diamino ligand is used. With this intention, we have investigated, by ^1H NMR and UV-CD spectroscopies, the addition of $ZnEt_2$ to p-trifluoromethylbenzaldehyde (TFMBA), as representative substrate, in the presence of the chiral ligand **1a** . Indeed this aldehyde reacts with high rate without formation of the reduction product **8** (entry 7, Table).

Table. Addition of $ZnEt_2$ to ArCHO catalyzed by (1S,3S)-**1a** or (1S,3S)-**1b**[a].

Entry	Catalyst	Ar	Products (%)[b]			e.e. (%)[c]
			6	**7**	**8**	
1	1a	Ph	21	64	15	15
2	"	2-Nph	46	41	13	20
3	"	o-MeC_6H_4	70	23	7	0
4	"	p-MeC_6H_4	45	30	25	0
5	"	o-$MeOC_6H_4$	37	53	10	0
6	"	p-$MeOC_6H_4$	100	0	0	-
7	"	p-$CF_3C_6H_4$	18	82	0	10
8[d]	1a	2-Nph	79	14	7	35
9	1b	Ph	19	70	11	13
10	"	2-Nph	33	57	10	15
11	"	o-MeC_6H_4	38	51	11	0
12	"	p-MeC_6H_4	35	46	19	0
13	"	o-$MeOC_6H_4$	6	84	10	5
14	"	p-$MeOC_6H_4$	100	0	0	-
15	"	p-$CF_3C_6H_4$	6	74	20	16

[a] The runs were carried out in toluene at room temperature for 22h. Molar ratio, aldehyde/$ZnEt_2$/catalyst = 1/2.0/0.06. [b] Percentages determined by NMR analysis. [c] By HPLC analysis (ionic DNBG Pirkle column, 254 nm UV detector, eluent 0.025% propan-2-ol in hexane; flow rate 1 ml/min). [d] Reaction carried out at -50°C.

^{1}H NMR and UV-CD analyses. The ^{1}H NMR spectra (300 MHz) were recorded at room temperature with sample solutions in toluene-d_8. The spectra of $ZnEt_2$, chiral ligand **1a** and TFMBA, separately, and of the two mixtures $ZnEt_2$/**1a** and $ZnEt_2$/**1a**/TFMBA were analyzed.

Figure 1 shows the proton spectra of $ZnEt_2$, of diamine ligand **1a** and of their mixture (molar ratio 1:1). On addition of $ZnEt_2$ to diamine **1a**, a remarkable change of the multiplicity of the signals due to the amine proton H(e), the adjacent protons of methine H(d) and methylene H(f) groups, is observed. The resonance of amine proton H(e) becomes a broad quartet because of the vicinal coupling with H(d) and H(f), which in turn double their signals. The changes of multiplicity can be reasonably attributed to a sensitive decreasing in the conformational freedom owing to the metallic nucleus coordination. The sole signal without variation of multiplicity, is that relative to the methylene protons H(c). A further addition of $ZnEt_2$ to the 1:1 mixture does not affect the ^{1}H NMR spectrum.

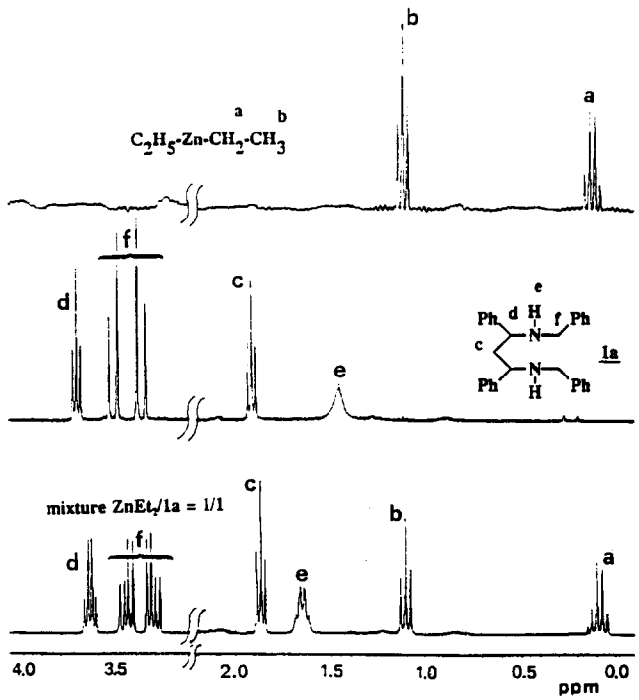
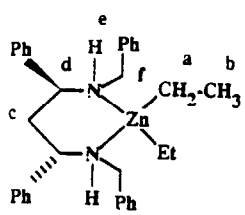


Figure 1. ^{1}H NMR spectrum (toluene-d_8, 300 MHz, 25°C) of $ZnEt_2$, chiral diamine **1a** and-$ZnEt_2$/**1a** mixture (1:1 molar ratio), in the region between 0 and 4 ppm, relative to the aliphatic proton resonances.

On the basis of these spectral data it seems plausible to postulate the formation of the coordination species **9.**



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As a matter of fact, the signal relating to the amine groups integrates for two protons indicating that NH groups are still present as just represented in structure **9.** In other words, the aggregate present in solution is somewhat stable towards protonolysis of the zinc-carbon by the nitrogen-bound hydrogens in the secondary amine[6].

The results of the absorption-circular dichroism (UV-CD) analysis are in keeping with the hypothesis about the structure of coordination compound **9.** In Figure 2 are shown the UV-CD spectra of the free diamine **1a,** and the mixture of **1a** and $ZnEt_2$ (molar ratio 1:1).

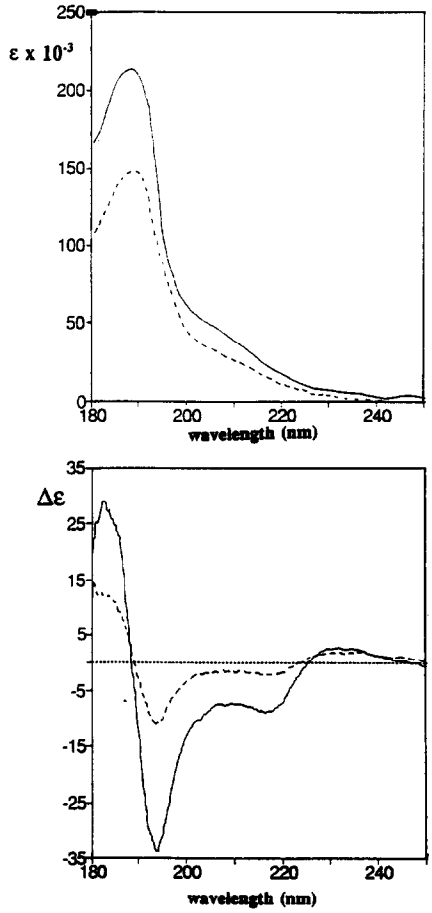


Figure 2. Circular dichroism (CD) and absorption (UV) spectra, at 25°C in n-hexane, of free diamine **1a** (- - - -), and **1a**/$ZnEt_2$ mixture (molar ratio 1:1) (———).

The UV and CD spectra of **1a** (dashed line) are very similar in shape (number, position and sign of the bands) to those of the 1:1 mixture (continuous line). After the addition of the equimolar amount of $ZnEt_2$ a general increase of the absorption is observed, the threefold increase of the dichroic intensity being significant for a reduced conformational freedom[7]. Namely a species is generated for which the number of the conformation appreciably populated is restricted, according to ^1H NMR results, and hence reasonably the optical activity increases[8]. A further addition of $ZnEt_2$ to the (1:1) mixture $ZnEt_2$/**1a** doesn't produce any variation in the CD spectrum indicating that a complex 1:1 between $ZnEt_2$ and **1a** is present in solution, also when an excess of $ZnEt_2$ is added. In Figure 3 are represented the proton spectra, relative to the regions -0.5-2.5 ppm and 3.2-4.8 ppm, when an equimolar amount of TFMBA is added to the mixture $ZnEt_2$/diamine ligand **1a** (molar ratio 1:1). The spectra are recorded after 20 minutes (A), 3.5 hours (B) and 3 days (C). By comparison, already after 20 minutes five new signal (see arrows in Figure 3) appear in addition with the old ones: their intensity increases with time, while the proton H(a) and H(b) resonances of the initial $ZnEt_2$-diamine **1a** complex decrease. The intensities of all the new signals are each other strictly correlated, showing that they belong to hydrogen nuclei of a single species. The position of the absorptions at 0.02 ppm (quartet) and 1.07 ppm (triplet) are tipical again of a zinc-bound ethyl group, but belonging to a species different from that present in the complex between $ZnEt_2$ and **1a** (0.12 ppm quartet, 1.12 ppm triplet; Figure 1). In addition, the chemical shift values and omonuclear decoupling measurements show that the resonances at 4.51 ppm (multiplet), 1.80 ppm (multiplet) and 0.53 ppm (triplet) are to assigne to a moiety as CH_3-CH_2-CH-O-.

The above ^1H NMR data seem to be in agreement with the formation of the intermediate **10**, which is in slow exchange with the coordination complex **9**.

In the course of all the ^1H NMR measurements the aldehydic proton resonance (9.4 ppm, singlet) always appears as a sharp signal and not as a broaded one, showing that the presence of an aldehydic coordinated species[9] was not detectable.

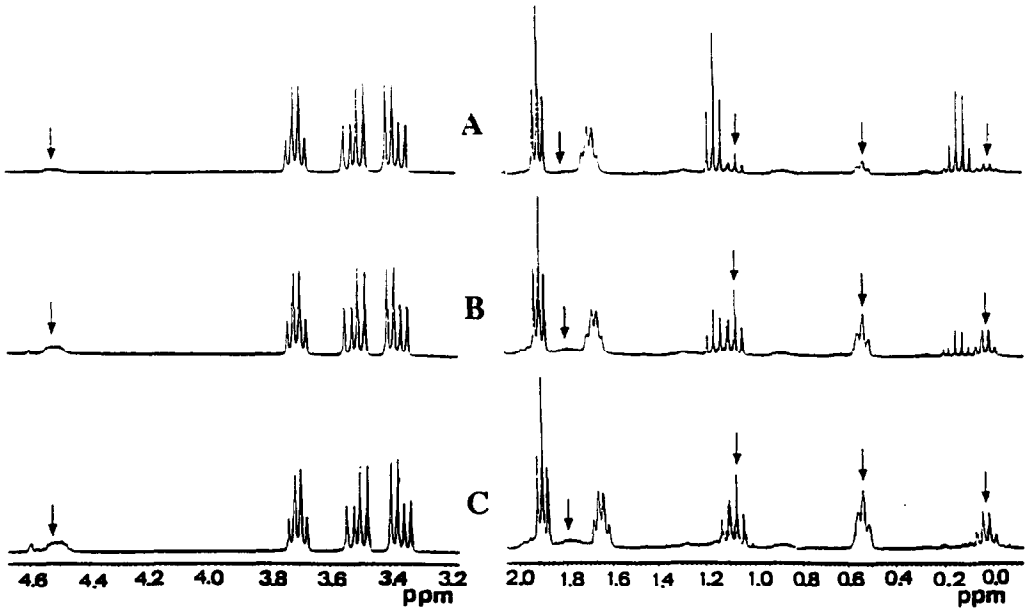
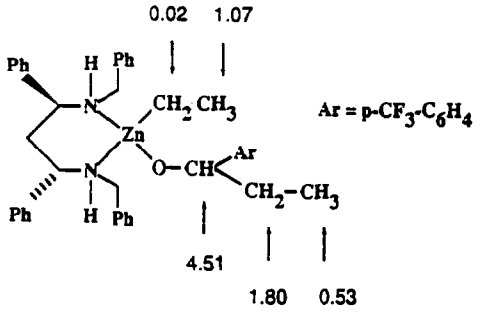


Figure 3. ^{1}H NMR spectra (toluene-d_8, 300 MHz, 25°C) of the mixture $ZnEt_2$/**1a**/TFMBA (1:1:1 molar ratio), relative to the regions -0.5 - 2.5 ppm and 3.2-4.8 ppm, recorded after 20 min (A), 3.5 hrs (B), 3 days (C).

Nevertheless the spectral evidence for the intermediate **10** is so unambiguous that it is reasonable to admit a previous coordination of the aldehyde oxygen to the Zn atom; more than likely the amount of the coordinated aromatic aldehyde, with respect to the non-coordinated one, is too low for being detectable by NMR spectroscopy and, in addition the step of the alkyl transfer on the coordinated aldehyde is very fast with respect to the NMR observation times.



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The Reaction Pathway. On the basis of the ^{1}H NMR and UV-CD measurements, we have postulated the catalytic cycle of Figure 4 which, consistent with all the data above reported, can rationalize the experimental results of the aldehyde alkylation entries.

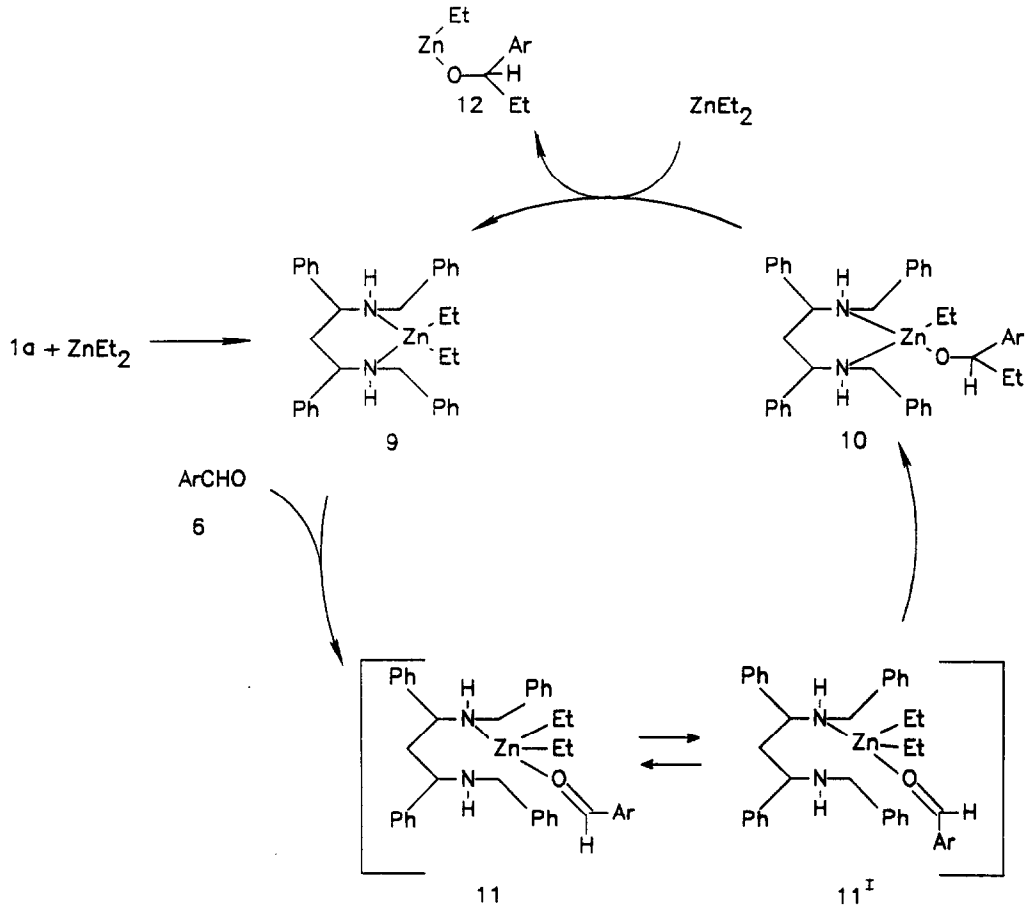

Figure 4. Postulated catalytic cycle of the diamine **1a**-catalyzed alkylation of aromatic aldehydes with $ZnEt_2$.

The diamine **1a** coordinates one equivalent of $ZnEt_2$ giving rise to the conformationally restricted intermediate **9**, in which the bonding situation around zinc is close to sp^3 hybridization with a tetrahedrally surrounded zinc atom. The 1:1 complex **9** is able to react with an equimolar amount of aldehyde, inserting the carbonyl group between the Zn-N bound and making the rapidly transient intermediate **11** and/or **11^I** in which one or the other prochiral face of the carbonyl group is attached. Although the zinc-nitrogen coordinate bond is stronger than zinc-oxygen one[10], it can be reasonably assumed that even if the species **11** (or **11^I**) is present at low concentration the catalytic cycle goes along. Such an assumption can be justified by the fact that in the next step, from **11** (or **11^I**) to **10**, a thermodynamically stable situation is restored by providing again two zinc-nitrogen coordinate bonds, owing to the intramolecular transfer of an ethyl group to carbonyl carbon atom. Finally, an additional equivalent of $ZnEt_2$ converts **10** to the alcoholate product **12**, releasing the ligand **1a** which can return into the catalytic cycle.

Taking into account the results above discussed the following conclusions can be drawn:
1) The ligands **1a** and **1b** are good promoters for the addition of the ethyl group to the aromatic aldehydes; the amide dianion **1b**, having a stronger coordinative power, is a better catalyst.
The above results obtained from the ^{1}H NMR investigation on the mixture (1:1:1) between chiral ligand **1a**, $ZnEt_2$ and aryl aldehyde, clearly show that the diamine ligand **1a** is able to promote the ethyl transfer also without an excess of $ZnEt_2$. This result is not in agreement with that reported[1] for the chiral β-dialkylamino alcohol, (-)-3-exo-(dimethyl-amino)-isoborneol, which, used in equimolar amount to respect with $ZnEt_2$, doesn't produce any alkylation of the aryl aldehyde.
2) The reaction rate and the amount of the addition product obtained are sensitive to the nature of the aldehyde benzene ring substituent: an electron-donor group (i.e. OCH_3) in ortho or para position, on one hand increases the nucleophilicity of the carbonyl oxygen atom, accelerating the coordination step **9** →**11** (or **11^I**), but on the other hand decreases the electrophilicity of the carbonyl carbon atom once the oxygen is coordinated, making slow the ethyl transfer step **11** (or **11^I**) → **10**. The same double effect, but in reversed direction, is generated by an electron-withdrawing group.

The complete unreactivity of p-methoxybenzaldehyde can be ascribed to the preferential complexation of the methoxy group with respect to the carbonyl one. In this way the intramolecular ethyl transfer should be hindered because of the distance between the donor and the acceptor.
3) The formation of the reduction byproduct increases, increasing the slowness by which the two consecutive steps, **9** → **11** (or **11^I**) and **11** (or **11^I**) → **10**, are accomplished.
4) The very low extent of asymmetric induction can be explained with the postulated mechanism of Figure 4. The coordination of the aromatic aldehyde at the intermediate **9** takes place at a symmetrically substituted zinc atom, somewhat distant from the C_2 chiral moiety. For this reason, the ethyl group intramolecular transfer, proceeding through the equilibrium between **11** and **11^I** intermediate forms, occurs with almost equal probability on the two enantiofaces of the prochiral aldehyde without any appreciable chiral discrimination.

In conclusion, from our investigation it is apparent that, by using catalytic amounts of C_2 symmetric N,N^I-monosubstituted 1,3-diamine or its dilithium salt as chiral chelating ligands of $ZnEt_2$, the addition of organozinc to aromatic aldehydes takes place with a mechanism completely different from that found employing chiral β-aminoalcohols[1]. The structural features of the intermediates **9** and **10**, for which experimental evidence was obtained, are in good agreement with the ability of these ligands to promote the reaction even without an excess of $ZnEt_2$ and can also justify the low degree of enantioselectivity of the process.

EXPERIMENTAL

General. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Model VXR 300 at 300 MHz or a Varian Model Gemini 200 at 200 MHz in deuterated chloroform with tetramethylsilane as the internal standard, unless otherwise specified. Optical rotations were measured on a Jasco DIP-360 polarimeter in 1-dm tube and the rotations refer to those of a pure liquid, unless otherwise specified. CD Spectra were recorded on a Jasco J-600 spectropolarimeter. Chiral HPLC analyses were performed on a Chiralcel OD column (4.6x250 mm) at a flow rate of 0.5 ml/min or on a Pirkle DNBPG column (4.6x250 mm) at a flow rate of 1 or 2 ml/min with a Jasco Twincle apparatus equipped with a UV Jasco Uvidec detector. The composition of the mobile phase is specified in the appropiate paragraph. TLC were carried out on commercial silica gel $60F_{254}$ plates. Melting points are uncorrected.

Unless noted, all reagents were obtained from commercial sources. All liquids were distilled before use, except where noted. Anhydrous ether and anhydrous CH_2Cl_2 were distilled prior to use from metallic Na and P_2O_5 respectively. Pyridine was distilled from KOH under Argon. Toluene anhydrous was distilled from Na under Argon. All $ZnEt_2$ runs were performed under Argon atmosphere.

1,3-Diphenylpropane-1,3-dioxime (3) *and 1,3-diphenylpropane-1,3-hydroxyamineoxime* (4).

To a stirred solution of 0.24 mmol of 1,3-diphenyl-2-propen-1-one in 300 mL of EtOH 95% mixed with 0.64 mmol of hydroxylamine hydrochloride in 50 mL of H_2O were added 1.03 mmol of solution of KOH in 70 mL of H_2O over 30 min at 50°C. The solution was refluxed for 20 min, cooled in ice water, and filtered to remove potassium chloride. The ethanol was removed under reduced pressure and enough water was added to the concentrate: the resulting suspension was extracted with ethylacetate. The organic layer was dried overnight with Na_2SO_4 anhydrous. Removal of the solvent gave 45.92 g of mixture of 3 and 4 (7:3).[11]

NMR (200 MHz, DMSO) δ 3.2 (m), 4.2 (t), 4.35 (s), 5.7-6.1 (s), 7-7.8 (m), 11.3 (s),11.65 (s).

meso/racemic 1,3-diphenyl-1,3-propanediamine, [(meso/racemic)-5].

To a stirred solution of 25 g of 3 and 4 in 1000 mL of EtOH 95% and of 500 mL of NaOH 2N were added 40 g of Ni/Al alloy in small portions, and the resulting mixture was stirred for 2h at room temperature. Then the suspension was filtered and the filtrate was concentrated evaporating the alcohol almost completely. The remaining aqueous solution was shaken with $CHCl_3$ and the organic layer was dried with Na_2SO_4 anhydrous. After evaporation of the solvent was obtained 20.8 g of (meso/racemic)-5.

NMR (200 MHz, $CDCl_3$) δ 1.5-1.8 (s, 4H), 2 (m, 2H), 3.9 (t, 2H), 7.2 (m, 10H)

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.64; H, 7.96; N, 12.38. Found: C, 79.90; H, 7.96; N, 12.45.

Separation of racemic 1,3-diphenyl-1,3-propanediamine, (racemic-5).

The pure racemic-5 was isolated by the method of Arakawa et coll.[4]: hydrogen chloride was bubbled into a ether solution of 66.3 mmol of (meso/racemic)-5 to give white precipitated of the corresponding dihydrochloride. From the mixture of meso and racemic dihydrochloride was obtained 31.3 mmol of pure racemic-5 and 34.6 mmol of pure meso-5.

^{13}C NMR (200 MHz, D_2O) δ 39.5, 55, 130-134 and 137 for racemic isomer

^{13}C NMR (200 MHz, D_2O) δ 41.5, 56, 130-134 and 139 for meso isomer

Resolution of racemic 5: (+)-(1S, 3S)-1,3-diphenyl-1,3-propanediamine, [(1S,3S)-(+)-5].

14.3 mmol of pure diamine (1S,3S)-(+)-5 were obtained for resolution[4] of 30 mmol of diamine (±)-5 with 15 mmol of (+)-di-O-benzoyltartaric acid .

NMR (200 MHz, $CDCl_3$) δ 1.4-1.6 (s, 4H), 2 (t, 2H), 3.9 (t, 2H), 7.2-7.6 (m, 10H)

$[\alpha]_D^{20}$ +16.5 (c 1.97, $CHCl_3$). The enantiomeric excess, determined by chiral HPLC of the corresponding dicarbamate on a Chiralcel OD column with the conditions above reported, was 96%.

Preparation of (±)- and (+)-N,N' bis[carboethoxy]-1,3-diphenyl-1,3-propanediamine

To a solution of 4.4 mmol of (±)- or (+)-1a in 10 ml of $CHCl_3$ were added 10 mL of Et_3N and, cooling at 0°C, 10 mmol of ethyl chloformate. The solution was allowed to reach room temperature, stirred for 24 h more and washed with HCl 10% and then with $NaHCO_3$.

The organic layer was separated and dried with Na_2SO_4 anhydrous. The solvent was removed under reduced pressure obtaining 1.51 g of viscous yellow liquid. The residue was purified by silica gel chromato graphy using a $CHCl_3$/Hexane (3:1) mixture as eluent to give 3.5 mmol of dicarbamate.

H NMR (200 MHz, $CDCl_3$) δ 1.2 (t, 6H), 2.3 (t, 2H), 4.1 (m,4H), 4.6 (m, 2H), 5.1 (d, 2H), 7.1-7.4 (m, 10H)

Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.10; H, 7.02; N, 7,56. Found C, 68.10; H, 7.16; N, 7.70.

*Preparation of (+)-(1R, 3R)-N,N' bis[benzyl]-1,3-diphenyl-1,3-propanediamine, [(+)-**1a**].*

A solution of 13.2 mmol of (+)-6 in 50 ml of toluene anhydrous and 30 mmol of benzaldehyde was stirred on molecular sieves (4Å) at 60°C for 24 h under argon atmosphere. After filtration, the filtrate was evaporated until to dryness obtaining a white solid (4.74 g). To the residue in 50 mL of MeOH was added 30 mmol of $NaBH_4$. The solution was allowed to stirr at 60°C for 12h. After the mixture was reduced by evaporating and the residue was extracted with Et_2O. Ether was removed at reduced pressure isolating 12.2 mmol of **(+)-1a.**

NMR (300 MHz, toluene-d^8) δ 2.19 (s, 2H), 2.1 (t, 2H), 3.5 (m, 4H), 3.7 (m, 2H) 7.1-7.5 (m, 20 H).

Anal. Calcd. for $C_{29}H_{30}N_2$: C, 87.71; H, 7.39; N, 6.90. Found C, 85.64; H, 7.39; N, 6.97.

$[\alpha]_D^{16}$ +34.8 (c 1.00, $CHCl_3$)

General procedures for the addition of diethylzinc to aldehydes catalyzed by (1S,3S)-N,N'-bis[benzyl]-1,3-diphenyl-1,3-propanediamine or its dilithium salt.

a) To an ice cooled solution of (+)-**1a** (0.092 mmol) in toluene (10 ml), Et_2Zn (3 mmol 1M hexane) was added. The mixture was stirred at room temperature for 30 min, and 1.5 mmol of aldehyde was added at 0°C.

After the reaction mixture was stirred for 20h at room temperature, HCl 1M was added to quench the reaction. The mixture was extracted with Et_2O, and the organic extract was dried (Na_2SO_4) and the solvent under reduced pressure was evaporated. On the crude product mixture the reaction conversion was evaluated by ^1H NMR spectroscopy and the e.e. of addition product was determined by HPLC on chiral phase.

b) To an ice cooled solution of (+)-**1a** (0.092 mmol) in toluene (10 ml), n-butyllithium (0.185 mmol, 1M hexane) was added. After 10 min, Et_2Zn (3 mmol, 1M hexane) was added over a period of 5 min. The mixture was stirred at room temperature for 30 min, and 1.5 mmol of aldehyde was added at 0°C. The reaction products were isolated with the same procedure reported at point a).

References and Notes

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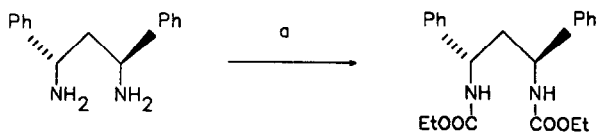
5. The dicarbamate derivative of **1a** was obtained, in quantitative yield, on the basis of the following scheme:



(a) ClCOOEt, Et_3N, $CHCl_3$, room temperature

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11. The ^{1}H signal assignement was performed on the basis of the spectra of the authentic samples of compounds **3** and **4**