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Molecular Modeling of Salt (Lithium Chloride) Effects on the Enantioselectivity of Diethylzinc Addition to Benzaldehyde in the Presence of Chiral β-Amino Alcohols

Martha Sosa-Rivadeneyra,[†] Omar Muñoz-Muñiz,[‡] Cecilia Anaya de Parrodi,[§] Leticia Quintero,*[,†] and Eusebio Juaristi*[,‡]

Centro de Investigación de la Facultad de Ciencias Químicas, Universidad Autónoma de Puebla, 72570 Puebla, México, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, 07000 México, D.F., México, and Centro de Investigaciones Químico Biológicas, Universidad de las Américas-Puebla, Santa Catarina Mártir, 72820 Cholula, México.

ejuarist@enigma.red.cinvestav.mx

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β-Amino alcohols (*S*,*S*,*S*)-**1** and (*R*,*R*,*S*)-**1**, derived from cyclohexene oxide and containing α-phenylethyl auxiliaries, were examined as chiral promoters in the addition of diethylzinc to benzaldehyde. In agreement with literature precedent, the *N*-α-phenylethyl chiral auxiliary had no significant impact on enantioinduction, which is determined by the configuration of the framework's C*(OH), with *unlike* induction. Contrary to some literature reports, stereoinduction by lithium salt derivatives of (*S*,*S*,*S*)-**1** and (*R*,*R*,*S*)-**1** was lower than that obtained with the free amino alcohol. Remarkable lithium chloride salt effects were observed in the reaction. In particular, an opposite chiral induction was found with (*S*,*S*,*S*)-**1**-Li_2 as ligand and in the presence of "inert" salt. *N*-Alkylated derivatives (*S*,*S*,*S*)-**3**−**7** proved to be more efficient ligands, providing higher yields and enantioselectivities in the formation of carbinols (*R*)- or (*S*)-**2**. BP86/DN**//PM3 theoretical calculations proved remarkably successful in reproducing the experimental observations and permitted expansion of Noyori's catalytic cycle [*J. Am. Chem. Soc.* **1995**, *117*, 6327] to understand the relevant *N*-substitution and medium salt effects that determine the enantioselection in this catalytic asymmetric reaction.

Introduction

Dialkylzinc addition to prochiral aldehydes in the presence of chiral β-amino alcohols constitutes a highly efficient procedure for the asymmetric construction of C−C bonds.[1−4] (Scheme 1).

A pioneering ab initio molecular orbital study {MP2//HF/3-21G (H,C,N,O) + [8s4p2d]/(14s9p5d) for Zn} of this reaction by Yamakawa and Noyori[5] afforded essential information on the structures, stabilities, and reactivities of the organozinc complexes that are involved in the catalytic process. Figure 1 summarizes the main features of the reaction course, modeled with dimethylzinc, 2-aminoethanol, and formaldehyde.[5] Consideration of chiral ligands instead of achiral 2-aminoethanol and prochiral aldehydes instead of formaldehyde leads to the formation of diastereomeric analogues of complex **D**, whose relative stabilities determine the sense and extent of stereoselection.[6−8]

[†] Universidad Autónoma de Puebla.

[‡] Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional.

[§] Universidad de las Américas-Puebla.

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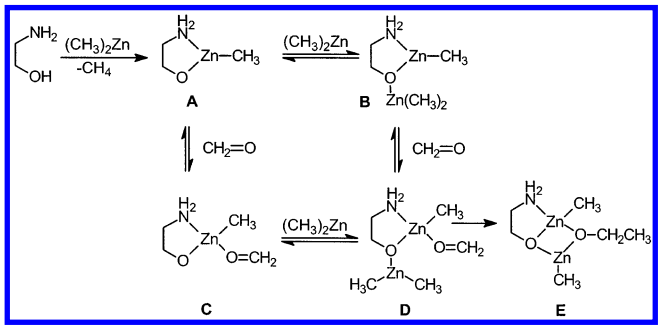
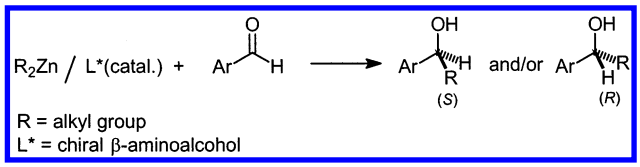
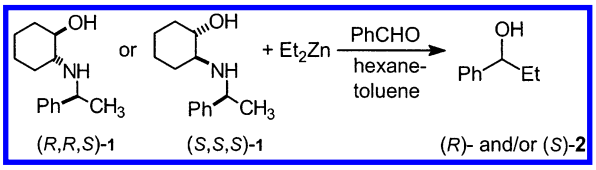


FIGURE 1. Catalytic cycle proposed by Yamakawa and Noyori[5] for the reaction of dimethylzinc and formaldehyde, under 2-aminoethanol activation.

SCHEME 1



SCHEME 2



In this context, Noyori et al.[7b] and others[9] have shown that the profile of asymmetric catalysis can be affected by molecular interaction of the chiral catalyst with *achiral* molecules present in the reaction medium, so that unusual phenomena may be seen. We were particularly interested in the determination of potential "inert" salt effects[10] on the stereochemical outcome of the addition of Et_2Zn to benzaldehyde catalyzed by *N*-[(*S*)-α-phenylethyl]-*β*-aminocyclohexanols (*R*,*R*,*S*)-**1** and (*S*,*S*,*S*)-**1** (Scheme 2).[11−13]

Results and Discussion

When benzaldehyde was treated with diethylzinc (2.0 equiv), in the presence of 6.0 mol % (0.06 equiv) of *β*-amino alcohol (*S*,*S*,*S*)-**1** and according to the standard procedure,[14] carbinol (*R*)-**2** was obtained in 58% isolated yield and with 57% enantiomeric excess (entry 1 in Table 1). Similarly, benzaldehyde reacted with diethylzinc in the presence of chiral ligand (*R*,*R*,*S*)-**1** to give carbinol (*S*)-**2** in 80% yield and 50% ee (entry 5, Table 1). Thus, it is apparent that the *N*-α-phenylethyl substituent does not have a significant influence on the stereoselectivity of the organometallic addition. This result is in line with the empirical rule that the configuration of the stereogenic center supporting the hydroxy group, $C^*_{(O)}$, is more relevant for the stereochemical outcome of the alkylation reaction than the configuration of the *β*-carbon, $C^*_{(N)}$.[15] Consequently, it is appreciated that stereoinduction by $C^*_{(O)}$ is *unlike*;[16] i.e., the configuration of the predominant product is opposite to the one present at $C^*_{(O)}$ in the chiral *β*-amino alcohol ligand.

TABLE 1. Enantioselective Addition of Et_2Zn to Benzaldehyde in the Presence of Chiral Ligands 1 (Scheme 2)

entry[a]	ligand[b]	additive (equiv)	yield[c] (%)	ee[d] (%)	major enantiomer[e]
1	(*S*,*S*,*S*)-**1**		58	57	(*R*)
2	(*S*,*S*,*S*)-**1**	LiCl (0.6)	50	53	(*R*)
3	(*S*,*S*,*S*)-**1**-Li_2		80	47	(*R*)
4	(*S*,*S*,*S*)-**1**-Li_2	LiCl (0.6)	58	24	(*S*)
5	(*R*,*R*,*S*)-**1**		80	50	(*S*)
6	(*R*,*R*,*S*)-**1**	LiCl (0.6)	65	52	(*S*)
7	(*R*,*R*,*S*)-**1**-Li_2		78	35	(*S*)
8	(*R*,*R*,*S*)-**1**-Li_2	LiCl (0.6)	55	22	(*S*)

[a] All reactions were carried out in toluene−hexane (2:1), at 25 °C for 20 h.[14] [b] Dilithiated ligand obtained by metalation of the *β*-amino alcohol ligand with 2 equiv of BuLi. [c] Isolated yield after purification by flash chromatography (petroleum ether−ethyl acetate (15:1). [d] Determined by HPLC using a Chiracel OD column. [e] The absolute configuration of the 1-phenyl-1-propanol was assigned from the sign of the specific optical rotation[17] and from the elution order in HPLC analysis on a Chiracel OD stationary phase column.[18]

Comparison of entries 1 and 2, and 5 and 6 in Table 1 shows that addition of LiCl to the reactions activated with free *β*-amino alcohols does not have any significant effect on chemical yield or enantiomeric ratio of carbinol **2**.

Some years ago, Corey and Hannon[19] reported the improved enantioselectivity achieved by lithium salt derivatives of chiral *β*-amino alcohol as ligands in the addition of Et_2Zn to aldehydes. Motivated by these observations,[20] we carried out two experiments (entries 3 and

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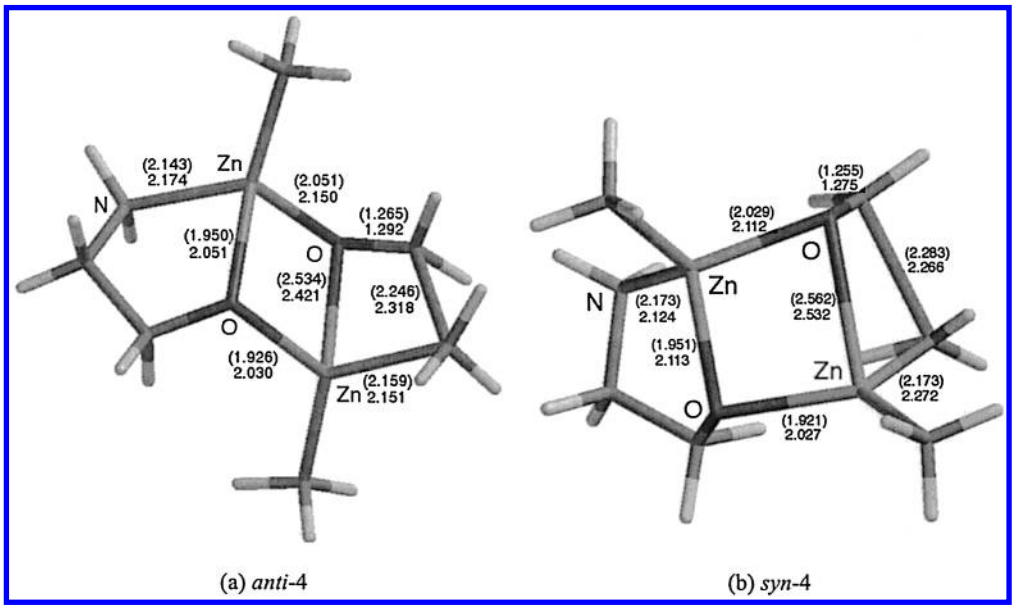

FIGURE 2. (a) BP86/DN** transition state structure for *anti*-(4). (b) BP86/DN** transition state structure for *syn*-(4) (ab initio results[5] are in parentheses).

7, Table 1) where (*S*,*S*,*S*)-**1** and (*R*,*R*,*S*)-**1** were treated with 2 equiv of BuLi, so that lithium salts (*S*,*S*,*S*)-**1**-Li_2 and (*R*,*R*,*S*)-**1**-Li_2 are the active ligands. It is important to emphasize that Corey and Soai et al.[19] use the "mono" lithium salt (alkoxide) of *β*-*tert*-amino alcohol, while the structure of the catalyst in the present manuscript is the "di" lithium salt of *β*-"*sec*"-amino alcohol. Unfortunately, the ee of product 1-phenylpropanol (**2**) actually decreased in these two cases (compare entries 1 vs 3 and 5 vs 7 in Table 1).

More intriguing to us was the effect of LiCl addition[21] on the reaction of Et_2Zn with PhCHO, activated by (*S*,*S*,*S*)-**1**-Li_2 and (*R*,*R*,*S*)-**1**-Li_2. Most interesting is the *opposite* chiral induction observed in entries 3 and 4 in Table 1. Thus, diethylzinc addition to benzaldehyde under (*S*,*S*,*S*)-**1**-Li_2 catalysis affords predominantly (*R*)-**2**, with 47% ee, whereas the same reaction in the presence of LiCl (10 equiv relative to the ligand) gives carbinol (*S*)-**2** as the main product (24% ee).

To better understand this dramatic salt effect, Noyori's catalytic cycle (Figure 1 and refs 5−8) was reexamined computationally, including ligands (*S*,*S*,*S*)-**1** and (*R*,*R*,*S*)-**1**, diethylzinc, benzaldehyde, and of course LiCl. In view of the large size of the system involved, fully ab initio theoretical methods are unsuitable for the proposed study. Instead, the semiempirical PM3 method[22] was used to optimize molecular structures of the organometallic complexes, and the hybrid BP/DN** method[22] was employed to determine the corresponding energies.

We first confirmed, as already done by Goldfuss and Houk,[8a] that PM3 correctly reproduces Noyori's ab initio geometries for the model transition structures **F**, **G**, and **H**. Agreement is even better between BP86/DN** and ab initio calculations, as shown in Figure 2.

TABLE 2. Imaginary Frequencies (in cm^{-1}) Calculated for Transition Structures F−H

transition structure	ab initio value[5]	BP86/DN** (this work)
anti-(**4**)	343 (*i*)	374 (*i*)
syn-(**4**)	308 (*i*)	329 (*i*)
anti-(**6**)	659 (*i*)	685 (*i*)

Furthermore, BP86/DN** calculations were particularly successful in performing the analysis of frequencies associated to transition structures **F**−**H** (Table 2). A single imaginary frequency was revealed for each transition structure, corresponding to the stretching frequency for the C−C bond that is formed upon methyl group transfer from dimethylzinc to formaldehyde (Table 2).

Having validated BP86/DN**//PM3 as a reliable computational method for the molecular modeling of the reaction of interest, we proceeded to include chiral ligands (*S*,*S*,*S*)-**1** and (*R*,*R*,*S*)-**1**, diethylzinc, and prochiral benzaldehyde in the calculations. It is clear that the sense and extent of stereoselection will be determined by the *relative* stabilities of the rate-determining diastereomeric transition states.

Scheme 3 summarizes the computed results from hypothetical equilibrium between diastereomeric transition structures leading to (*R*)-**2** and (*S*)-**2** under *standard conditions*; i.e., free *β*-amino alcohol ligand in the absence of LiCl. It is appreciated that with (*S*,*S*,*S*)-**1** ligand, alkyl addition to the *pro*-(*R*) face of benzaldehyde is favored by 1.12 kcal/mol. This calculated ΔE value corresponds to an anticipated (*R*)-**2**:(*S*)-**2** ratio = 87:13 and ee = 74%. Experimentally, (*R*)-**2** is indeed the major product, with ee = 57% (entry 1, Table 1).

Scheme 3b presents the results with (*R*,*R*,*S*)-**1** ligand. Ethyl addition to the *pro*-(*S*) face in benzaldehyde is now predicted to be more favorable relative to addition to the

(20) See, also: Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.

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(22) *PC Spartan-Pro*, version 1.0; Wavefunction, Inc.: Irvine, CA, 1999.

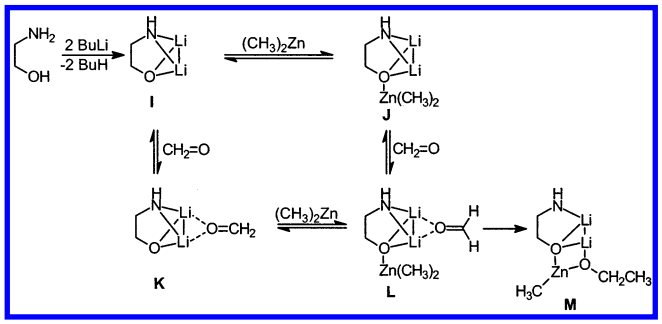
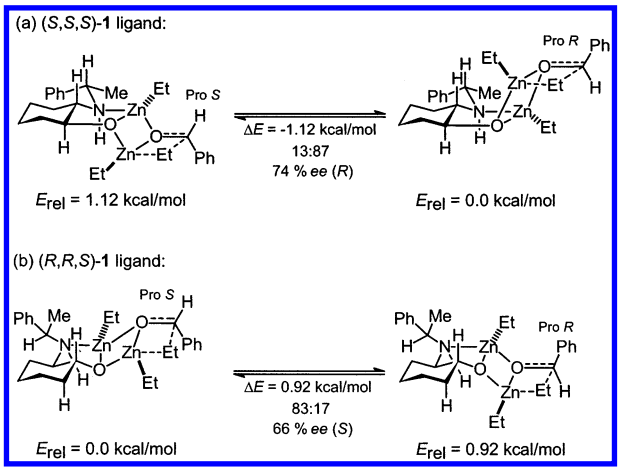


FIGURE 3. Catalytic cycle proposed in this work for the reaction of dimethylzinc and formaldehyde, under dilithiated 2-amino alcohol activation. All organometallic structures were optimized by semiempirical PM3 calculations.

SCHEME 3



pro-(*R*) face, with $\Delta E = 0.92$ kcal/mol, calculated (*R*)-**2**:(*S*)-**2** ratio = 17:83, and ee = 66%. These results are in good agreement with experiment, since the (*R*,*R*,*S*)-**1** *β*-amino alcohol induces the predominant formation of the (*S*)-**2** carbinol, with 50% ee (Table 1, entry 5).

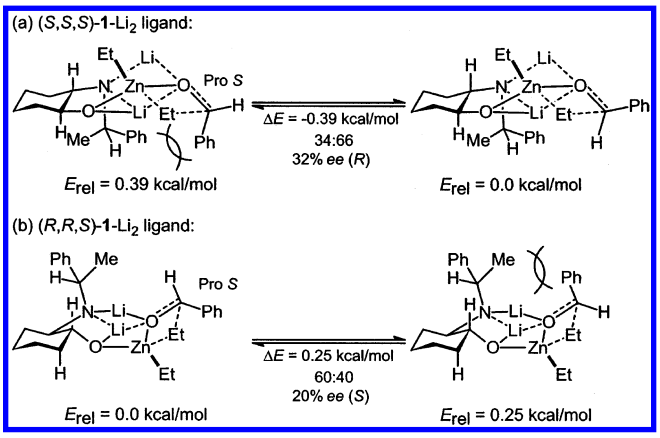
Also in agreement with the experimental results, stereoinduction by the *N*-phenylethyl group is marginal.

Molecular modeling of the alkylation reactions activated by dilithiated ligands (*S*,*S*,*S*)-**1**-Li_2 and (*R*,*R*,*S*)-**1**-Li_2 (entries 3 and 7, Table 1) required reexamination of Noyori's model catalytic cycle of 2-aminoethanol-promoted reaction of dimethylzinc and formaldehyde[5] (Figure 1). Calculations (BP86/DN**//PM3) support the modified catalytic cycle presented in Figure 3.

Salient features in the catalytic cycle advanced in Figure 3 are (1) the lowest-energy structures **I**−**M**, presenting ion-triplet configuration[23] of the dilithium salts, and (2) in contrast with the mechanism presented in Figure 1,[5] *only 1 equiv* of dialkylzinc should be required for the alkyl addition to take place.

Scheme 4 summarizes the computed data for the diastereomeric transition structures that lead, irreversibly, to carbinols (*R*)-**2** and (*S*)-**2** under the activation of dilithiated ligands (*S*,*S*,*S*)-**1**-Li_2 and (*R*,*R*,*S*)-**1**-Li_2. Again, the sense of stereoinduction is little affected by the *N*-α-phenylethyl chiral substituent and seems to be determined by the configurations at the stereogenic centers in the carbocyclic framework. *Unlike*[16] stereoinduction is favored, in agreement with the experimental results, although the extent of both the calculated (Scheme 4) and experimental (Table 1) enantioselectivity is lower in the case of the dilithiated ligands.

SCHEME 4



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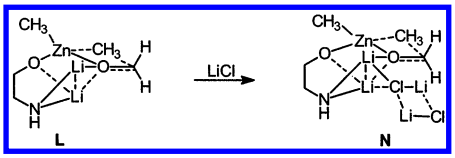
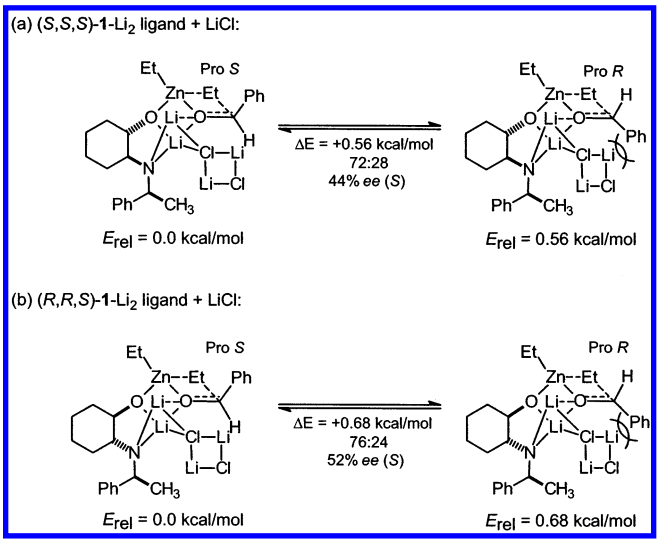


SCHEME 6



To understand the effect produced by the presence of LiCl in the reaction of diethylzinc and benzaldehyde, with activation by dilithiated amino alcohol (entries 4 and 8, Table 1), transition structure **L** (Figure 3) was optimized following incorporation of one, two, and three molecules of LiCl. The mixed aggregate of lowest energy at the BP86/DN**//PM3 level corresponds to **N**, as shown in Scheme 5.

Substitution in **N** by chiral ligands, incorporation of benzaldehyde, and diethylzinc provided the calculated (BP86/DN**//PM3) data that is summarized in Scheme 6. Most relevant, the calculations predict that both transition structures incorporating (*S*,*S*,*S*)-**1**-Li_2 (Scheme 6a) and (*R*,*R*,*S*)-**1**-Li_2 (Scheme 6b) favor alkyl group

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SCHEME 7

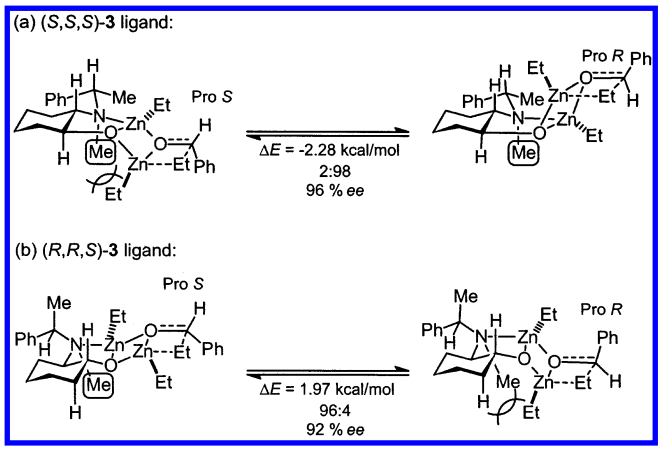
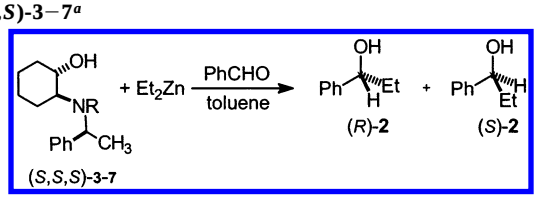


TABLE 3. Enantioselectivity of Diethylzinc Addition to Benzaldehyde in the Presence of *N*-Alkylated Ligands (*S*,*S*,*S*)-3−7[a]



entry	ligand	R	yield (%)	enantiomer ratio (*R*:*S*)
1	(*S*,*S*,*S*)-**1**	H	65	78:22
2	(*S*,*S*,*S*)-**3**	Me	81	82:18
3	(*S*,*S*,*S*)-**4**	Et	85	87:13
4	(*S*,*S*,*S*)-**5**	Pr	80	88:12
5	(*S*,*S*,*S*)-**6**	Bu	90	82:12
6	(*S*,*S*,*S*)-**7**	Pen	82	84:16

[a] All reactions were carried out in toluene, at 25 °C for 20 h. Molar ratio, Et_2Zn/PhCHO/ligand = 2.03:1.00:0.06.

addition on the *pro*-(*S*) face of benzaldehyde, although enantioselection is anticipated to be low. Both of these predictions are in line with the experimental results (entries 4 and 8, Table 1).

Steric bulk around the nitrogen atom in chiral β-amino alcohol ligands generally enhances the enantioselectivity of Et_2Zn addition to benzaldehyde.[4a,24] As can be seen in Scheme 7, this empirical observation is reproduced by our BP86/DN**//PM3 calculations incorporating *N*-methyl derivatives (*S*,*S*,*S*)-**3** and (*R*,*R*,*S*)-**3**. The former ligand induces preferential ethyl group addition on the *pro*-*R* face of benzaldehyde, leading to the formation of (*R*)-**2** with a calculated ee = 96%. By comparison, N−H ligand (*S*,*S*,*S*)-**1** is predicted to give (*R*)-**2** in a lower ee = 74% (Scheme 3). Similarly, according to the calculations, *N*-CH_3 ligand (*R*,*R*,*S*)-**3** favors formation of carbinol (*S*)-**2** by 1.97 kcal/mol; i.e., ee = 92% (Scheme 7). By comparison, N−H ligand is anticipated to furnish (*S*)-**2** in a lower 66% ee (Scheme 3).

Intrigued by this remarkable prediction, we prepared *N*-alkylated β-amino alcohols (*S*,*S*,*S*)-**3**−**7**, whose effectiveness as chiral activators in the enantioselective addition of diethylzinc to benzaldehyde was then examined (Table 3). It is seen that both the catalytic efficiency and the enantioselectivity are higher with ligands (*S*,*S*,*S*)-**3**−**7** relative to N−H ligand (*S*,*S*,*S*)-**1**. *N*-Ethylated ligand provided the best results, 85% yield and er = 87:13.

TABLE 4. Comparison of Calculated (BP86/DN//PM3) and Experimental (Tables 1 and 3) Results**

entry	ligand	additive (equiv)	er (*R*:*S*) exptl	er (*R*:*S*) calcd
1	(*S*,*S*,*S*)-**1**		78:22	87:13
2	(*S*,*S*,*S*)-**1**-Li_2		73:27	66:34
3	(*S*,*S*,*S*)-**1**-Li_2	LiCl (0.6)	38:62	28:72
4	(*R*,*R*,*S*)-**1**		25:75	17:83
5	(*R*,*R*,*S*)-**1**−Li_2		33:67	40:60
6	(*R*,*R*,*S*)-**1**−Li_2	LiCl (0.6)	39:61	24:76
7	(*S*,*S*,*S*)-**3**		82:18	98:2
8	(*R*,*R*,*S*)-**3**			4:96

Conclusions

Although many reports in the literature describe enantioselective additions of diethylzinc to benzaldehyde using chiral β-amino alcohols, this paper involves interesting new results. Most important, the use of the dilithium salts of β-amino alcohols (*S*,*S*,*S*)-**1** and (*S*,*S*,*R*)-**1** is described, and the opposite sense of enantioselectivity by the addition of lithium chloride (Table 4, entries 2 and 3) is described.

BP86/DN**//PM3 theoretical calculations proved remarkably successful in the reproduction of experimental results from the reaction of diethylzinc with benzaldehyde with activation by chiral β-amino alcohols (*S*,*S*,*S*)-**1** and (*R*,*R*,*S*)-**1**. Molecular modeling of the transition structures provided ΔE values for the diastereomeric organozinc complexes that are in good agreement with the experimentally observed enantioselectivities (Table 4).

Most relevant, modification of Noyori's catalytic cycle permitted the rationalization of the empirical data gathered from reactions carried out under activation by the lithium salts of (*S*,*S*,*S*)-**1** and (*R*,*R*,*S*)-**1**, with or without the addition of lithium chloride "inert" salts. Finally, the calculations were also able to reproduce the beneficial effect of *N*-alkylation on enantioselectivity (Table 4).

Experimental Section

General Experimental Procedures. Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organometallic compounds were dried for ca. 12 h at 120 °C and allowed to cool in a desiccator over anhydrous $CaSO_4$. Anhydrous toluene was obtained by distillation from benzophenone ketyl. *N*,*N*′-Dimethylpropyleneurea (DMPU) and acetonitrile were dried over CaH_2 and then distilled at reduced pressure. The BuLi employed was titrated according to the method we developed.[25] TLC: DC-F_{254} plates, with detection by UV light. Flash column chromatography: silica gel (0.040−0.063 mm). HPLC: instrument fitted with UV−vis detector and a chiral stationary phase of Chiralcel OD for the determination of the enantiomeric ratios. Melting points are not corrected. ^{1}H NMR spectra: 400 MHz. ^{13}C NMR spectra: 100 MHz. Chemical shifts (δ) in ppm downfield from internal TMS reference; the coupling constants (*J*) are given in Hz. Elemental analyses were obtained from Galbraith Laboratories, Inc., Knoxville, TN, and Service of Microanalyses, I.C.S.N.-C.N.R.S.

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91198, Gif sur Yvette. HRMS were obtained from Instituto de Química, UNAM, México.

(1*R*,2*R*,1′*S*)- and (1*S*,2*S*,1′*S*)-2-[*N*-α-Phenylethyl)-amino]cyclohexanols [(*R*,*R*,*S*)-1 and (*S*,*S*,*S*)-1]. A dry two-necked flask provided with addition funnel, condenser, and magnetic stirrer was loaded, with stirring and under argon, with an equimolar mixture of cyclohexene oxide (0.98 g, 10 mmol) and anhydrous lithium perchlorate (10 mmol) in freshly dried acetonitrile (10 mL). The reaction mixture was cooled in an ice−water bath to 0 °C before the dropwise addition of (*S*)-α-phenylethylamine (1.2 g, 10 mmol). The resulting solution was heated to reflux for 18 h. Water (25 mL) was added to the reaction mixture, and the organic phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give 2.1 g (98% yield) of the diastereomeric mixture of (*S*,*S*,*S*)-**1** and (*R*,*R*,*S*)-**1**, in a 55:45 ratio. This crude mixture was redissolved in dry ethanol (40 mL) and treated with anhydrous oxalic acid (0.22 g, 0.25 equiv), and the resulting solution was heated to reflux for 1 h. Upon standing, the oxalate salt derived from (*S*,*S*,*S*)-**1** precipitated, whereas (*R*,*R*,*S*)-**1** remained in solution. The precipitate was washed several times with hot ethanol until no more β-amino alcohol (*R*,*R*,*S*)-**1** was detected by TLC. The combined organic layers were treated at room temperature with anhydrous oxalic acid (0.22 g, 0.25 equiv) to precipitate the oxalate salt of diastereomer (*R*,*R*,*S*)-**1**. Each oxalate was hydrolyzed with aqueous 7% K_2CO_3 to give the free β-amino alcohol.

(1*R*,2*R*,1′*S*)-1. The oxalate salt, a white powder, mp 199−201 °C, gave the free β-amino alcohol (1.2 g, 54% yield) as white crystals, mp 65−66 °C (lit.[11c] mp 51−56 °C. The chlorhydrate salt was prepared by addition of HCl in ether, followed by recrystallization from CH_2Cl_2, mp 282−283 °C; $[\alpha]^{28}_D = -69.4$ (*c* = 1, EtOH). Lit.[11c] mp 284−286 °C; $[\alpha]^{28} = -69.8$ (*c* = 1, EtOH). ^{1}H NMR, see ref 11b. ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.7, 25.5, 26.2, 30.0, 33.5, 54.4, 60.4, 74.6, 127.2, 127.5, 129.0, 145.0.

(1*S*,2*S*,1′*S*)-1. The oxalate salt, a white powder, mp 234−235 °C, gave the free β-amino alcohol (0.92 g, 43% yield) as a colorless oil (lit.[11c] mp 25 °C). The chlorhydrate salt was prepared by treatment with HCl in ether, followed by recrystallyzation from CH_2Cl_2, mp 206−207 °C; $[\alpha]^{28}_D = -11.7$ (*c* = 1, EtOH). Lit.[11c] mp 207 °C; $[\alpha]^{28}_D = -11.5$ (*c* = 1, EtOH). ^{1}H NMR, see ref 11b. ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.0, 24.8, 25.9, 31.8, 33.5, 55.7, 62.0, 74.6, 126.9, 127.6, 129.0, 142.1.

General Procedure for *N*-Alkylation of (1*S*,2*S*,1′*S*)-1.[26] The β-amino alcohol (1.0 mmol) was dissolved in 10 mL of DMPU−EtOH (1:10) before the addition of 2.0 equiv of Na_2CO_3. To the resulting suspension was then added 1.5 equiv of the alkylating agent, and the reaction mixture was heated to reflux for 24 h. The reaction flask was brought to ambient temperature before dilution with 10 mL of water, and the crude product was extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and evaporated. Final purification was achieved by flash chromatography (petroleum ether).

(1*S*,2*S*,1′*S*)-2-*N*-Methyl-[*N*-(α-phenylethyl)amino]cyclohexanol [(1*S*,2*S*,1′*S*)-3]. According to the general procedure, β-amino alcohol (1*S*,2*S*,1′*S*)-**1** (0.22 g, 1.0 mmol) was treated with 0.09 mL (1.5 mmol) of methyl iodide to furnish 0.09 g (40% yield) of the desired *N*-methyl derivative, $[\alpha]^{28}_D = +19.0$ (*c* = 1.37, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (m, 5H), 1.36 (d, *J* = 6.6 Hz, 3H), 1.59 (m, 1H), 1.72 (m, 2H), 2.04 (s, 3H), 2.16 (m, 1H), 2.66 (m, 1H), 3.40 (m, 1H), 3.68 (q, *J* = 6.6 Hz, 1H), 7.23−7.31 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 22.7, 24.3, 25.6, 32.7, 33.4, 62.1, 64.8, 69.1, 127.1, 127.3, 128.5, 145.4. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.25; H, 9.87. Found: C, 77.48; H, 9.96.

(1*S*,2*S*,1′*S*)-2-*N*-Ethyl-[*N*-(α-phenylethyl)amino]cyclohexanol [(1*S*,2*S*,1′*S*)-4]. According to the general procedure, β-amino alcohol (1*S*,2*S*,1′*S*)-**1** (0.22 g, 1.0 mmol) was treated with 0.12 mL (1.5 mmol) of ethyl iodide to furnish 1.0 g (39% yield) of the desired *N*-ethyl derivative, $[\alpha]^{28}_D = +87.2$ (*c* = 3.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.0 Hz, 3H), 1.20 (m, 4H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.70 (m, 3H), 2.05 (m, 1H), 2.41 (m, 1H), 2.65 (m, 2H), 3.28 (m, 1H), 3.58 (bs, 1H), 4.06 (q, *J* = 7.0 Hz, 1H), 7.31−7.53 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 16.9, 24.3, 26.0, 26.5, 33.4, 39.5, 56.7, 63.6, 69.7, 126.9, 127.5, 128.4, 145.1. HMRS (FAB) *m*/*z* calcd for $C_{16}H_{25}NO$ 247.1936 $[M + H]^+$, found 247.1929.

(1*S*,2*S*,1′*S*)-2-*N*-Propyl-[*N*-(α-phenylethyl)amino]cyclohexanol [(1*S*,2*S*,1′*S*)-5]. According to the general procedure, β-amino alcohol (1*S*,2*S*,1′*S*)-**1** (0.22 g, 1.0 mmol) was treated with 0.15 mL (1.5 mmol) of propyl iodide to furnish 0.11 g (41% yield) of the desired *N*-propyl derivative, $[\alpha]^{28}_D = +96.2$ (*c* = 2.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (t, *J* = 7.3 Hz, 3H), 1.17 (m, 5H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.45 (m, 1H), 1.65 (m, 1H), 1.75 (m, 2H), 2.06 (m, 1H), 2.35 (m, 1H), 2.53 (m, 2H), 3.26 (m, 1H), 3.58 (bs, 1H), 4.04 (q, *J* = 6.9 Hz, 1H), 7.30−7.50 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 16.2, 23.1, 24.3, 26.0, 26.7, 33.4, 47.7, 56.9, 63.7, 69.7, 127.0, 127.7, 128.4, 144.9. HMRS (FAB) *m*/*z* calcd for $C_{17}H_{27}NO$ 261.2093 $[M + H]^+$, found 261.2089.

(1*S*,2*S*,1′*S*)-2-*N*-Butyl-[*N*-(α-phenylethyl)amino]cyclohexanol [(1*S*,2*S*,1′*S*)-6]. According to the general procedure, β-amino alcohol (1*S*,2*S*,1′*S*)-**1** (0.22 g, 1.0 mmol) was treated with 0.16 mL (1.5 mmol) of butyl bromide to furnish 0.09 g (32% yield) of the desired *N*-butyl derivative, $[\alpha]^{28}_D = +87.7$ (*c* = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.0 Hz, 3H), 1.22 (m, 8H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.64 (m, 1H), 1.74 (m, 2H), 2.06 (m, 1H), 2.35 (m, 1H), 2.56 (m, 2H), 3.26 (m, 1H), 3.56 (bs, 1H), 4.05 (q, *J* = 7.0 Hz, 1H), 7.31−7.47 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 16.3, 20.6, 24.3, 26.0, 26.7, 32.3, 33.4, 45.5, 56.9, 63.7, 69.7, 126.9, 127.6, 128.4, 144.9. HMRS (FAB) *m*/*z* calcd for $C_{18}H_{29}NO$ 275.2249 $[M + H]^+$, found 275.2250.

(1*S*,2*S*,1′*S*)-2-*N*-Pentyl-[*N*-(α-phenylethyl)amino]cyclohexanol [(1*S*,2*S*,1′*S*)-7]. According to the general procedure, β-amino alcohol (1*S*,2*S*,1′*S*)-**1** (0.22 g, 1.0 mmol) was treated with 0.19 mL (1.5 mmol) of pentyl bromide to furnish 0.09 g (30% yield) of the desired *N*-pentyl derivative, $[\alpha]^{28}_D = +72.9$ (*c* = 1.9, $CHCl_3$). ^{1}H NMR (400 MHZ, $CDCl_3$) δ 0.83 (t, *J* = 7.0 Hz, 3H), 1.20 (m, 11H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.64 (m, 1H), 1.75 (m, 2H), 2.07 (m, 1H), 2.36 (m, 1H), 2.54 (m, 2H), 3.27 (m, 1H), 4.05 (q, *J* = 7.0 Hz, 1H), 7.02−7.33 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 16.3, 22.6, 24.3, 26.0, 26.6, 29.6, 29.8, 33.4, 45.7, 57.0, 63.7, 69.7, 126.9, 127.6, 128.4, 144.9. Anal. Calcd for $C_{19}H_{31}NO$: C, 78.84; H, 10.78. Found: C, 78.86; H, 10.44.

General Procedure for Reaction of Diethylzinc with Benzaldehyde in the Presence of Ligands 1, 3−7. To an ice-cooled solution of chiral ligand (0.184 mmol) in dry toluene (3 mL) was added Et_2Zn (6.2 mmol, 6.2 mL of 1 M hexane solution) over a period of 5 min. The mixture was stirred at room temperature for 30 min, and benzaldehyde (0.32 mL, 3.05 mmol) was added at 0 °C. The reaction mixture was stirred for 20 h at room temperature, and 1 M HCl was added to quench the reaction. The mixture was extracted with CH_2Cl_2, the organic extract was dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane and ethyl acetate (15:1) as eluent. The product was characterized by ^{1}H NMR, and the enantiomeric excess was determined by HPLC (Chiralcel OD, hexane/2-propanol (97:3) as eluent, 0.5 mL/min flow rate).

General Procedure for Reaction of Diethylzinc with Benzaldehyde in the Presence of Dilithiated Ligands. To an ice-cooled solution of chiral ligand (0.184 mmol) in dry toluene (3 mL) was added butyllithium (0.368 mmol, 0.245 mL of 1.5 M hexane solution). After 10 min of stirring, Et_2Zn (6.2 mmol, 6.2 mL of 1 M hexane solution) was added over a period of 5 min. The mixture was stirred at room temperature for 30

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min, and benzaldehyde (0.32 mL, 3.05 mmol) was added at 0 °C. The reaction mixture was stirred for 20 h at room temperature, and then 1 M HCl was added to quench the reaction. The mixture was extracted with CH_2Cl_2, and the organic extract was dried with Na_2SO_4 before the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane and ethyl acetate (15:1) as eluent. The product was characterized by ^{1}H NMR, and the enantiomeric excess was determined by HPLC (Chiralcel OD, hexane/2-propanol (97:3) as eluent, flow rate 0.5 mL/min.).

General Procedure for Reaction of Diethylzinc with Benzaldehyde in the Presence of Dilithiated Ligands and LiCl. To an ice-cooled solution of chiral ligand (0.184 mmol) and LiCl (1.84 mmol, 0.08 g) in dry toluene (3 mL) was added *n*-butyllithium (0.368 mmol, 0.245 mL of 1.5 M hexane solution). After 10 min, Et_2Zn (6.2 mmol, 6.2 mL of 1 M hexane solution) was added over a period of 5 min. The mixture was stirred at room temperature for 30 min, and benzaldehyde (0.32 mL, 3.05 mmol) was added at 0 °C. The reaction mixture was stirred for 20 h at room temperature, and then 1 M HCl was added to quench the reaction. The mixture was extracted with CH_2Cl_2, and the organic extract was dried with Na_2SO_4, before the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane and ethyl acetate (15:1) as eluent. The product was characterized by ^{1}H NMR, and the enantiomeric excess was determined by HPLC (Chiralcel OD, hexane/2-propanol (97:3) as eluent, flow rate 0.5 mL/min.).

General Procedure for Reaction of Diethylzinc with Benzaldehyde in the Presence of Free Ligands and LiCl. To an ice-cooled solution of chiral ligand (0.184 mmol) and LiCl (1.84 mmol, 0.077 g) in dry toluene (3 mL) was added Et_2Zn (6.2 mmol, 6.2 mL of 1 M hexane solution) over a period of 5 min. The mixture was stirred at room temperature for 30 min, and benzaldehyde (0.32 mL, 3.05 mmol) was added at 0 °C. The reaction mixture was stirred for 20 h at room temperature, and then 1 M HCl was added to quench the reaction. The mixture was extracted with CH_2Cl_2, and the organic extract was dried with Na_2SO_4 before the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane and ethyl acetate (15:1) as eluent. The product was characterized by ^{1}H NMR, and the enantiomeric excess was determined by HPLC (Chiralcel OD, hexane/2-propanol (97:3) as eluent, flow rate 0.5 mL/min.).

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Supporting Information Available: Computational results (Cartesian coordinates for intermediates and transition states) at BP/DN** level of theory. This material is available free of charge via the Internet at http://pubs.acs.org.

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