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Increased Enantioselectivity in the Addition of Diethylzinc to Benzaldehyde by the Use of Chiral Ligands Containing the α-Phenylethylamino Group in Combination with Achiral Ligands

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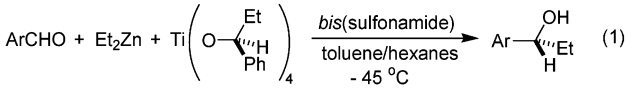
Chiral ligands (*S*,*S*)-**1**, (*S*,*S*)-**2**, (*S*,*S*)-**3**, (*S*)-**4**, (*S*)-**5**, (*S*,*S*)-**6**, (*S*,*S*)-**7**, and (*S*,*S*)-**8** turned out to be effective promoters in the enantioselective addition of diethylzinc to benzaldehyde. Interestingly, diamine (*S*,*S*)-**3** and amino alcohols (*S*)-**5** and (*S*,*S*)-**7** induce the preferential formation of carbinol (*R*)-**10** (*unlike* stereoinduction) whereas amido analogues (*S*,*S*)-**2**, (*S*)-**4**, and (*S*,*S*)-**6** favor (*S*)-**10** (*like* stereoinduction). Molecular modeling at the semiempirical PM3 level provided a reasonable interpretation based on conformational effects in the corresponding transition structures. Combinations of chiral ligands **1**−**8** with an achiral, flexible ligand (**9**) gave rise to an activated catalytic system that resulted in faster and higher yielding reactions. Furthermore, substantial increases in the observed enantiomeric excesses of product **10** confirmed the relevant role of achiral bis(sulfonamide) **9** as activator and "chiral environment amplifier".

Introduction

The development of new and more efficient catalytic asymmetric reactions is presently one of the most relevant and challenging goals in organic chemistry.[1] In this area, dialkylzinc addition to prochiral aldehydes in the presence of chiral β-amino alcohols or diamines constitutes a highly efficient procedure for the enantioselective construction of C−C bonds[2−5] (Scheme 1).

Very recently, pioneering work by Katsuki,[6] Mikami,[7] Kobayashi,[8] Walsh,[9] and others[10] has demonstrated that flexible achiral ligands can be used in combination with enantiopure chiral ligands to produce optimized asymmetric catalysts. The working hypothesis in this approach is that the chiral ligand interacts with the flexible achiral ligand, causing the latter to preferentially adopt an asymmetric conformation that is largely responsible for defining the chiral environment.[9]

Inspired by the observations from the Walsh group,[9,11] showing evidence for what they term *chiral environment amplification* in the asymmetric addition of diethylzinc to aldehydes with activation by chiral titanium alkoxide complexes, and in the presence of achiral bis(sulfonamide) ligands (eq 1), and further motivated by our



(1)

previous experience with the use of α-phenylethylamino group-containing ligands in enantioselective diethylzinc addition to benzaldehyde,[12,13] we undertook the study of this reaction under catalysis by novel chiral catalysts **1**−**8** (Chart 1), and in the absence or presence of achiral bis(sulfonamide) **9** (Scheme 2).

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SCHEME 1

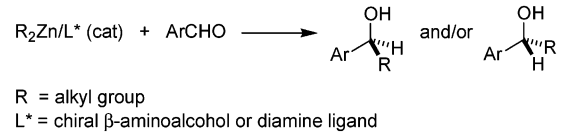
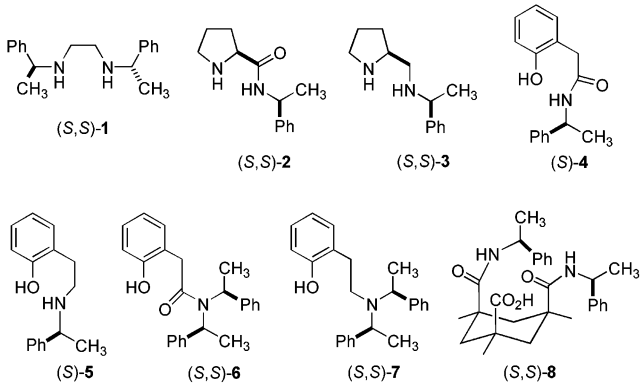


CHART 1



Results and Discussion

Table 1 summarizes the enantioselectivities recorded from the addition of diethylzinc to benzaldehyde under catalysis with chiral ligands **1**−**8**.

Highest enantioselectivities were obtained with chiral ligands (*S*,*S*)-**3** (65% ee, entry 3 in Table 1), (*S*)-**5** (58% ee, entry 5 en Table 1), and (*S*,*S*)-**7** (66% ee, entry 7 in Table 1). It is then clear that stereoinduction from the α-phenylethylamino auxiliary is much more effective in amino moieties (entries 3, 5, and 7) than in amide segments (cf. entries 2, 4, and 6).

Strikingly, whereas (*S*)-configured ligands **3**, **5**, and **7** induced the preferential formation of carbinol (*R*)-**10** (i.e., *unlike*[16] enantioinduction), by contrast (*S*)-configured ligands **2**, **4**, and **6** led to the predominance of (*S*)-**10** (i.e., *like* enantioinduction). To better understand this dramatic ligand effect, Noyori's catalytic cycle (Figure 1 and refs 17−20) was reexamined computationally, including ligands (*S*,*S*)-**6** and (*S*,*S*)-**7**, diethylzinc, and benzaldehyde. 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[21] was used to optimize molecular structures of the ligands and the organometallic complexes.

We first found that PM3 predicts fundamentally different conformational preferences in amide ligand (*S*,*S*)-**6** and amine analogue (*S*,*S*)-**7**. Indeed, intramolecular hydrogen bonding involving the hydroxy and carbonyl groups in (*S*,*S*)-**6** stabilizes a conformation with the chiral auxiliary outside the bridged lowest energy structure (Figure 2a). By contrast, intramolecular hydrogen bonding in aminophenol (*S*,*S*)-**7** involves the amine nitrogen, leading to a conformation where the phenethyl auxiliaries are close to the hydroxy group (Figure 2b).

Incorporation of ligands (*S*,*S*)-**6** and (*S*,*S*)-**7** in Noyori's transition structures afforded the PM3-calculated relative energies for the diastereomeric transition states leading

SCHEME 2

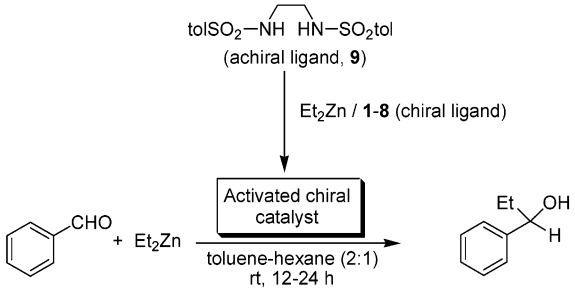


TABLE 1. Enantioselective Addition of Et_2Zn to Benzaldehyde in the Presence of Chiral Ligands 1−8

entry	L* (5 mol %)	yield[a] (%)	ee[b] (%)	major enantiomer[c]
1	(*S*,*S*)-**1**	72	29	(*R*)
2	(*S*,*S*)-**2**	88	42	(*S*)
3	(*S*,*S*)-**3**	73	65	(*R*)
4	(*S*)-**4**	79	27	(*S*)
5	(*S*)-**5**	72	58	(*R*)
6	(*S*,*S*)-**6**	84	45	(*S*)
7	(*S*,*S*)-**7**	81	66	(*R*)
8	(*S*,*S*)-**8**	44	14	(*S*)

[a] Isolated yield after purification by flash chromatography (hexanes−ethyl acetate, 9:1). [b] Determined by HPLC analysis on a Chiracel-OD chiral column. [c] The absolute configuration of 1-phenyl-1-propanol was assigned from the sign of the specific optical rotation[14] and from the elution order in HPLC.[15]

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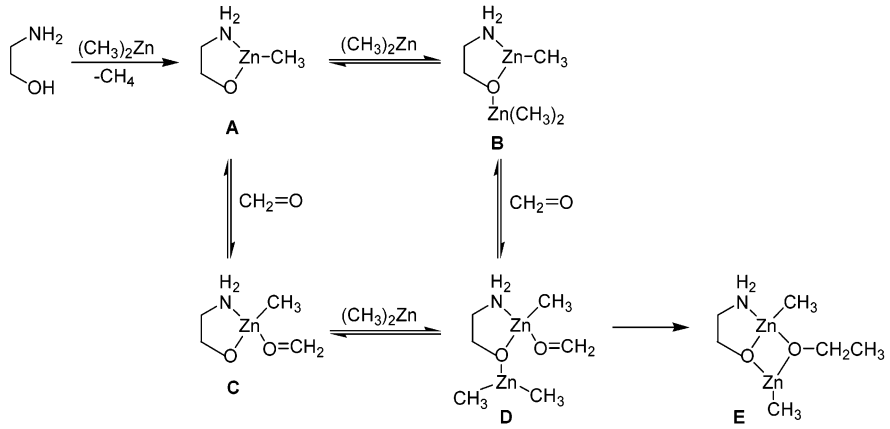


FIGURE 1. Catalytic cycle proposed by Yamakawa and Noyori[17] for the reaction of dimethylzinc and formaldehyde, under 2-aminoethanol activation.

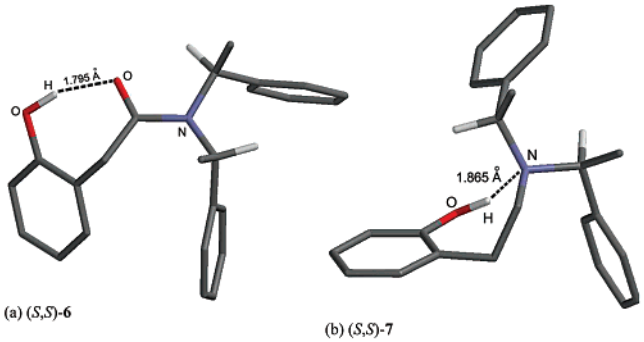


FIGURE 2. PM3 lowest energy structure and conformation for (a) chiral amide ligand (*S*,*S*)-**6** and (b) chiral amine ligand (*S*,*S*)-**7**.

to (*S*)-**10** and (*R*)-**10**. Scheme 3 summarizes the computed results from hypothetical equilibria between such diastereomeric transition structures. It is appreciated that with amide ligand (*S*,*S*)-**6**, alkyl addition to the *pro*-(*S*) face of benzaldehyde is favored by 0.65 kcal/mol (Scheme 3a). This calculated ΔE value corresponds to an anticipated (*R*)-**10**:(*S*)-**10** ratio of 25:75, and ee 50%. Experimentally (entry 6 in Table 1), (*S*)-**10** is indeed the major product, with ee 45%.

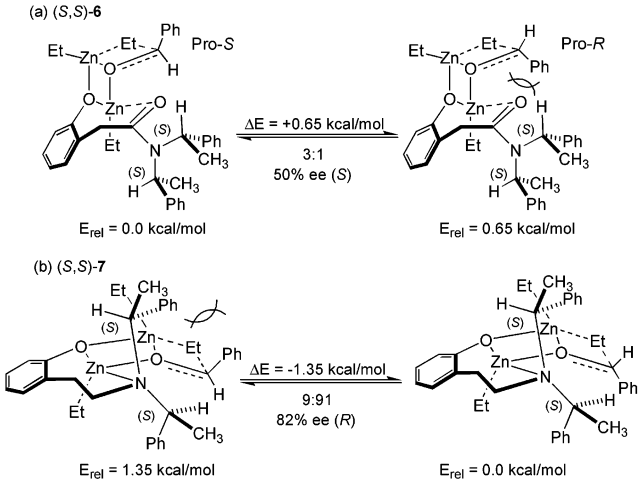
Scheme 3b presents the results with amine ligand (*S*,*S*)-**7**. Ethyl addition to the *pro*-(*R*) face in benzaldehyde is now predicted to be more favorable relative to addition to the *pro*-(*S*) face, with $\Delta E = 1.35$ kcal/mol, calculated (*R*)-**10**:(*S*)-**10** ratio 91:1, and ee 82%. These results are in good agreement with experiment, since the (*S*,*S*)-**7** amino alcohol induces the predominant formation of the (*R*)-**10** carbinol, with 66% ee (Table 1, entry 7).

The potential effect of achiral bis(sulfonamide) ligand **9** as chirality "amplifier" (Scheme 2) was then examined. In particular, one may anticipate that **9** will coordinate to the zinc atom, modifying the chiral metal environment.[9] Figure 3 outlines a possible catalytic cycle that incorporates both chiral ligand (*S*,*S*)-**7** and achiral ligand **9**.

Table 2 summarizes the enantioselectivities obtained when the addition of diethylzinc to benzaldehyde was carried out in the presence of both chiral ligands **1**−**8** and achiral ligand **9**.

From analysis of the data presented in Table 2 it is concluded that the presence of achiral ligand **9** did have

SCHEME 3



a remarkable activating effect on the reaction. Indeed, significantly shorter reaction times were required (12 h, versus 24 h in the absence of **9**) and the reaction yields were higher (61−95%, versus 44−88% in the absence of **9**). Most interestingly, the enantioselectivity was higher in all experiments carried out in the presence of achiral ligand **9**. Table 2 also presents a comparison of chemical yields and enantiomeric excesses, in the absence and the presence of bis(sulfonamide) **9**. It is appreciated that the amplifying effect by the achiral ligand reached remarkable levels, up to 64% ee increase in the case of (*S*,*S*)-**8** (entry 8 in Table 2).

In conclusion, chiral ligands **1**−**8** are effective promoters in the enantioselective addition of diethylzinc to benzaldehyde. When the reaction is carried out in the presence of achiral bis(sulfonamide) ligand **9**, an activated catalyst is generated that accelerates the reaction and affords higher enantiomeric excesses in the carbinol product, (*R*)- or (*S*)-**10**. These results provide additional confirmation of the relevant role that achiral ligands, in combination with enantiopure ligands, can play for the development of optimized asymmetric catalysts.

Experimental Section

General Experimental Procedures. Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organometallic compounds were dried for ca.

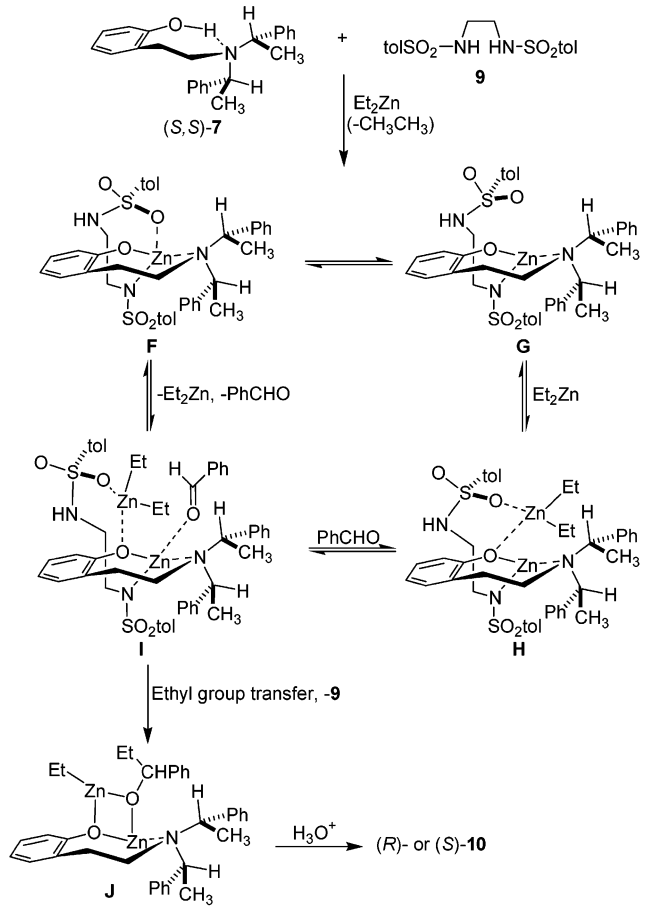
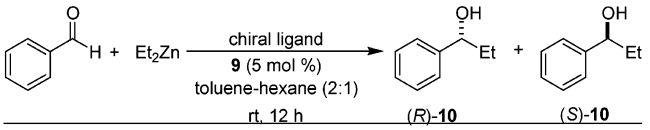


FIGURE 3. Suggested alkylation catalytic cycle in the presence of both chiral ligand (*S*,*S*)-**7** and achiral bis(sulfonamide) **9**.

TABLE 2. Enantioselective Addition of Et_2Zn to Benzaldehyde in the Presence of Both Chiral Ligands 1−8 and Achiral Bis(sulfonamide) 9



entry	L* (5 mol %)	yield[a] (%)	ee[b] (%)	% increase in ee	major enantiomer[c]
1	(*S*,*S*)-**1**	87	35	21	(*R*)
2	(*S*,*S*)-**2**	95	61	45	(*S*)
3	(*S*,*S*)-**3**	89	79	22	(*R*)
4	(*S*)-**4**	92	40	48	(*S*)
5	(*S*)-**5**	90	71	22	(*R*)
6	(*S*,*S*)-**6**	89	59	31	(*S*)
7	(*S*,*S*)-**7**	88	79	20	(*R*)
8	(*S*,*S*)-**8**	61	23	64	(*S*)

[a] Isolated yield after purification by flash chromatography (hexanes−ethyl acetate, 9:1). [b] Determined by HPLC analysis on a Chiracel-OD chiral stationary phase column. [c] The absolute configuration of 1-phenyl-1-propanol was assigned from the signal of the specific optical rotation[14] and from the elution order in HPLC.[15]

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. TLC: DC-F_{254} plates, 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.

(1′*S*,1″*S*)-*N*,*N*-Bis(1-phenylethyl)ethane-1,2-diamine, (*S*,*S*)-1. A two-necked flask was loaded with (*S*)-α-phenylethylamine (7.2 g, 59 mmol) and heated to 90 °C before the slow addition of 1,2-dichloroethane (2.2 g, 23 mmol). The resulting mixture was heated at 90 °C for 24 h and allowed to cool to 60 °C, then 150 mL of aqueous saturated KOH was added under vigorous stirring. The reaction mixture was allowed to cool to room temperature before extraction of the product with CH_2Cl_2 (3 × 50 mL). The organic phases were combined and washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The amine excess was removed by distillation on a Kugelrohr apparatus (40 °C, 5 mmHg) to give 8.5 g of crude product. The purification of (*S*,*S*)-**1** was accomplished by crystallization of the corresponding hydrochloride with gaseous HCl in ether. The diamine (*S*,*S*)-**1** was liberated by treatment with aqueous saturated KOH until pH 10 followed by extraction with CH_2Cl_2 (3 × 50 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to afford 7.2 g (74% yield) of the desired product. $[\alpha]^{28}_D$ −69.4 (*c* 1.5, $CHCl_3$) [lit[22] $[\alpha]^{28}_D$ −69.0 (*c* =1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, J = 6 Hz, 6H), 1.45 (m, 2H), 1.88 (br s, 2H), 2.59 (m, 4H), 3.7 (q, J = 6 Hz, 2H), 7.11−7.43 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 28.2, 47.9, 58.1, 127.1, 127.3, 129.3, 146.8.

(*S*)-Pyrrolidine-2-carboxylic Acid (1′*S*-Phenylethyl)-amide, (*S*,*S*)-2. The procedure described by Mukaiyama et al.[23] was followed with (*S*)-proline (5.75 g, 50 mmol) and (*S*)-α-phenylethylamine (6.05 g, 50 mmol) to give 9.1 g (84% yield). $[\alpha]^{28}_D$ −61.9 (*c* 2.3, EtOH) [lit[23] $[\alpha]^{28}_D$ −63.2 (*c* 1.0, EtOH)].

(1′*S*-Phenylethyl)-(*S*)-pyrrolidin-2-ylmethylamine, (*S*,*S*)-3. The desired product was prepared according to the procedure described by Mukaiyama et al.[23] $[\alpha]^{28}_D$ +124.5 (*c* 1.1, $CHCl_3$) [lit.[23] $[\alpha]^{28}_D$ +124.7 (*c* 1.0, $CHCl_3$)].

General Procedure for the Preparation of Chiral Ligands (*S*)-4, (*S*)-5, (*S*,*S*)-6, and (*S*,*S*)-7. To a 100-mL flask provided with a Dean−Stark trap and a magnetic stirrer was added (2-hydroxyphenyl)acetic acid (4.4 g, 29 mmol) in 60 mL of toluene and catalytic amounts of *p*-TsOH. The resulting mixture was refluxed for 4 h with removal of water and then the residual solvent was removed at reduced pressure to give 3*H*-benzofuran-2-one in quantitative yield (3.9 g), mp 52 °C (lit.[24] mp 50−51 °C). Acetamides (*S*)-**4** and (*S*,*S*)-**6** were obtained by refluxing 3*H*-benzofuran-2-one and (*S*)-phenylethylamine or (*S*,*S*)-bisphenylethylamine (equimolar amounts) in toluene. Amino alcohols (*S*)-**5** and (*S*,*S*)-**7** were prepared by refluxing of the corresponding acetamides with $LiAlH_4$ (3.3 equiv) in THF for 24−48 h.

2-(2-Hydroxyphenyl)-*N*-(1*S*-phenylethyl)acetamide, (*S*)-4. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 1.42 (d, J = 7.3 Hz, 3H), 3.55 (dd, J = 11.6 Hz, J = 4.1 Hz, 2H), 5.04 (m, 1H), 6.89−7.32 (m, 9H), 9.96 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 21.8, 40.6, 49.6, 117.6, 120.5, 121.7, 126.1, 127.5, 128.8, 129.1, 130.9, 142.5, 155.8, 177.7. $[\alpha]^{28}_D$ −34.7 (*c* 1.1, $CHCl_3$), mp 105 °C. Anal. Calcd for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71. Found: C, 75.05; H, 6.74.

2-(2-Hydroxyphenyl)-*N*,*N*-bis(1*S*-phenylethyl)acetamide, (*S*,*S*)-6. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 1.29 (d, J = 7.2 Hz, 3H), 1.37 (d, J = 7.2 Hz, 3H), 3.58 (q, J = 7.2 Hz, 1H), 3.70 (dd, J = 11.9 Hz, J = 6.9 Hz, 2H), 4.21 (q, J = 7.1 Hz, 1H), 7.11−7.55 (m, 14H), 9.37 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 21.9, 22.1, 40.6, 40.8, 49.9, 50.2, 117.6, 120.4, 121.9, 127.5, 129.1, 129.2, 130.4, 142.6, 155.9, 179.8.

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$[\alpha]^{28}_D$ −75.4 (*c* 1.0 $CHCl_3$), oil. Anal. Calcd for $C_{16}H_{20}ONCl$: C, 66.92; H,7.22. Found: C, 66.62; H, 7.26.

2-[2-(1*S*-Phenylethylamino)ethyl]phenol, (*S*)-5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, J = 6.9 Hz, 3H), 2.71−2.83 (m, 4H), 3.84 (q, J = 6.9 Hz, 1H), 6.95−7.39 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 34.4, 47.7, 58.1, 117.6, 118.9, 119.0, 126.3, 126.5, 127.3, 127.6, 128.2, 128.8, 130.9, 143.2, 156.9. $[\alpha]^{28}_D$ −56.9 (*c* 1.5, $CHCl_3$), wax. Anal. Calcd for $C_{24}H_{25}O_2N$: C, 80.19; H, 7.01. Found: C, 80.31; H, 7.18.

2-{[2-Bis(1*S*-phenylethyl)amino]ethyl}phenol, (*S*,*S*)-7. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 6.9 Hz, 3H), 1.42 (d, J = 6.9 Hz, 3H), 2.69−2.80 (m, 4H), 3.79 (q, J = 6.9 Hz, 1H), 3.93 (q, J = 6.9 Hz, 1H), 7.11−7.62 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 22.8, 33.7, 39.6, 46.1, 48.3, 56.5, 57.3, 116.3, 116.9, 117.7, 118.2, 118.9, 119.3, 120.1, 125.4, 126.1, 126.8, 127.5, 129.8, 133.4, 142.9, 147.3, 157.3. $[\alpha]^{28}_D$ −95.0 (*c* 1.1, $CHCl_3$), oil. Anal. Calcd for $C_{24}H_{27}ON$: C, 83.44; H, 7.88. Found: C, 83.59; H, 7.63.

1,3,5-Trimethyl-3,5-bis(1*S*-phenylethylcarbamoyl)cyclohexanecarboxylic Acid, (*S*,*S*)-8. To a round-bottom flask provided with a magnetic stirring was added under inert atmosphere *cis*,*cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylic acid (0.3 g, 1.16 mmol) and 3 mL (41.2 mmol) of thionyl chloride. The resulting mixture was stirred for 48 h at room temperature. The excess thionyl chloride was then removed under reduced pressure, and the residue was redissolved in anhydrous CH_2Cl_2 (20 mL) at 0 °C before the slow addition of 4-(dimethylamino)pyridine (0.42 g, 3.5 mmol) dissolved in 5 mL of the same solvent. The reaction mixture was stirred for 30 min and then (*S*)-α-phenylethylamine (0.43 g, 3.5 mmol) was added dropwise with continued stirring for 24 h at room temperature. The reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were washed with aqueous 10% HCl, saturated aqueous $NaHCO_3$, and brine, and finally dried over Na_2SO_4. The solvent was evaporated in a rotary evaporator to afford 0.44 g (67% yield) of the desired product, mp 155−156 °C (lit.[24] mp 156−158 °C). $[\alpha]^{28}_D$ −77.0 (*c* 1.5, EtOH), [lit[25] $[\alpha]^{28}_D$ −77.4 (*c* 1.0, EtOH)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, J = 15.5 Hz, 1H), 1.08 (d, J = 15.5 Hz, 2H), 1.19 (s, 3H), 1.20 (s, 3H), 1.36 (s, 3H), 1.47 (d, J = 7 Hz, 3H), 1.53 (d, J = 7 Hz, 3H), 2.78 (d, J = 15 Hz, 2H), 2.95 (d, J = 15 Hz, 2H), 4.99 (m, 2H), 6.96 (d, J = 7.4 Hz, 1H), 7.26 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9, 33.6, 35.1, 41.3, 42.4, 42.7, 43.1, 43.3, 126.2, 128.4, 128.7, 139.0, 177.1, 180.3.

1,2-Bis(toluene-4-sulfonilamino)ethane, 9. The desired product was prepared according to the standard procedure described by Whitesides et al.[26a] to afford bis(sulfonamide) **9** in 74% yield, mp 175 °C (lit.[26b] mp 175 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 6H), 3.05 (m, 4H), 5.08 (br s, 2H), 7.23−7.69 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 43.0, 127.1, 129.9, 139.9, 140.1.

General Procedure for the Addition of Diethylzinc to Benzaldehyde in the Presence of Chiral Ligands 1−8. To an ice-cooled solution of chiral ligand (0.155 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 24 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 with 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, and 0.5 mL/min of flow rate).

General Procedure for the Addition of Diethylzinc to Benzaldehyde in the Presence of a Combination of Chiral Ligands 1−8 and Achiral Amplifier 9. 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 resulting mixture was stirred at room temperature for 30 min, and then 0.155 mmol of bis(sulfonamide) **9** in dry toluene (3 mL) was added with stirring at the same temperature for 30 min before the addition of benzaldehyde (0.32 mL, 3.05 mmol) 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 with 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, and 0.5 mL/min of flow rate).

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