# A Superior, Readily Available Enantiopure Ligand for the Catalytic Enantioselective Addition of Diethylzinc to α-Substituted Aldehydes

Lluís Solà,[†] Katamreddy Subba Reddy,[†] Anton Vidal-Ferran,[†] Albert Moyano,[†] Miquel A. Pericàs,*[,†] Antoni Riera,[†] Angel Alvarez-Larena,[‡] and Joan-F. Piniella[‡]

*Unitat de Recerca en Síntesi Asimètrica, Departament de Química Orgànica, Universitat de Barcelona, c/ Martí i Franquès, 1-11, 08028 Barcelona, Spain, and Unitat de Cristal·lografia, Facultat de Ciències, Universitat Autònoma de Barcelona, 08193 Barcelona, Spain*

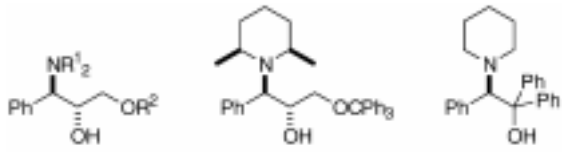
*Received July 8, 1998*

The lithium perchlorate-induced ring opening of (*S*)-triphenylethylene oxide (**3**) with secondary amines (piperidine (**a**), *N*-methylpiperazine (**b**), *N*-phenylpiperazine (**c**) and morpholine (**d**)) takes place in a stereospecific and completely regioselective manner to afford (*R*)-2-(dialkylamino)-1,1,2-triphenylethanols (**4a**−**d**). These amino alcohols catalytically induce the addition of diethylzinc to benzaldehyde with high enantioselectivity at 0 °C and at room temperature. Ligand **4a**, which provides the highest enantioselectivity at 0 °C, has been studied in the addition of $Et_2Zn$ to a family of 20 representative aliphatic and aromatic aldehydes **5a**−**t**. For a 17-membered set of α-substituted substrates (**5a**−**m**,**q**−**t**), including *ortho*-, *meta*-, and *para*-substituted benzaldehydes, the naphthaldehydes, α,*β*-unsaturated and aliphatic (cyclic and acyclic) aldehydes, the mean enantiomeric excess of the resulting alcohols **6a**−**m**,**q**−**t** is 97%, whereas for three α-unsubstituted specimens (**5n**−**p**) the addition takes place with an enantioselectivity of 92−93%.

## Introduction

Despite the ever-increasing repertoire of metal-catalyzed asymmetric organic reactions available to chemists, the chiral amino alcohols ubiquitously employed as ligands in these processes are still mostly based on a few naturally occurring skeletons, thus belonging to a limited number of structural types.[1] It is virtually impossible that such a limited set of ligands can satisfactorily cope with all of the conceivable situations (diversity of metals, substrates, and reagents) in catalysis. The synthesis of new ligands, based on processes that are compatible with structural diversity, is thus a matter of enormous interest. When the preparation of *β*-amino alcohols is scrutinized under the prism of diversity, the regioselective and stereospecific ring opening of epoxides with nitrogen nucleophiles appears as the method of choice. If enantiopurity of the target amino alcohols is an additional requirement, the current availability of synthetic methods such as the Sharpless[2] and Jacobsen[3] epoxidations for the catalytic production of enantiomerically pure epoxides of great structural diversity provides a satisfactory answer to this demand.

We have recently reported the synthesis of a family of fine-tunable *β*-amino alcohol ligands (**1**), based on enantiopure epoxycinnamyl alcohol (**2**) and its structural refinement leading to ligand **1a** through mechanism-guided molecular design.[4] We wish to report now on the identification of a superior, general ligand for the enantioselective addition of diethylzinc to α-substituted aldehydes, among the products arising from the completely regioselective ring-opening with secondary amines of (*S*)-triphenylethylene oxide (**3**). This reagent, in turn, is readily available in enantiopure form at the molar scale through Jacobsen epoxidation of inexpensive triphenylethylene[5] followed by enantiomeric enrichment by crystallization.[6]




**1** **1a** **4a**

## Results and Discussion

To define our initial space of candidate structures, the dialkylamino moiety was restricted to cyclic, six-membered ring secondary amines, which have provided the highest enantioselectivities in ligands **1**.[4] The ring-opening processes were initially performed in the presence of lithium perchlorate according to Crotti[7] (conditions A in Scheme 1). Epoxide **3** behaved in these

* To whom correspondence should be addressed. E-mail: mpb@ursa.qo.ub.es.
[†] Unitat de Recerca en Síntesi Asimètrica.
[‡] Unitat de Cristal·lografia.

(1) For general reviews, see: (a) *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Seyden-Penne, J., Ed.; John Wiley & Sons: New York, 1995. (b) Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935−952.

(2) For reviews, see: (a) Katsuki, T.; Martín, V. S. *Org. React.* **1996**, *48*, 1−299. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; pp 101−158.

(3) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; pp 159−202.

(4) (a) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970−4982. (b) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773−8776.

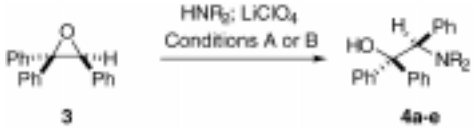
(5) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378−4380.

(6) (*S*)-Triphenylethylene oxide (**3**) is obtained in 94% ee following Jacobsen's epoxidation procedure and can be enantiomerically enriched by a single recrystallization from hexane up to >99.9% ee.

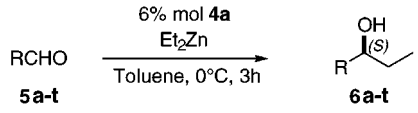
(7) Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Giovani, E.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1993**, *58*, 1221−1227.

S0022-3263(98)01336-X CCC: $15.00 
Published on Web 09/11/1998

**Scheme 1**




**Scheme 2**




reactions as a highly congested substrate, with satisfactory results being only recorded in the case of piperidine. However, after some experimentation, we found that much better results were obtained if the reaction was perfomed in excess amine in the presence of only 2 equiv of lithium perchlorate at 100 °C (conditions B in Scheme 1). Even under these improved conditions, the rather hindered *cis*-2,6-dimethylpiperidine failed to provide amino alcohol **4e**, but for the other studied amines, amino alcohols **4a**−**c** were obtained in excellent yield. In all the studied cases, the reactions were completely regioselective, and the precise regiochemistry could be established by X-ray diffraction in the case of **4b**.[8] Also for **4b**, HPLC analysis on a chiral column showed that the ring-opening process takes place with complete stereospecificity.[9]

Ligands **4a**−**d** were initially tested in the enantioselective addition of diethylzinc to benzaldehyde (**5a**).[10] Whereas all four ligands are essentially equivalent at room temperature, affording (*S*)-**6a** of 92−93% ee, **4a** shows a very interesting enantioselectivity/temperature profile, a 6% increase in the ee of **6a** being recorded by simply lowering the reaction temperature to 0 °C.[11] Moreover, this ligand exhibits a very high catalytic activity, the reaction being essentially complete (98% conversion) after only 0.5 h at 0 °C. If desired, the amount of ligand can be lowered to 2%, the reaction then requiring 4 h for 99% conversion without significant loss (ca. 1%) in enantioselectivity.

Ligand **4a** was subsequently employed to induce the enantioselective addition of diethylzinc to a representative family of aromatic aldehydes **5b**−**m** (Scheme 2 and Table 2). Very interestingly, the enantiomeric purity of the resulting *S* alcohols was in all cases higher than 95%.[12] Most remarkable are the results with ortho-substituted benzaldehydes and with 1-naphthaldehyde, since these more congested substrates tend to experience dialkylzinc addition with comparatively lower enantioselectivity than other aromatic substrates.[13j,l] We next tested the reaction on aliphatic aldehydes **5n**−**p**: In these cases, a slightly lower (90−92%) enantioselectivity was observed. This could, however, be increased to 92−93% by simply performing the addition reaction at −20 °C.

**Table 1. Lithium Perchlorate-Induced Ring Opening of (*S*)-Triphenylethylene Oxide with Secondary Amines**

| amine | β-amino alcohol | condn A[a] yield (%) | condn B[a] yield (%) |
|---|---|---|---|
| piperidine | **4a** | 92 | 98 |
| *N*-methylpiperazine | **4b** | 54 | 96 |
| *N*-phenylpiperazine | **4c** | 28[c] | 96 |
| morpholine | **4d** | | 86 |
| *cis*-2,6-dimethylpiperidine | **4e** | | 0 |

[a] Reaction in acetonitrile at reflux for 24 h in the presence of the amine (10 equiv) and lithium perchlorate (15 equiv). [b] Reaction in excess amine at 100 °C for 24 h in the presence of lithium perchlorate (2 equiv). [c] By extending reaction time to 72 h, yield can be improved to 44%, and a 50% amount of the starting material is recovered unchanged.

The results obtained with ortho-substituted benzaldehydes, along with the fact that the addition to aromatic aldehydes mediated by **4a** appears to be completely insensitive to the electronic nature (electron donating or electron withdrawing) of the substituents, suggested that the decrease in enantioselectivity with **5n**−**p** could be simply due to the absence of substitution at the α carbon. To test this hypothesis, we also studied the addition to the α-substituted aliphatic aldehydes **5q**−**s** and to α-methylcinnamaldehyde **5t**, which cover both cyclic and acyclic substrates. Gratifyingly enough, the enantiomeric purity of the resulting alcohols was again very high (95−99%).

Given the large number of species that have been used to catalyze with more or less success the enantioselective addition of diethylzinc to aldehydes, a solid assessment of the merits of **4a** requires a comparison of availability, experimental conditions involved in use, and overall performance with previously known ligands. To allow this comparison, we have collected in Table 3 relevant information on the characteristics of some of the most popular ligands for this chemistry.[13]

The simple inspection of Table 3 reveals that **4a** is placed at the top among these ligands in mean enantiomeric excess despite the large family of aldehydes it has been studied with. Even more importantly, the standard deviation ($\sigma_n$) in ee when using **4a** is extremely small, specially when the 17-membered set of α-substituted aldehydes is considered. *This means, in practice, that when the enantioselective addition of diethylzinc to one such aldehyde is considered, the use of* ***4a*** *can be decided with almost absolute confidence.*[14]

(8) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(9) The ring-opening process was assumed to occur with complete stereospecifity in the other substrates.

(10) For reviews, see: (a) Soai, K. *Chem. Rev.* **1992**, *92*, 833−856. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; pp 255−297.

(11) A 2−3% increase in ee was observed with **4b**−**d** under similar conditions.

(12) The *S* configuration was established by comparison of the optical rotation with published values and, for **6t**, by comparison of retention times of the corresponding acetate derivative (GC, β-DEX column). For **6b**,**f**,**h**,**r** the *S* configuration has been assumed.

(13) (a) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321−1323. (b) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 99−101. (c) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264−4268. (d) Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1690−1. (e) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111−7115. (f) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071−6072. (g) Watanabe, M.; Araki, S.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2218−2224. (h) Kang, J.; Lee, J. W.; Kim, J. I. *J. Chem. Soc., Chem. Commun.* **1994**, 2009−2010. (i) Kang, J.; Kim, D. S.; Kim, J. I. *Synlett* **1994**, 842−844. (j) Qiu, J.; Guo, C.; Zhang, X. *J. Org. Chem.* **1997**, *62*, 2665−2668. (k) Zhang, F. Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651−3655. (l) Huang, W. S.; Hu, Q. S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364−1365. (m) For the use of bis-sulfonamides derived from enantiomerically pure *trans*-1,2-diaminocyclohexane as ligands for the highly efficient addition of diethylzinc to a limited set of aldehydes (four specimens), see: Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691−5700.

(14) The configuration of the resulting alcohols is in agreement with Noyori's empirical rule. See ref 10b, pp 265−266.

**Table 2. Catalytic Enantioselective Addition of $Et_2Zn$ to Aldehydes 5a−t Leading to Alcohols 6a−t Mediated by Ligand 4a**

| starting aldehyde | resulting alcohol | conversion[a] (%) | selectivity[b] (%) | enant excess[c] (%) |
|---|---|---|---|---|
| benzaldehyde (**5a**) | **(*S*)-6a** | 100 | 99 | **98** |
| *o*-chlorobenzaldehyde (**5b**) | **(*S*)-6b** | 100 | 98 | **95** |
| *o*-fluorobenzaldehyde (**5c**) | **(*S*)-6c** | 99 | 99 | **96** |
| *o*-tolualdehyde (**5d**) | **(*S*)-6d** | 100 | 97 | **97** |
| *o*-methoxybenzaldehyde (**5e**) | **(*S*)-6e** | 99 | 92 | **96** |
| *m*-fluorobenzaldehyde (**5f**) | **(*S*)-6f** | 99 | 97 | **97** |
| *m*-tolualdehyde (**5g**) | **(*S*)-6g** | 99 | 99 | **97** |
| *m*-methoxybenzaldehyde (**5h**) | **(*S*)-6h** | 99 | 100 | **97** |
| *p*-fluorobenzaldehyde (**5i**) | **(*S*)-6i** | 100 | 99 | **98** |
| *p*-tolualdehyde (**5j**) | **(*S*)-6j** | 100 | 100 | **98** |
| *p*-methoxybenzaldehyde (**5k**) | **(*S*)-6k** | 98 | 98 | **98** |
| 1-naphthaldehyde (**5l**) | **(*S*)-6l** | 99 | 99 | >**99** |
| 2-naphthaldehyde (**5m**) | **(*S*)-6m** | 99 | 99 | **98** |
| heptanal (**5n**) | **(*S*)-6n** | 100[e] | 100[e] | **92**[e] |
| isovaleraldehyde (**5o**) | **(*S*)-6o**[d] | 99[e] | 99[e] | **92**[e] |
| 3-phenylpropanal (**5p**) | **(*S*)-6p**[d] | 99[e] | 99[e] | **93**[e] |
| cyclohexanecarbaldehyde (**5q**) | **(*S*)-6q** | 99 | 98 | **98** |
| 3-cyclohexenecarbaldehyde (**5r**)[f] | **(*S*)-6r** | 99 | 99 | **99**[g] |
| 2-ethylbutyraldehyde (**5s**) | **(*S*)-6s** | 99 | 99 | **97** |
| (*E*)-α-methylcinnamaldehyde (**5t**) | **(*S*)-6t** | 88 | 99 | **95** |

[a] Determined by integration of residual **5** in front of all new products in the gas chromatogram of the reaction crude. [b] Determined by integration of **6** (both enantiomers) in front of all new compounds in the gas chromatogram of the reaction crude. [c] Determined by GC on a *β*-DEX 120 column. [d] Reaction was performed at −20 °C. [e] Determined by GC on a α-DEX 120 column. [f] Commercial, racemic compound was used. [g] Diastereomeric excess for both enantiomers of starting material.

**Table 3. Comparative Analysis of Ligands for the Enantioselective Addition of $Et_2Zn$ to Aldehydes**

| | | conditions of use | | no. of | performance | |
|---|---|---|---|---|---|---|
| entry | ligand | % mol | T (°C)/ *t*(h) | tested aldehydes | mean ee (%) | *σ* (%) |
| 1 | Seebach[13a] | 20 | −22/15 | 9 | 97.6 | 2.4 |
| 2 | Seebach[13b] | 10 | −75/15−24 | 9 | 91.4 | 5.6 |
| 3 | Soai[13c,d] | 6 | 0/16 | 7 | 89.3 | 5.4 |
| 4 | Soai[13e] | 2 | 0/*a* | 7 | 91.3 | 11.6 |
| 5 | Noyori[13f] | 2 | 0/6−64 | 6 | 88.7 | 12.7 |
| 6 | Butsugan[13g] | 5 | 25/1−4 | 10 | 89.3 | 14.0 |
| 7 | Kang[13h,i] | 5 | 0/8−12 | 12 | 95.9 | 7.5 |
| 8 | Zhang[13j] | 20 | −23/4 | 16 | 90.8 | 11.9 |
| 9 | Chan[13k] | 20 | 0/5 | 14 | 94.0 | 4.0 |
| 10 | Pu[13l] | 5−30 | 0/4−45 | 23 | 96.5 | 2.8 |
| 11 | **4a**, this work[b] | 6 | 0/3 | 17 | 97.3 | 1.3 |
| 12 | **4a**, this work[c] | 6 | −20 or 0/3−4 | 20 | 96.6 | 2.2 |

[a] Not reported. [b] For α-substituted aldehydes. [c] For the full set of studied aldehydes.

If we attend to conditions of use, **4a** is again one of the most favorable options. Thus, ligands in entries 1 and 10 (Table 3), which are considered to be among the best for this particular process, require for high enantioselectivity either the use of substantially higher amounts of catalyst at unconveniently low temperatures or extended reaction periods. With a 6% molar amount of ligand **4a** (Table 3, entry 11), in turn, conversions higher than 95% are recorded after 1 h at 0 °C, and the reactions are complete after 3 h at that temperature (see Table 3). Also in this respect, an additional practical advantage of ligand **4a** is that the use of additives, such as titanium alkoxides,[13a,b,j−m] is not required for the achievement of high enantiomeric excesses.

A final aspect to be considered is the ease of preparation of the different ligands. Again in this respect, **4a** reveals as a superior option. Thus, amounts of this ligand in the 0.1−1.0 mol range can be prepared from inexpensive triphenylethylene in just a few days work through a very simple, two-step sequence taking place in 95% overall yield. Moreover, the enantiomerically pure ligand is a completely stable, highly crystalline solid. In contrast, other ligands in Table 3 with similar performance are only available through lengthy sequences from expensive starting materials[13l] or have to be prepared immediately prior to use due to stability problems.[13a,b]

All these characteristics should contribute to the introduction of **4a** as a synthetic reagent. Extension of the use of **4a** as a ligand in related processes is underway in our laboratories. Results will be reported in due course.

## Experimental Section

**General Methods.** $^1H$ NMR and $^{13}C$ NMR spectra were recorded in $CDCl_3$ at 300 and 75.4 MHz, respectively. Elemental analyses were carried out by the *Servei d'Anàlisis Elementals del C.S.I.C. de Barcelona*. Optically pure compound (*S*)-triphenylethylene oxide (**3**) was prepared according to the procedure described by Jacobsen et al.[5] followed by recrystallization.

**Lithium Perchlorate-Induced Regioselective Ring Opening of (*S*)-Triphenylethylene Oxide (3). Method A. (*R*)-2-Piperidino-1,1,2-triphenylethanol (4a).** Piperidine (1.7 mL, 17 mmol) was added via syringe into a mixture of (*S*)-**3** (0.50 g, 1.84 mmol) and $LiClO_4$ (2.93 g, 27.6 mmol) in acetonitrile (2 mL) under $N_2$. The resulting mixture was heated at 80 °C. After 24 h, the solution was cooled to room temperature, and $CH_2Cl_2$ (25 mL) was added. The organic layer was washed with $H_2O$ (2 × 25 mL), dried, and concentrated in vacuo. The residual solid was purified by chromatography in $SiO_2/Et_3N$ (2.5% v/v) using hexane/EtOAc (100:0−95:5) as eluent to give 0.61 g (92%) of (*R*)-**4a** as white crystals: mp 158 °C; $[\alpha]^{23}_D = -141.5$ ($c = 0.755$ in $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.65 (d, $J = 7.2$ Hz, 2H), 7.00−7.30 (m, 13H), 5.85 (brs, 1H), 4.52 (s, 1H), 2.35−2.40 (m, 2H), 2.00−2.10 (m, 2H), 1.37−1.44 (m, 4H), 1.25−1.29 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 149.3 (C), 145.8 (C), 137.3 (C), 131.3 (CH), 127.9 (CH), 127.4 (CH), 127.2 (CH), 126.8 (CH), 126.2 (CH), 125.6 (CH), 78.6 (C), 77.7 (CH), 54.4 ($CH_2$), 26.8 ($CH_2$), 24.1 ($CH_2$); IR (KBr) 3475, 3100, 3050, 3025, 2937, 2800, 1493, 1449, 1034, 972, 751, 700, 635 $cm^{-1}$; MS (CI, $NH_3$) *m*/*z* 358 ($C_{25}H_{27}NO{\cdot}H^+$, 100). Anal. Calcd for $C_{25}H_{27}NO$: C, 83.99; H, 7.61; N, 3.92. Found: C, 83.99; H, 7.62; N, 3.91.

**(*R*)-2-(4-Methylpiperazin-1-yl)-1,1,2-triphenylethanol (4b).** A mixture of (*S*)-**3** (0.27 g, 1.00 mmol), $LiClO_4$ (1.65 g,

15.5 mmol), and *N*-methylpiperazine (1.1 mL, 10 mmol) in $CH_3CN$ (2.5 mL) was heated at 80 °C during 24 h and treated as described for **4a** to give 0.20 g (54%) of (*R*)-**4b** as white crystals: The enantiomeric purity was determined by HPLC analysis (column, Chiralcel-OD; eluent, hexane/2-propanol 99:1; flow rate, 0.5 mL/min; *R* isomer, $t_R$ 8.7 min, and *S* isomer, $t_R$ 11.2 min) and found to be >99.9%: mp 154 °C; $[\alpha]^{23}_D = -121.6$ ($c = 1.02$ in $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.77 (d, $J = 8.7$ Hz, 2H), 7.00−7.40 (m, 13H), 5.60 (s, 1H), 4.66 (s, 1H), 2.30−2.50 (m, 8H), 2.22 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 149.1 (C), 145.6 (C), 137.3 (C), 131.0 (CH), 128.0 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 126.4 (CH), 126.2 (CH), 125.6 (CH), 125.4 (CH), 78.6 (C), 76.6 (CH), 55.7 ($CH_2$), 53.0 ($CH_2$), 45.7 ($CH_3$); IR (KBr) 3400, 2950, 2790, 1495, 1449, 1138, 1001, 743, 704 cm$^{-1}$; MS (CI, $NH_3$) *m*/*z* 373 ($C_{25}H_{28}N_2O{\cdot}H^+$, 100). Anal. Calcd for $C_{25}H_{28}N_2O$: C, 80.61; H, 7.57; N, 7.52. Found: C, 80.46; H, 7.61; N, 7.53.

**(*R*)-2-(4-Phenylpiperazin-1-yl)-1,1,2-triphenylethanol (4c).** A mixture of (*S*)-**3** (0.27 g, 1.00 mmol), $LiClO_4$ (1.65 g, 15.5 mmol), and *N*-phenylpiperazine (1.53 mL, 10 mmol) in $CH_3CN$ (2.5 mL) was heated at 80 °C during 24 h and treated as described for **4a** to give 0.122 g (28%) of (*R*)-**4c** as white crystals: mp 181 °C; $[\alpha]^{23}_D = -92.6$ ($c = 0.225$ in $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.73 (d, $J = 8.4$ Hz, 2H), 6.80−7.34 (m, 18H), 5.40 (bs, 1H), 4.66 (s, 1H), 2.98−3.03 (m, 4H), 2.53−2.61 (m, 2H), 2.22−2.30 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 151.0 (C), 149.0 (C), 145.6 (C), 137.2 (C), 131.0 (CH), 129.0 (CH), 128.1 (CH), 127.7 (CH), 127.3 (CH), 127.1 (CH), 126.4 (CH), 126.3 (CH), 125.7 (CH), 125.5 (CH), 119.6 (CH), 115.7 (CH), 78.8 (C), 76.7 (CH), 53.0 ($CH_2$), 49.6 ($CH_2$); IR (KBr) 3450, 2830, 2800, 1599, 1495, 1449, 1237, 1001, 764, 700 cm$^{-1}$; MS (CI, $NH_3$) *m*/*z* 435 ($C_{30}H_{30}N_2O{\cdot}H^+$, 100). Anal. Calcd for $C_{30}H_{30}N_2O$: C, 82.91; H, 6.96; N, 6.45. Found: C, 82.83; H, 6.86; N, 6.44.

**Lithium Perchlorate-Induced Regioselective Ring Opening of (*S*)-3. Method B. (*R*)-2-Piperidino-1,1,2-triphenylethanol (4a).** A mixture of (*S*)-**3** (10.88 g, 0.04 mol), $LiClO_4$ (8.5 g, 0.08 mol), and piperidine (40 mL, 0.4 mol) was heated at 100 °C under $N_2$. After 24 h, the excess amine was distilled under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (250 mL), washed with water (2 × 100 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure to give crude product. The residual solid was purified by chromatography in $SiO_2$/$Et_3N$ (2.5% v/v) using hexane/EtOAc (100: 0−95: 5) as eluent to afford 14.02 g (98%) of (*R*)-**4a** as white crystals.

**(*R*)-2-(4-Methylpiperazin-1-yl)-1,1,2-triphenylethanol (4b).** A mixture of (*S*)-**3** (0.50 g, 1.84 mmol), $LiClO_4$ (0.39 g, 3.67 mmol, 2 equiv) and *N*-methypiperazine (7.1 mL, 64 mmol, 35 equiv) was heated at 100 °C during 24 h and treated as described for **4a** to give 0.66 g (96%) of (*R*)-**4b** as white crystals.

**(*R*)-2-(4-Phenylpiperazin-1-yl)-1,1,2-triphenylethanol (4c).** A mixture of (*S*)-**3** (0.54 g, 2.0 mmol), $LiClO_4$ (0.42 g, 4.0 mmol), and *N*-phenylpiperazine (3.1 mL, 20 mmol) was heated at 100 °C during 24 h and treated as described for **4a** to give 0.83 g (96%) of (*R*)-**4c** as white crystals after chromatography.

**(*R*)-2-Morpholino-1,1,2-triphenylethanol (4d).** A mixture of (*S*)-**3** (0.50 g, 1.84 mmol), $LiClO_4$ (0.39 g, 3.67 mmol, 2 equiv) and morpholine (6 mL, 60 mmol, 35 equiv) was heated at 100 °C during 24 h and treated as described for **4a** to give 0.57 g (86%) of (*R*)-**4d** as white crystals: mp 176 °C; $[\alpha]^{23}_D = -118.6$ ($c = 0.545$ in $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.70 (d, $J = 8.7$ Hz, 2H), 7.00−7.30 (m, 13H), 5.42 (s, 1H), 4.57 (s, 1H), 3.48−3.52 (m, 4H), 2.30−2.40 (m, 2H), 2.10−2.20 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 149 (C), 145.6 (C), 137.0 (C), 131.0 (CH), 128.1 (CH), 127.6 (CH), 127.3 (CH), 127.2 (CH), 126.4 (CH), 126.3 (CH), 125.6 (CH), 125.4 (CH), 78.7 (C), 77.1 (CH), 67.3 ($CH_2$), 53.7 ($CH_2$); IR (KBr) 3450, 2846, 1495, 1451, 1318, 1119, 999, 740, 704 cm$^{-1}$; MS (CI, $NH_3$) *m*/*z* 360 ($C_{24}H_{25}NO_2{\cdot}H^+$, 100). Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.03; H, 7.01; N, 3.93.

**Enantioselective Amino Alcohol-Catalyzed Addition of Diethyzinc to Aldehydes. (a) General Procedure for Analytical Experiments.** To a solution of the chiral catalyst (0.06 mmol, 6 mol %) in toluene (2 mL) was added the aldehyde (1 mmol) at room temperature. The mixture was stirred for 20 min and then cooled to the desired temperature if necessary. Diethylzinc (2.2 mL of a 1 M hexanes solution, 2.2 mmol) was added dropwise. The mixture was stirred for the corresponding reaction time under $N_2$. The reaction was quenched by the addition of a saturated $NH_4Cl$ solution (10 mL). The mixture was then extracted with $CH_2Cl_2$ (3 × 10 mL), and the combined organic extracts were dried and concentrated in vacuo. Conversion, selectivity, and enantiomeric purity of the resulting alcohols was determined from the crude mixture by GC analyses. Conditions of GC analyses: Supelco *β*-DEX or α-DEX 120 column, 30 m length, 0.25 mm inner diameter, isotherm temperature program, He as carrier gas (2.4 mL/min). For 1-phenylpropanol: *β*-DEX 120 column, 112 °C, $t_R$ *R* isomer 49.3 min, $t_R$ *S* isomer 52.0 min. For 1-(*o*-tolyl)-propanol: *β*-DEX 120 column, 120 °C, $t_R$ *R* isomer 59.1 min, $t_R$ *S* isomer 63.8 min. For 1-(*m*-tolyl)propanol: *β*-DEX 120 column, 120 °C, $t_R$ *R* isomer 52.2 min, $t_R$ *S* isomer 53.8 min. For 1-(*p*-tolyl)propanol: *β*-DEX 120 column, 120 °C, $t_R$ *R* isomer 50.4 min, $t_R$ *S* isomer 53.3 min. For 1-(2-methoxyphenyl)propanol: *β*-DEX 120 column, 135 °C, $t_R$ *S* isomer 48.1 min, $t_R$ *R* isomer 54.1 min. For 1-(3-methoxyphenyl)propanol: *β*-DEX 120 column, 135 °C, $t_R$ *R* isomer 66.2 min, $t_R$ *S* isomer 68.0 min. For 1-(4-methoxyphenyl)propanol: *β*-DEX 120 column, 135 °C, $t_R$ *R* isomer 68.2 min, $t_R$ *S* isomer 70.4 min. For 1-(2-fluorophenyl)propanol: *β*-DEX 120 column, 112 °C, $t_R$ *R* isomer 51.0 min, $t_R$ *S* isomer 54.5 min. For 1-(3-fluorophenyl)propanol: *β*-DEX 120 column, 112 °C, $t_R$ *R* isomer 60.0 min, $t_R$ *S* isomer 63.2 min. For 1-(4-fluorophenyl)-propanol: *β*-DEX 120 column, 112 °C, $t_R$ *R* isomer 57.3 min, $t_R$ *S* isomer 61.2 min. For 1-(1-naphthyl)propanol: *β*-DEX 120 column, 160 °C, $t_R$ *S* isomer 98.9 min, $t_R$ *R* isomer 103.2 min. For 1-(2-naphthyl)propanol: *β*-DEX 120 column, 160 °C, $t_R$ *R* isomer 100.2 min, $t_R$ *S* isomer 102.4 min. For 5-methyl-3-hexanol: α-DEX 120 column, 65 °C, $t_R$ *R* isomer 15.1 min, $t_R$ *S* isomer 15.5 min. For 1-(3-cyclohexenyl)propanol: *β*-DEX 120 column, 100 °C, $t_R$ *S* isomer 69.8−70.6 min, $t_R$ *R* isomer 74.2−74.4 min. For (*E*)-1-phenyl-2-methyl-pent-1-en-3-ol: (acetate derivative) *β*-DEX 120 column, 140 °C, $t_R$ *S* isomer 54.3 min, $t_R$ *R* isomer 55.7 min. For 4-ethyl-3-hexanol: (acetate derivative) *β*-DEX 120 column, 65 °C, $t_R$ *S* isomer 46.9 min, $t_R$ *R* isomer 49.7 min. For 1-cyclohexylpropanol: α-DEX 120 column, 90 °C, $t_R$ *R* isomer 41.7 min, $t_R$ *S* isomer 43 min. For 3-nonanol: α-DEX 120 column, 70 °C, $t_R$ *R* isomer 71.9 min, $t_R$ *S* isomer 74.3 min. For 1-phenyl-3-pentanol: α-DEX 120 column, 118 °C, $t_R$ *R* isomer 64.5 min, $t_R$ *S* isomer 65.7 min.

To establish the absolute configuration of the final compounds, the alcohols were purified by bulb-to-bulb distillation of the crude mixtures. The optical rotation was measured in each case, and its sign was compared with the reported value *(S)*-1-phenylpropanol,[13f] *(S)*-1-(*o*-tolyl)propanol,[15a] *(S)*-1-(*m*-tolyl)propanol,[15b] *(S)*-1-(*p*-tolyl)propanol,[15c] *(R)*-1-(2-methoxyphenyl)propanol,[15d] *(S)*-1-(4-methoxyphenyl)propanol,[15c] *(R)*-1-(2-fluorophenyl)propanol,[15e] *(R)*-1-(4-fluorophenyl)propanol,[13h] *(R)*-1-(1-naphthyl)propanol,[15f] *(R)*-1-(2-naphthyl)propanol,[15g] *(S)*-5-methyl-3-hexanol,[13e] (*S*)-1-cyclohexylpropanol,[13d] (*S*)-3-nonanol,[15h] (*S*)-1-phenyl-3-pentanol,[15i] and (*S*)-4-ethyl-3-hexanol.[13g] For (*R*)-(*E*)-1-phenyl-2-methylpent-1-en-3-ol retention times of acetate derivative were compared with reported values.[13l] For **6b**,**f**,**h**,**r**, the absolute configuration was assumed to be *S*.

**(b) Typical Procedure for Preparative Experiments: (*S*)-1-Cyclohexylpropanol (6q).**[13d] To a solution of **4a** (22 mg, 0.06 mmol) in toluene (2 mL) was added cyclohexanecarbaldehyde **5q** (112 mg, 120 $\mu$L, 1 mmol) at ambient temper-

(15) (a) Chelucci, G.; Conti, S.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1991**, *47*, 8251−8257. (b) Chaloner, P. A.; Perera, S. A. R. *Tetrahedron Lett.* **1987**, *28*, 3013−3014. (c) Capillon, J.; Guétté, J. P. *Tetrahedron* **1979**, *35*, 1817−1820. (d) Smaardijk, A. A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135−137. (e) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363−4384. (f) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2717−2720. (g) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841−842. (h) Soai, K.; Niwa, S.; Watanabe, M. *J. Org. Chem.* **1988**, *53*, 927−8. (i) Sato, T.; Gotoh, T.; Wakabayashi, Y.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 4123−4126.

ature under $N_2$. The mixture was stirred for 20 min and then cooled to 0 °C. Diethylzinc (2.2 mL of 1 M hexanes solution, 2.2 mmol) was added dropwise over a period of 10 min. The mixture was stirred for 3 h, by which time the starting material disappeared (TLC). The reaction mixture was then quenched by the addition of a saturated $NH_4Cl$ solution (10 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL) and dried ($Na_2SO_4$) before concentration in vacuo to afford crude **6q** in quantitative yield. The addition product and the ligand **4a** were separated by column chromatography to give 136 mg (96%) of **6q** of 98% ee and 21 mg of **4a** (95% recovery).

**Acknowledgment.** We thank DGICYT (PB95-0265) and CIRIT (1996SGR 00013) for financial support. K.S.R. thanks MEC for a fellowship under the program "Estancias Temporales de Científicos y Tecnólogos Extranjeros en España" and A. V.-F. thanks MEC for a contract under the program "Acciones para la Incorporación a España de Doctores y Tecnólogos".

JO981336I