Highly Efficient Synthesis of Enantiomerically Pure (*S*)-2-Amino-1,2,2-triphenylethanol. Development of a New Family of Ligands for the Highly Enantioselective Catalytic Ethylation of Aldehydes§

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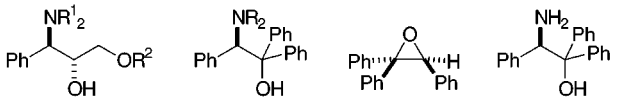
The reaction of (*S*)-triphenylethylene oxide (**3**) with diisopropoxytitanium(IV) diazide in benzene solution at 70 °C takes place readily in a completely regioselective and stereospecific manner to afford (*S*)-2-azido-1,2,2-triphenylethanol (**6**). Reduction of the azide by catalytic hydrogenation leads to (*S*)-2-amino-1,2,2-triphenylethanol (**5**) that, by N,N-dialkylation with 1,4-dibromobutane, 1,5-dibromopentane, 1,5-dibromo-3-oxapentane, α,α′-dibromo-*o*-xylene, and methyl iodide, affords the corresponding (*S*)-2-dialkylamino-1,2,2-triphenylethanols (**7a**−**e**). On the other hand, the reaction of **5** with benzyl bromide or 1-iodobutane takes place as a monoalkylation, leading to the corresponding (*S*)-2-alkylamino-1,2,2-triphenylethanols (**8f**,**g**). The performance of amino alcohols **7a**−**e** as ligands for the catalytic enantioselective addition of diethylzinc to benzaldehyde has been studied, with enantioselectivities of 94−97% being recorded. The best performing ligands in this family, **7a** [(*S*)-1,2,2-triphenyl-2-(1-pyrrolidinyl)-ethanol] and **7c** [(*S*)-2-morpholino-1,2,2-triphenylethanol] have been studied in the addition of Et_2Zn to a representative family of aldehydes. With **7a**, a 96.6% mean ee is recorded for a family of 16 α-substituted aldehydes and a 92.8% mean ee for a family of six α-unsubstituted aldehydes. With **7c** working on the same families of aldehydes, the mean enantioselectivities are 96.8% and 91.8%, respectively.

Introduction

Enantiomerically pure *β*-amino alcohols represent one of the most widely employed types of ligands for asymmetric catalysis.[1] Besides the classically used members of this family of compounds, which derive from natural products, enantiomerically pure amino alcohols of synthetic origin are gaining progressive importance.[2]

In this context, we have recently reported the synthesis of new families of enantiomerically pure *β*-amino alcohols through the regioselective and stereospecific ring opening of epoxides arising from the Sharpless[3] (**1**)[4] and the Jacobsen[5] (**2**)[6] epoxidations. When the use of these substances as ligands is considered, they offer the clear advantage of their modular construction, this characteristic being important for the fine-tuning of catalytic properties through structural variation.



1 **2** **3** **4**

Among these ligands, 2-dialkylamino-1,1,2-triphenylethanols[6] (**2**) obtained from readily available, enantiopure triphenylethylene oxide[7] (**3**) possess superb characteristics of turnover and enantioselectivity in the addition of diethylzinc to α-substituted aldehydes, in addition to a great ease of preparation.

As an extension of this work, we planned to accede the enantiomerically pure 2-amino-1,1,2-triphenylethanol (**4**) through the ring opening of **3** with an azide-delivering reagent plus reduction. This useful amino alcohol, which is normally prepared from (*R*)-phenylglycine by a process not exempt of difficulties,[8] has been employed by Garcia and co-workers as starting material for the preparation of efficient oxazaborolidine-type reducing agents[9] and by Braun and co-workers for the preparation of catalytically active imine−alkoxytitanium (IV) complexes.[10]

We wish to report here on how the azide-induced ring opening of **3** takes place in a completely unexpected manner and how the amino alcohol, ultimately arising from the ring opening plus reduction process, can be

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§ Dedicated to Professor José Elguero on the occasion of his 65th birthday.

(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.

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(3) 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.

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

(6) Solà, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J.-F. *J. Org. Chem.* **1998**, *63*, 7078−7082.

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

(8) Bach, J.; Berenguer, R.; Garcia, J.; Loscertales, T.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021−9025.

(9) Berenguer, R.; Garcia, J.; Vilarrasa, J. *Tetrahedron: Asymmetry* **1994**, *5*, 165−168.

(10) Fleischer, R.; Wunderlich, H.; Braun, M. *Eur. J. Org. Chem.* **1998**, *1063*, 3−1070.

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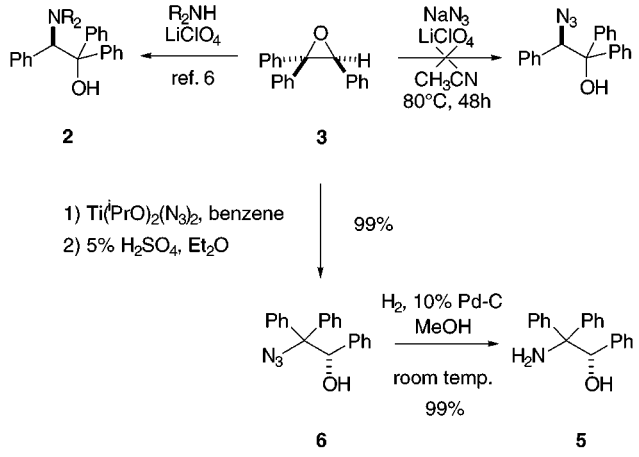
Scheme 1



successfully used as starting material for the preparation of a new family of amino alcohols with useful characteristics as ligands for the highly enantioselective catalytic alkylation of aldehydes.

Results and Discussion

The starting material for our study, (*S*)-triphenylethylene oxide (**3**), is easily prepared in enantiopure form (>99.9% ee) in multigram amounts from commercially available triphenylethylene through Jacobsen epoxidation[7] followed by a simple crystallization from hexane. The ring opening of **3** was initially attempted with NaN_3 as the azide source in conjunction with $LiClO_4$ as a promoter according to Crotti[11] (Scheme 1), since these reaction conditions are those normally providing the best results in the ring opening of epoxyalcohols with azides. Surprisingly, no reaction was detected at all, although high temperatures and long reaction times were used. It is important to note that this result is in sharp contrast with the apparently similar and even more difficult reactions with secondary amines, which take place in high yields and with complete regioselectivity to afford amino alcohols **2**.[6]

In view of the failure of this procedure, we centered our attention on the use of diisopropoxytitanium(IV) diazide [$Ti(^iPrO)_2(N_3)_2$], a reagent first used by Sharpless for similar purposes.[12] When (*S*)-**3** was treated with 1.2 equiv of this reagent at 70 °C in benzene solution, we were pleased to observe that a fast reaction was taking place (complete conversion after 0.5 h). The reaction product was easily characterized as an azido alcohol, and HPLC analysis (Chiralcel OD) established that it was enantiomerically pure. Reduction of this azido alcohol (H_2/Pd−C) led in quantitative yield to an amino alcohol, but this compound was clearly different from 2-amino-1,1,2-triphenylethanol (**4**).[8] The analysis of the spectroscopic data of this material allowed its structural assignment as the regioisomer of **4**, 2-amino-1,2,2-triphenylethanol (**5**):[13] Surprisingly enough, the ring-opening process had taken place by nucleophilic attack at the more hindered, doubly benzylic position leading to the azido alcohol **6**. This behavior could be interpreted as indicative of an intermediate *O*-titanyl species, responsible for the activation of the epoxide, possessing an important carbocationic character at the more substituted position (Figure 1).

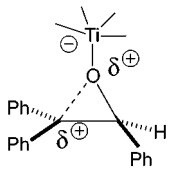


Figure 1.

Scheme 2

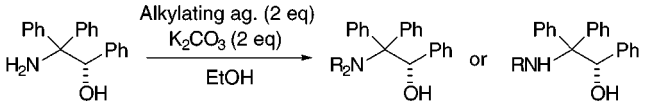
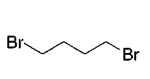
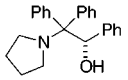
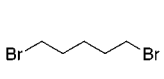
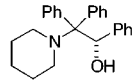
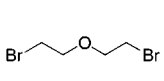
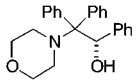
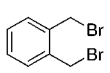
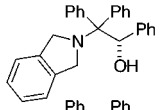
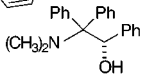
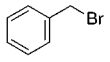
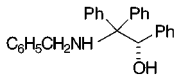
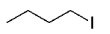
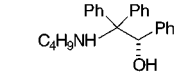


Table 1. Alkylation of (*S*)-2-Amino-1,2,2-triphenylethanol

alkylating agent	product		yield (%)
		**(7a)**	70
		**(7b)**[a]	41
		**(7c)**	48
		**(7d)**	43
CH_3I		**(7e)**	91
		**(8f)**	42
		**(8g)**	38

[a] CH_3CN was used as solvent.

Since the chiral center in (*S*)-**3** is not involved in the reaction, the absolute configuration of **5** was assigned as *S*. With this enantiomerically pure amino alcohol in hand, the possibility of preparing a new family of ligands (**7**) by N-alkylation became apparent. Given the regioisomeric relationship between **7** and **2**, a comparison of the enantioselectivities recorded with both families of compounds in a common situation could help in the understanding of the mechanism of the considered processes.

The alkylation of **5** was performed under standard conditions by reaction with a series of α,ω-dibromides and alkyl halides in ethanol solution in the presence of potassium carbonate (Scheme 2). The results of these reactions have been summarized in Table 1.

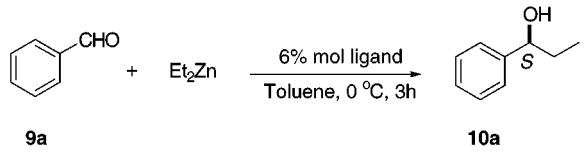
Compounds **7a**−**d**, where the nitrogen atom in the dialkylamino residue is part of a ring, were selected as

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

(12) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185−5187.

(13) After this paper was submitted for publication, an alternative preparation of enantiomerically pure 2-amino-1,2,2-triphenylethanol starting from mandelic acid has been reported: Fleischer, R.; Braun, M. *Synlett* **1998**, 1441−1443.

Scheme 3



9a **10a**

Table 2. Screening of Ligands 7a−e and 8f,g in the Catalytic Enantioselective Addition of Diethylzinc to Benzaldehyde

ligand	conversion[a] (%)	selectivity[b] (%)	ee[c] (%)
7a	**100**	**98**	**97**
7b	98	97	95
7c	**100**	**97**	**97**
7d	100	93	97
7e	99	97	94
8f	99	99	17
8g	100	100	74

[a] Determined by integration of residual **9a** in front of all new products in the gas chromatogram of the reaction crude. [b] Determined by integration of **10a** (both enantiomers in front of all new products in the gas chromatogram of the reaction crude. [c] Determined by GC on a *β*-DEX 120 column.

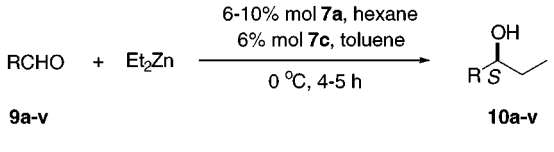
targets bearing in mind the excellent catalytic results provided by this type of amino residues in the regioisomeric products **2**[6] and in related ligands.[2a,4,14] The preparation of **7a**−**d** was achieved without problem with the yields reported in Table 1, which have not been optimized. On the other hand, when simple halides were used as alkylating agents, dialkylation could only be achieved with methyl iodide (**7e**); with benzyl bromide and 1-iodobutane, the reactions were very slow leading to secondary amines **8f** and **8g** as the result of a monoalkylation.

As an initial estimate of their performance, dialkylaminoethanols **7a**−**e** and alkylaminoethanols **8f**−**g** were tested as ligands in the enantioselective addition of diethylzinc to benzaldehyde[15] (**9a**) in toluene solution (Scheme 3 and Table 2). We were most pleased to find that, at 0 °C, all dialkylated ligands (**7a**−**e**) exhibited a high catalytic activity, the reactions being complete after 3 h, and displayed a very high level of enantioselection, affording (*S*)-1-phenylpropanol (**10a**) of 94−97% ee. On the other hand, as anticipated for monoalkylaminoethanols,[16] enantioselectivities were substantially lower when ligands **8f** and **8g** were used.

Among the dialkylaminoethanols, best results were recorded for ligands **7a** and **7c**. Ligand **7d**, albeit providing a comparable enantioselectivity, induces slightly less selective reactions than **7a** and **7c**. Noteworthy is the very high enantioselectivity observed with the ligand containing a 1-pyrrolidinyl module (**7a**), since this structural unit did not provide particularly good results in the previously studied family of amino alcohols, **1**.[4]

The best performing ligands resulting from this preliminary screening, **7a** and **7c**, were subsequently tested in the addition of diethylzinc to a representative family of aldehydes, comprising aromatic (ortho-, meta-, and para-substituted), aliphatic, and α,*β*-unsaturated specimens (Scheme 4 and Table 3). It is worth noting that the optimum reaction medium varied from one ligand to the other. Thus, when using ligand **7c**, toluene was found to be the solvent where the reactions took place with higher enantioselectivity, whereas with ligand **7a**, the use of hexane as the solvent resulted in a slightly higher (ca. 1%) enantioselectivity. Consequently, all additions involving the use of ligand **7c** were performed in toluene, and additions using ligand **7a** were run in hexane. Also from a practical perspective, in all experiments involving ligand **7c** a 6% molar amount of ligand was used, whereas with **7a** a 10% molar amount of ligand was used in some instances.

Scheme 4



9a-v **10a-v**

As can be seen, excellent results are obtained for the set of α-substituted aldehydes (**9a**−**p**), irrespectively of their nature being aromatic, aliphatic, or α,*β*-unsaturated. For this family of compounds, the resulting alcohols are obtained in ≥ 95% ee. With **7c**, a mean enantiomeric excess of 96.8%, with a standard deviation of 0.8%, is recorded for the set of 16 α-substituted aldehydes (**9a**−**p**), while for **7a** the mean enantiomeric excess is 96.6% and the standard deviation is 0.9% with the same set of aldehydes.

A very interesting characteristic of **7a** and **7c** is their behavior in the addition to α-unsubstituted aldehydes. These are, in general, substrates that experience catalytic ethylation with low enantioselectivity, and probably for this reason they are not well represented in the lists of substrates on which newly developed ligands are tested. Up to now, only the procedures developed by Seebach[17] and by Pu[18] provide consistently high enantioselectivities in this particular situation, albeit at the expenses of using a high percentage of ligand at rather inconveniently low temperatures[17] or involving the use of a difficultly available ligand.[18]

With the readily available ligands **7a** and **7c**, when α-unsubstituted aldehydes, either α,*β*-unsaturated (**9q**) or aliphatic (**9r**−**v**), are employed as substrates for the reaction, the addition proceeds for all examples with high enantioselectivity at the convenient temperature of 0 °C. Thus, using **7c** with the six considered α-unsubstituted substrates, the mean ee is 91.8%, with a standard deviation of 2%, while with **7a** the mean ee is 92.8%, with the even lower standard deviation of 1.3%.

Conclusions

In summary, the unexpected regiochemistry of the ring opening of (*S*)-triphenylethylene oxide with diisopropoxytitanium(IV) diazide has allowed, after hydrogenation of the resulting azido compound **6**, the development of a straightforward synthesis of enantiomerically pure (*S*)-2-amino-1,2,2-triphenylethanol (**5**). The alkylation of

(14) (a) Kang, J.; Lee, S. W.; Kim, J. I. *J. Chem. Soc., Chem. Commun.* **1994**, 2009−2010. (b) Hayashi, M.; Kaneko, T.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1991**, 25−28.

(15) 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.

(16) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69.

(17) (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.

(18) Huang, W. S.; Hu, Q. S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364−1365.

Table 3. Catalytic Enantioselective Addition of Et_2Zn to Aldehydes 9a−v Leading to Alcohols 10a−v Mediated by Ligands 7a and 7c

		ligand **7a**			ligand **7c**		
starting aldehyde	resulting alcohol	conversion[a] (%)	selectivity[b] (%)	ee[c] (%)	conversion[a] (%)	selectivity[b] (%)	ee[c] (%)
benzaldehyde (**9a**)	(*S*)-**10a**	100	97	97	100	97	97
o-tolualdehyde (**9b**)	(*S*)-**10b**	99	92	98	100	90	98
o-chlorobenzaldehyde (**9c**)	(*S*)-**10c**	100	91	95	100	88	95
o-methoxybenzaldehyde (**9d**)	(*S*)-**10d**	100	96	96	100	95	96
m-tolualdehyde (**9e**)	(*S*)-**10e**	100	97	97	98	96	97
m-fluorobenzaldehyde (**9f**)	(*S*)-**10f**	100	98	97	100	97	96
m-methoxybenzaldehyde (**9g**)	(*S*)-**10g**	100	97	96	100	98	97
p-tolualdehyde (**9h**)	(*S*)-**10h**	100	98	97	100	98	98
*p*fluorobenzaldehyde (**9i**)	(*S*)-**10i**	100	97	97	100	99	97
p-methoxybenzaldehyde (**9j**)	(*S*)-**10j**	100[g]	99	98	85	99	97
1-naphtaldehyde (**9k**)	(*S*)-**10k**[d]	99	91	96	99	90	97
2-naphtaldehyde (**9l**)	(*S*)-**10l**[d]	99	99	96	99	98	97
2-furfuraldehyde (**9m**)	(*S*)-**10m**[e]	100	99	96	100	99	96
2-ethylbutyraldehyde (**9n**)	(*S*)-**10n**[e]	100	89	98	100	89	97
cyclohexanecarbaldehyde (**9o**)	(*S*)-**10o**[f]	85	89	96	84	89	98
(*E*)-α-methylcinnamaldehyde (**9p**)	(*S*)-**10p**[e]	95[g]	97	96	85	96	96
cinnamaldehyde (**9q**)	(*S*)-**10q**[d]	99[g]	90	90	84	98	90
dihydrocinnamaldehyde (**9r**)	(*S*)-**10r**[f]	93	98	94	93	96	94
isovaleraldehyde (**9s**)	(*S*)-**10s**[f]	95	96	94	99	98	94
hexanal (**9t**)	(*S*)-**10t**	96	99	93	99	99	93
heptanal (**9u**)	(*S*)-**10u**[e]	99[g]	99	93	80	96	91
nonanal (**9v**)	(*S*)-**10v**[e]	96[g]	98	93	80	95	89

[a] Determined by integration of residual **9** in front of all new products in the gas chromatogram of the reaction crude. [b] Determined by integration of **10** (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 unless otherwise specified. [d] Determined by HPLC on a Chiralcel OD column. [e] The alcohol was converted into its acetate derivative and analyzed by GC on a β-DEX 120 column. [f] Determined by GC on a a-DEX 120 column. [g] A 10% molar amount of ligand was used.

5 with α,ω-dibromides allows the construction of a cycle at nitrogen, and the resulting (*S*)-2-dialkylamino-1,2,2-triphenylethanols (**7a−d**) present interesting properties as catalytic ligands for the enantioselective addition of diethylzinc to aldehydes. In concrete, **7a**, containing a 1-pyrrolydinyl fragment, and **7c**, containing a morpholino fragment, turn out to be among the best ligands described to date for this reaction. The ease of preparation of these substances, along with the convenience of the experimental conditions involved in their use, should foster the search for new catalytic applications. Work along these lines is being undertaken in our laboratories and will be reported in due course.

Experimental Section

General Methods. Optical rotations were measured at room temperature (23 °C) (concentration in g/100 mL). Melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were recorded using NaCl film or KBr pellet techniques. ^{1}H NMR were recorded at 200 or 300 MHz (s = singlet, d = doublet, t = triplet, m = multiplet, b = broad). ^{13}C NMR were recorded at 50.3 or 75.4 MHz. Carbon multiplicities have been assigned by distortionless enhancement by polarization transfer (DEPT) experiments. High-resolution mass spectra (CI) were measured by the Servicio de Espectrometría de Masas, Universidad de Córdoba. Elemental analyses were performed by the Servei de Microanàlisi del CSIC de Barcelona. Chromatographic separations were carried out using NEt_3 pretreated (2.5% v/v) SiO_2 (70−230 mesh), eluting (unless otherwise stated) with hexanes−ethyl acetate mixtures of increasing polarity. HPLC analyses were performed on an instrument equipped with a Chiralcel OD (25 cm) column. Optically pure (*S*)-triphenylethylene oxide (**3**) was prepared according to the procedure described by Jacobsen et al.[7] followed by recrystallization.

***(S)*-2-Azido-1,2,2-triphenylethanol, 6.** A solution of (*S*)-**3** (10.88 g, 40 mmol, >99.9% ee) in dry benzene (100 mL) was added to a suspension of $[Ti(O^iPr)_2(N_3)_2]$ (12.0 g, 48 mmol) in 100 mL of benzene under argon at 70 °C. After being stirred for 30 min, the reaction mixture was allowed to cool to room temperature and benzene was removed under reduced pressure. The concentrate was dissolved in 250 mL of diethyl ether, 300 mL of 5% H_2SO_4 was added, and the resulting mixture was stirred until two phases formed (ca. 1h). Phases were separated; the aqueous phase was extracted with diethyl ether (4 × 100 mL), and the combined ethereal phases were dried (Na_2SO_4) and concentrated. The residual solid was purified by column chromatography to afford 12.50 g (99% yield) of **6** as a white solid: The enantiomeric purity was determined by HPLC analysis (column, Chiralcel-OD; eluent, hexane/2-propanol 90:10; flow rate, 1 mL/min; *S* isomer, t_R 7.3 min, and *R* isomer, t_R 9.9 min) and found to be >99.9%: mp 101 °C; $[\alpha]^{23}_D$ = −105.0 (*c* = 1.35 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−6.93 (m, 15H), 5.64 (d, *J* = 3.1 Hz, 1 H), 2.41 (d, *J* = 3.1 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8 (C), 140.1 (C), 139.1 (C), 128.8 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 79.0 (CH), 75.9 (C); IR (KBr) 3560, 2116, 1447, 698 cm^{-1}; MS (CI, NH_3) *m*/*z* (relative intensity) 333 ($C_{20}H_{17}N_3O{\cdot}NH_4^+$, 100). Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 75.95; H, 5.42; N, 13.30.

***(S)*-2-Amino-1,2,2-triphenylethanol, 5.** A solution of **6** (12.0 g, 38 mmol) in MeOH (200 mL) was added on a suspension of 10% Pd/C (1.44 g) in MeOH (200 mL) under hydrogen. The suspension was vigorously stirred for 10 h at room temperature and then filtered through a pad of Celite and concentrated under reduced pressure to furnish the crude amino alcohol **5** in quantitative yield. Purification of this product by column chromatography, eluting with a 19:1 mixture of chloroform/MeOH, afforded 10.95 g (99% yield) of **5** as a white crystalline solid: mp 166 °C; $[\alpha]^{23}_D$ = −237.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.64−6.87 (m, 15H), 5.65 (s, 1 H), 3.10 (b, 1H, OH), 1.90 (b, 2H, NH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.7 (C), 145.2 (C), 139.6 (C), 128.2 (CH), 127.8 (CH), 127.7 (CH), 127.3 (CH), 127.2 (CH), 126.7 (CH), 126.4 (CH), 77.4 (CH), 65.6 (C); IR (KBr) 3390, 3367, 1447, 700 cm^{-1}; MS (CI, NH_3) *m*/*z* (relative intensity) 290 ($C_{20}H_{19}NO{\cdot}H^+$, 100). Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.00; H, 6.69; N, 4.86.

General Procedure for the Alkylation of 5: (*S*)-1,2,2-Triphenyl-2-(1-pyrrolidinyl)ethanol, 7a. A mixture of **5** (2.89 g, 10 mmol), 1,4-dibromobutane (4.32 g, 20 mmol), K_2-

CO_3 (2.76 g, 20 mmol), and absolute ethanol (10 mL) was refluxed for 48 h under N_2. The reaction mixture was allowed to cool to room temperature and filtered and the precipitate washed with ethanol. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography to afford 2.41 g (70% yield) of **7a** as an oil that solidified on standing at room temperature: mp 122−123 °C; $[\alpha]^{23}_D = -20.9$ ($c = 1.06$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−6.88 (m, 13H), 6.72−5.69 (m, 2 H), 5.91 (s, 1H), 4.68 (b, 1H, OH), 2.48 (b, 4H), 1.63 (b, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1 (C), 137.4 (C), 133.9 (C), 130.9 (CH), 128.1 (CH), 127.1 (CH), 126.7 (CH), 126.6 (CH), 125.9 (CH), 74.6 (C), 72.4 (CH), 45.9 (CH_2), 22.1 (CH_2); IR (KBr) 3405, 1493, 710 cm^{-1}; MS (CI, NH_3) *m/z* (relative intensity) 344 ($C_{24}H_{25}NO{\cdot}H^+$, 100). Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.89; H, 7.33; N, 4.20.

(*S*)-1,2,2-Triphenyl-2-piperidinoethanol, 7b. A mixture of **5** (289 mg, 1 mmol), 1,5-dibromopentane (506 mg, 2.2 mmol), K_2CO_3 (304 mg, 2.2 mmol), and CH_3CN (2 mL) was refluxed for 42 h under N_2 and treated as described for **7a** to afford, after purification by column chromatography, 148 mg (41% yield) of **7b** as a white solid: mp 130−131 °C; $[\alpha]^{23}_D = +2.7$ ($c = 1.05$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.48−6.71 (m, 15H), 6.08 (s, 1H), 4.64 (b, 1H, OH), 2.38 (b, 3H), 1.69 (b, 5H), 1.38 (b, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C) δ 140.8 (C), 137.4 (C), 134.6 (C), 130.5 (CH), 127.6 (CH), 127.1 (CH), 126.8 (CH), 126.7 (CH), 126.5 (CH), 77.2 (C), 70.8 (CH), 49.0 (CH_2), 26.8 (CH_2), 24.9 (CH_2); IR (KBr) 3397, 2927, 708 cm^{-1}; MS (CI, NH_3) *m/z* (relative intensity) 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, 83.80; H, 7.67; N, 4.06.

(*S*)-2-Morpholino-1,2,2-triphenylethanol, 7c. A mixture of **5** (1.5 g, 5.2 mmol), bis(2-bromoethyl) ether (2.4 g, 10.4 mmol), K_2CO_3 (1.44 g, 10.4 mmol), and absolute ethanol (6 mL) was refluxed for 48 h under N_2 and treated as described for **7a** to afford, after purification by column chromatography, 0.901 g (48% yield) of **7c** as a colorless oil that solidified on standing at room temperature: mp 175−176 °C; $[\alpha]^{23}_D = -0.69$ ($c = 2.02$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−6.88 (m, 13H), 6.67 (d, $J = 6.9$ Hz, 2H), 6.01 (s, 1H), 4.46 (b, 1H, OH), 3.80−3.78 (m, 4H), 2.89−2.05 (b, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1 (C), 136.1 (C), 133.7 (C), 133.7 (CH), 130.6 (CH), 127.7 (CH), 127.5 (CH), 126.9 (CH), 126.8 (CH), 126.3 (CH), 76.6 (C), 70.4 (CH), 67.4 (CH_2), 47.9 (CH_2); IR (KBr) 3411, 1115, 710 cm^{-1}; MS (CI, NH_3) *m/z* (relative intensity) 359 ($C_{24}H_{25}NO_2{\cdot}H^+$, 100). Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.34; H, 7.06; N, 3.92.

(*S*)-2-(1,3-Dihydroisoindol-2-yl)-1,2,2-triphenylethanol, 7d. A mixture of **5** (200 mg, 0.69 mmol), α,α′-dibromo-*o*-xylene (400 mg, 1.52 mmol), K_2CO_3 (194 mg, 1.40 mmol), and absolute ethanol (2 mL) was refluxed for 48 h under N_2 and treated as described for **7a** to afford, after purification by column chromatography, 115 mg (43% yield) of **7d** as white crystals: mp 159−160 °C; $[\alpha]^{23}_D = -46.3$ ($c = 1.52$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, $J = 7.8$ Hz, 2H), 7.37 (t, $J = 7.5$ Hz, 2H), 7.29−7.00 (m, 11H), 6.94 (t, $J = 7.5$ Hz, 2H), 6.75 (d, $J = 7.8$ Hz, 2H), 5.99 (s, 1H), 4.46 (b, 1H, OH), 4.11 (d, $J = 11.9$ Hz, 2H), 3.98 (bd, $J = 11.9$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.7 (C), 138.8 (C), 136.4 (C), 134.2 (CH), 131.3 (CH), 130.9 (CH), 128.4 (CH), 127.4 (CH), 127.2 (CH), 126.9 (CH), 126.9 (CH), 126.8 (CH), 126.6 (CH), 126.3 (CH), 122.1 (CH), 74.9 (C), 72.9 (CH), 51.6 (CH_2), 70.8 (CH), 49.0 (CH_2), 26.8 (CH_2), 24.9 (CH_2); IR (KBr) 3378, 752, 712 cm^{-1}; MS (CI, NH_3) *m/z* (relative intensity) 391 ($C_{28}H_{25}NO^+$, 100), 392 ($C_{28}H_{25}NO{\cdot}H^+$, 30); HRMS (CI) calcd for $C_{28}H_{24}N$ [$M^+ - OH$] 374.1890, found 374.1909.

(*S*)-2-Dimethylamino-1,2,2-triphenylethanol, 7e. A mixture of **5** (200 mg, 0.69 mmol), methyl iodide (320 mg, 0.14 mL, 2.25 mmol), K_2CO_3 (194 mg, 1.4 mmol), and absolute ethanol (2 mL) was heated at 50 °C for 48 h under N_2 and treated as described for **7a** to afford, after purification by column chromatography, 200 mg (91% yield) of **7e** as white crystals: mp 103 °C; $[\alpha]^{23}_D = -12.1$ ($c = 1.5$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41−6.85 (m, 13H), 6.69 (d, $J = 8$ Hz, 2H), 5.96 (s, 1H), 4.58 (b, 1H, OH), 2.12 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.4 (C), 136.9 (C), 133.2 (C), 130.9 (CH), 130.7 (CH), 127.7 (CH), 127.1 (CH), 126.6 (CH), 126.5 (CH), 120.0 (CH), 76.4 (C), 71.1 (CH), 39.5 (CH_3); IR (KBr) 3403, 1441, 710 cm^{-1}; MS (CI, NH_3) *m/z* (relative intensity) 318 ($C_{22}H_{23}NO{\cdot}H^+$, 100); HRMS (CI) calcd for $C_{22}H_{22}N$ [$M^+ - OH$] 300.1749, found 300.1752.

(*S*)-2-Benzylamino-1,2,2-triphenylethanol, 8f. A mixture of **5** (450 mg, 1.56 mmol), benzyl bromide (720 mg, 0.5 mL, 4.2 mmol), K_2CO_3 (538 mg, 3.9 mmol), and absolute ethanol (5 mL) was refluxed for 48 h under N_2 and treated as described for **7a** to afford, after purification by column chromatography, 250 mg (42% yield) of **8f** as an oil: $[\alpha]^{23}_D = -3.78$ ($c = 1.47$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.42 (m, 2H), 7.31−7.20 (m, 12H), 7.12−7.01 (m, 4H), 6.74 (d, $J = 8.4$ Hz, 2H), 5.66 (s, 1H), 3.51 (part A of AB system, $J = 12.8$ Hz, 1H), 3.46 (part B of AB system, $J = 12.8$ Hz, 1H), 3.45 (b, 1H, OH), 1.95 (b, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1 (C), 141.5 (C), 140.6 (C), 140.1 (CH), 129.8 (CH), 129.3 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 127.3 (CH), 127.1 (CH), 127.0 (CH), 126.9 (CH), 126.9 (CH), 77.5 (CH), 70.8 (C), 47.6 (CH_2); IR (KBr) 3559, 3426, 1495, 698 cm^{-1}; MS (CI, NH_3) *m/z* (relative intensity) 379 ($C_{27}H_{25}NO^+$, 100), 380 ($C_{27}H_{25}NO{\cdot}H^+$, 24). Anal. Calcd for $C_{27}H_{25}NO$: C, 85.45; H, 6.64; N, 3.69. Found: C, 85.27; H, 6.74; N, 3.57.

(*S*)-2-Butylamino-1,2,2-triphenylethanol, 8g. A mixture of **5** (200 mg, 0.69 mmol), *n*-butyl iodide (368 mg, 0.25 mL, 2 mmol), K_2CO_3 (194 mg, 1.4 mmol), and absolute ethanol (2 mL) was refluxed for 48 h under N_2 and treated as described for **7a** to afford, after purification by column chromatography, 130 mg (38% yield) of **8g** as an oil: $[\alpha]^{23}_D = -125.6$ ($c = 0.72$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.00 (m, 13H), 6.78 (d, $J = 11.4$ Hz, 2H), 5.59 (s, 1H), 2.29−2.24 (m, 2H), 1.8−0.4 (b, 2H, OH + NH), 1.42−1.22 (m, 4H), 0.84 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.0 (C), 141.8 (C), 140.1 (C), 129.7 (CH), 129.3 (CH), 128.1 (CH), 127.3 (CH), 127.1 (CH), 126.9 (CH), 76.5 (CH), 70.7 (C), 42.7 (CH_2), 32.9 (CH_2), 20.5 (CH_2), 14.1 (CH_3); IR (KBr) 3421, 3300, 700 cm^{-1}; MS (CI, NH_3) *m/z* 346 ($C_{24}H_{27}NO{\cdot}H^+$, 100). Anal. Calcd for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.47; H, 8.04; N, 4.08.

Enantioselective Amino Alcohol-Catalyzed Addition of Diethyzinc to Aldehydes. General Procedure. 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 0 °C. 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 were determined from the crude mixture by GC or HPLC analysis. 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 **10a**−**b**,**d**−**l**,**n**−**p**,**r**−**s**,**u**, conditions of analysis and retention times of the *R* and *S* isomers have been reported elsewhere.[6] For 1-(2-chlorophenyl)propanol (**10c**): β-DEX 120 column, 135 °C, t_R *R* isomer 47.1 min, t_R *S* isomer 51.4 min. For 1-(2-furyl)propanol (**10m**): (acetate derivative) β-DEX 120 column, 100 °C, t_R *S* isomer 20.9 min, t_R *R* isomer 22.2 min. For 3-octanol (**10t**): (acetate derivative) β-DEX 120 column, 80 °C, t_R *S* isomer 32.9 min, t_R *R* isomer 36.0 min. For 3-undecanol (**10v**): (acetate derivative) β-DEX 120 column, 112 °C, t_R *S* isomer 53.2 min, t_R *R* isomer 56.8 min. Conditions of HPLC analyses: Chiralcel-OD column, 25 cm, 30 °C. For 1-(1-naphthyl)propanol (**10k**): eluent, hexane/2-propanol 90:10; flow rate, 1 mL/min; *S* isomer, t_R 7.8 min and *R* isomer, t_R 13.7 min. For 1-(2-naphthyl)propanol (**10*l***): eluent, hexane/

2-propanol 95:5; flow rate, 1 mL/min; *S* isomer, t_R 15.3 min and *R* isomer, t_R 17.0 min. For (*E*)-1-phenyl-1-penten-3-ol: eluent, hexane/2-propanol 90:10; flow rate, 1 mL/min; *R* isomer, t_R 7.5 min and *S* isomer, t_R 11.4 min. For **10a**−**l**,**n**−**p**,**r**,**s**,**u**, the establishment of the absolute configuration of the major enantiomer resulting from the reaction has been performed as already reported.[6] For (*S*)-1-(2-furyl)propanol (**10m**),[18] (*S*)-3-octanol (**10t**),[18] and (*S*)-3-undecanol (**10v**),[18] retention times of the acetate derivatives were compared with reported values. For (*S*,*E*)-1-phenyl-1-penten-3-ol (**10q**),[18] retention times were compared with reported values.

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