Synthesis of a Family of Fine-Tunable New Chiral Ligands for Catalytic Asymmetric Synthesis. Ligand Optimization through the Enantioselective Addition of Diethylzinc to Aldehydes

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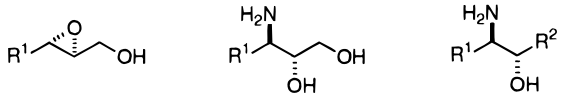
A family of enantiomerically pure (1*R*,2*R*)-1-(dialkylamino)-1-phenyl-3-(R-oxy)-2-propanols (**4**) has been synthesized from (2*S*,3*S*)-2,3-epoxy-3-phenylpropanol (**1a**), arising from the Sharpless epoxydation of cinnamyl alcohol, by two alternative sequences involving either the regioselective ring opening of the epoxide by a secondary amine (C-3 attack) and subsequent chemoselective protection of the primary hydroxy group or the reverse of these operations. A total of 19 different derivatives **4** have been prepared in an iterative process aimed at the optimization of their catalytic properties in the enantioselective addition of diethylzinc to benzaldehyde. In doing this, the steric bulk of the R-oxy group and the choice of the dialkylamino substituent as a nitrogen-containing six-membered ring have been identified as the key structural parameters for high catalytic activity and enantioselectivity in **4**. Two optimized ligands fulfilling these structural requirements, **4d-Tr** (R-oxy = trityloxy, dialkylamino = piperidino) and **4i-Tr** (R-oxy = trityloxy, dialkylamino = 4-methylpiperazin-1-yl), depict a convenient activity and selectivity profile in the addition of Et_2-Zn to a structurally diverse family of aldehydes. These results show how chiral ligands based on non-natural starting materials can accommodate subtle variations of the steric/electronic characteristics key to the fine tuning of catalytic properties and thus represent a convenient alternative to ligands based on natural products.

Introduction

Chiral ligands for asymmetric catalysis[1,2] have been generally derived from a small number of readily available natural products. They thus belong to just a few structural types and do not allow in many cases significant optimization of catalytic properties through structural modification.[3] Synthetic substances of high enantiomeric purity arising from well-established processes can represent an advantageous alternative to ligands of natural origin and can allow the circumvention of the aforementioned limitation.

We have recently reported the highly enantioselective synthesis of amino acids of many different structural types from epoxy alcohols (**1**), through the intermediacy of 3-amino 1,2-diols (**2**).[4] These substances contain all the structural characteristics of 1,2-amino alcohols (**3**), a well-established class of chiral ligands, plus an additional primary hydroxy group that allows further modification and can provide an additional binding site.



1 **2** **3**

A large number of epoxy alcohols (**1**) are readily available in enantiomerically pure form in both enantiomeric series *via* the asymmetric Sharpless epoxidation.[5] These alcohols can, in principle, be converted into amino diols with full control of all structural and stereochemical parameters (Figure 1). This encouraged us to consider that properly substituted 3-amino 1,2-diols (**4**) could constitute an interesting new class of chiral ligands, and the work described here details our initial efforts in this area.

Results and Discussion

General Strategies for the Synthesis of Protected 3-Amino 1,2-Diols 4. Two different strategies can be envisaged for the conversion of epoxy alcohols **1** into protected 3-amino 1,2-diols **4**, as shown in Scheme 1. In the first (route A), the epoxy alcohol is first submitted to a regioselective ring-opening by a secondary amine, under the conditions developed by Caron and Sharpless,[6] and the resulting amino diol (**5**) is then protected by means of an appropriate R^3-X reagent. In the second (route B),

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(1) (a) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; John Wiley & Sons, Inc.: New York, 1994. (b)*Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993.

(2) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1050−1070.

(3) For compilations of natural and non-natural enantioselective catalysts and auxiliaries, see, for example: (a) Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935−952. (b) *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Seyden-Penne, J., Ed.; John Wiley & Sons, Inc.: New York, 1995.

(4) (a) Canas, M.; Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6931−6934. (b) Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6935−6938. (c) Alcón, M.; Canas, M.; Poch, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1994**, *35*, 1589−1592. (d) Poch, M.; Alcón, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1993**, *34*, 7781−7784. (e) Castejón, P.; Pastó, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1995**, *36*, 3019−3022. (f) Pastó, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1995**, *6*, 2329−2342. (g) Pastó, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1996**, *61*, 6033−6037. (h) Castejón, P.; Moyano, A.; Pericàs, M. A.; Riera, A. *Chem. Eur. J.* **1996**, *2*, 1001−1006. (i) Castejón, P.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1996**, *52*, 7063−7086.

(5) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. (b) Reference 1b, pp 101−158. (c) Katsuki, T.; Martin, V. S. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: New York, 1996; Vol. 48, pp 1−299.

(6) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557−1560.

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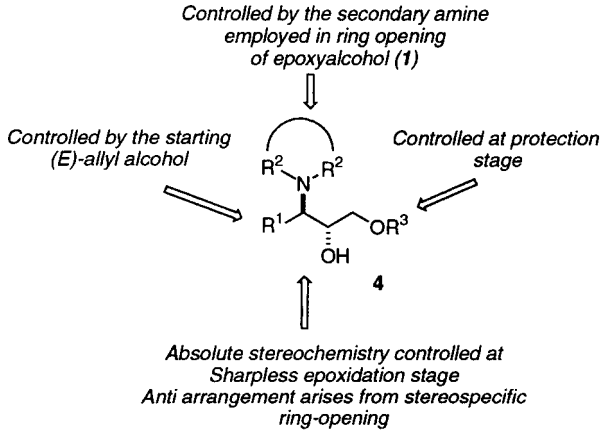
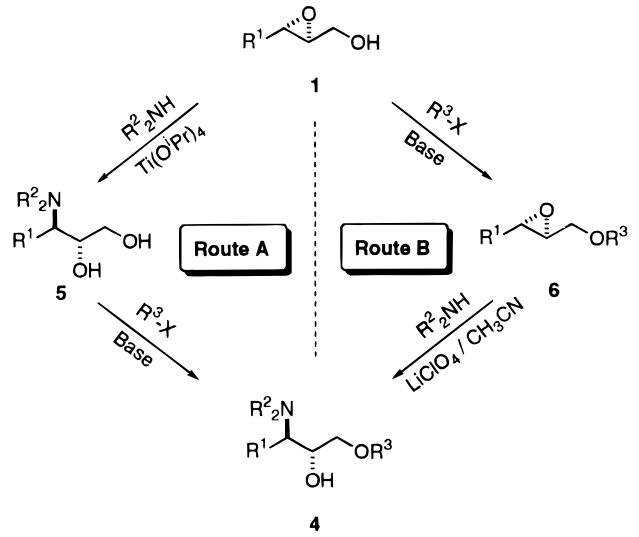


Figure 1.

Scheme 1



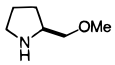
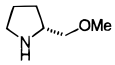
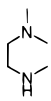
the primary hydroxy group in the starting epoxy alcohol is initially protected, and the resulting epoxy ether (**6**) is subjected to regioselective ring opening by a secondary amine under the conditions developed by Crotti and coworkers.[7]

In the present work, we have used both routes for the preparation of protected 3-amino 1,2-diols **4**, starting in all cases from the 2*S*,3*S* enantiomer of the epoxide of cinnamyl alcohol (**1a**).[8]

Route A to Protected 3-Amino 1,2-Diols: Regioselective Ring-Opening plus Protection. When epoxy alcohol **1a** was treated with 1.5 equiv of a secondary amine in the presence of 1.5 equiv of titanium tetraisopropoxide at room temperature in dichloromethane solution (Scheme 2), a completely regioselective reaction took place,[6] leading to 3-amino 1,2-diols **5** (Table 1).

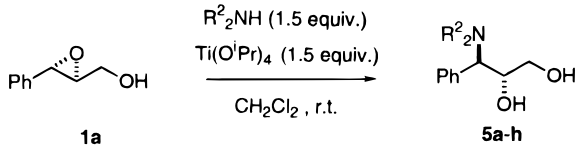
The reactions proceeded smoothly at room temperature, with the amino diols **5** being formed in generally high yield after short reaction periods. Only when the rather bulky diisopropylamine was used (entry **g**), the process turned out to be considerably slower.

Table 1. Regioselective Ring Opening[a] of Epoxy Alcohol 1a[b] by Secondary Amines in the Presence of Ti(O^{i}Pr)$_4$

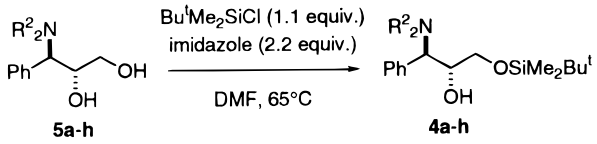
Entry	Secondary Amine	Reaction time [h]	Yield[c] [%]	Product
a		5	85	**5a**
b		5	80	**5b**
c		9	72	**5c**
d		4	91	**5d**
e		5	87	**5e**
f		8	91	**5f**
g		7	14	**5g**
h		8	70	**5h**

[a] All reactions were performed in CH_2Cl_2 solution, in the presence of a 50% molar excess of both secondary amine and Ti(O^{i}Pr)$_4$. [b] Results are for the 2*S*, 3*S* enantiomer. [c] Yields are referred to pure isolated material and are not optimized.

Scheme 2



Scheme 3



The selective protection of the primary hydroxy group of **5a**−**h** could be conveniently achieved by reaction with *tert*-butyldimethylsilyl chloride and imidazole in DMF solution at 65 °C (Scheme 3 and Table 2),[4e,9a] the target amino alcohols **4a**−**h** being obtained in good yield. In the case of the very polar derivative **5h** the protection could not be driven to completion, and the resulting mixture (**4h**/**5h** ≈ 8/1) could not be separated by standard chromatographic procedures. As a result, **4h** was not tested as a ligand in catalytic reactions.

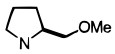
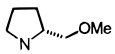
For amino diol **5d**, several alternative protections of the primary hydroxy group were also studied (Scheme 4). Thus, treatment of **5d** with *tert*-butyldiphenylsilyl chloride and imidazole in DMF at 65 °C[9b] afforded the corresponding silyl ether **4d-Bp** in essentially quantitative yield, whereas reaction with trityl chloride in pyri-

(7) (a) Chini, M.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 5939−5942. (b) Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 7043−7048. (c) For the regioselective ring opening of some racemic epoxyethers with different nucleophiles, see: Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Giovani, E.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1993**, *58*, 1221−1227. (d) Calvani, F.; Crotti, P.; Gardelli, C.; Pineschi, M. *Tetrahedron* **1994**, *50*, 12999−13022. (e) Colombini, M.; Crotti, P.; Di Bussolo, V.; Favero, L.; Gardelli, C.; Macchia, F.; Pineschi, M. *Tetrahedron* **1995**, *51*, 8089−8112. (f) Azzena, F.; Calvani, F.; Crotti, P.; Gardelli, C.; Macchia, F.; Pineschi, M. *Tetrahedron* **1995**, *51*, 10601−10626.

(8) Similar ligands derived from other epoxides are currently studied in our laboratories. The results of these studies will be reported in due time.

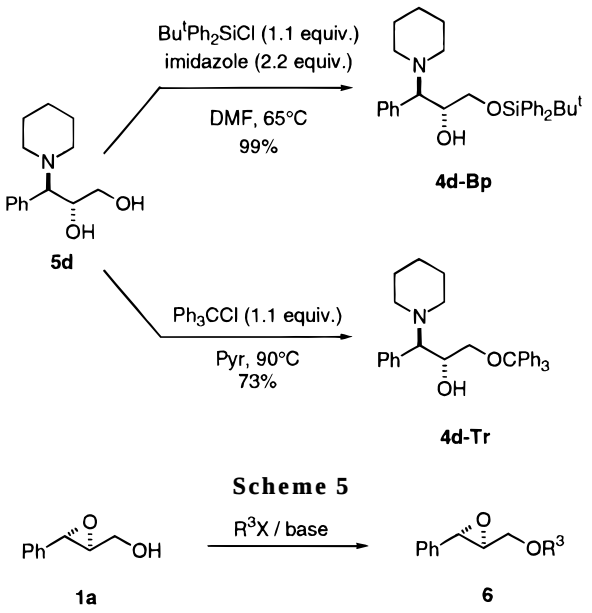
(9) (a) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190−6191. (b) Hanessian, S.; Lavallee, P. *Canad. J. Chem.* **1975**, *53*, 2975−2977.

Table 2. Selective Protection[a] of the Primary Hydroxy Group in 5a−h as a *tert*-Butyldimethylsilyl Ether

Starting diol	$R^2_NR^2$	Reaction time [h]	Yield[b] [%]	Product
5a		24	79	**4a**
5b		24	76	**4b**
5c		24	85	**4c**
5d		14	76	**4d**
5e		24	74	**4e**
5f		24	71	**4f**
5g		24	52	**4g**
5h		24	61[c]	**4h**

[a] All reactions were performed at 65 °C in DMF solution, in the presence of a 10% molar excess of *tert*-butyldimethylsilyl chloride and a 120% molar excess of imidazole. [b] Yields are referred to pure isolated material and are not optimized. [c] Product was obtained in admixture with a 7.5% yield of starting material.

Scheme 4



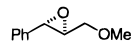
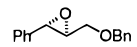
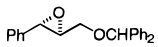
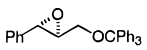
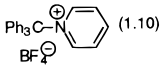
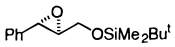
Scheme 5

dine at 90 °C[10] allowed the isolation of the trityl ether **4d-Tr** in 73% yield.

Route B to Protected 3-Amino 1,2-Diols: Protection plus Regioselective Ring Opening. For the first part of the sequence (Scheme 5), epoxy alcohol **1a** was subjected to a variety of protection schemes, which have been summarized in Table 3.

As a first goal, we sought to develop reaction conditions that minimized possible side reactions of the starting epoxy alcohol **1a**, such as Payne rearrangement[11] or ring-opening polymerization. We were pleased to find that formation of the sodium alkoxide of **1a** with a slight excess of NaH in DMF at −20 to 0 °C was free of any of the conceivable side reactions.

Table 3. Protection of 1a with R^{3}X Reagents

R^3 (equiv.)	Reaction Conditions	Yield [%]	Product
CH_3I (1.30)	NaH (1.15) DMF, -20°C, 4h	91	 **6-Me**
$PhCH_2Cl$ (1.05)	NaH (1.15) DMF, -20°C, 36h	82	 **6-Bn**
$PhCH_2Br$ (1.05)	NaH (1.15) DMF, -20°C, 4h	91	**6-Bn**
Ph_2CHBr (1.08)	NaH (1.15) DMF, 0°C, 22h	68	 **6-Bzh**
Ph_3CCl (1.01)	NaH (1.15) DMF, 0°C, 72h	13	 **6-Tr**
Ph_3CCl (1.05)	4-DMAP (0.10) Pyr, 90°C, 1.5h	45	**6-Tr**
 (1.10)	CH_3CN, 25°C, 24h	66	**6-Tr**
Bu^{t}Me$_2$SiCl (1.10)	Imidazole (2.20) DMF, 25°C, 12h	79	 **6-Tbs**

Reaction of the so-generated alkoxide with methyl iodide allowed the isolation of the expected methyl ether **6-Me** in 91% yield.[12] The same reaction conditions were employed for the preparation of the corresponding benzyl (**6-Bn**), benzhydryl (**6-Bzh**), and trityl (**6-Tr**) ethers. Whereas the preparation of the benzyl ether was fast even at −20 °C, higher temperatures and longer reaction times were required as the steric bulk of the alkylating agent increased. The preparation of **6-Bzh** was therefore best performed at 0 °C, while that of **6-Tr** only proceeded to 13% (15% conversion) after 3 days at 0 °C. In order to improve the yield of **6-Tr** while preventing the occurrence of secondary reactions, less basic reaction conditions were investigated. The yield of **6-Tr** was increased to 45% by performing the reaction in pyridine solution, at 90 °C for 1.5 h in the presence of a 10% molar amount of 4-DMAP.[13] The best reaction conditions, however, (66% isolated yield) involved the use of 1.1 equiv of *N*-(triphenylmethyl)pyridinium tetrafluoroborate in acetonitrile at room temperature.[14] Finally, the *tert*-butyldimethylsilyl ether **6-Tbs** was also prepared in 79% yield under the standard conditions.

For the regioselective and stereospecific ring opening of epoxy ethers **6** with secondary amines, the procedure

(10) (a) García, M. L.; Pascual, J.; Borràs, L.; Andreu, J. A.; Fos, E.; Mauleon, D.; Carganico, G.; Arcamone, F.; *Tetrahedron* **1991**, *47*, 10023−10034. (b) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988−2006.

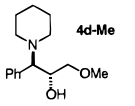
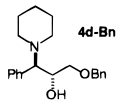
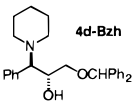
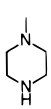
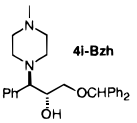
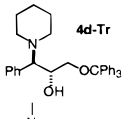
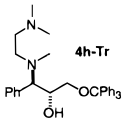
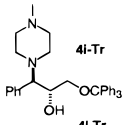
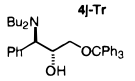
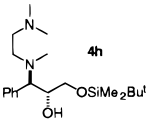
(11) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687−5696.

(12) Fukuzawa, A.; Sato, H.; Masamune, T. *Tetrahedron Lett.* **1987**, *28*, 4303−4306.

(13) (a) Chaudhary, S. C.; Hernandez, O. *Tetrahedron Lett.* **1979**, *20*, 99−102. (b) *Protecting Groups;* Kocienski, P. J., Ed.; Georg Thieme Verlag: Stuttgart 1994; pp 58.

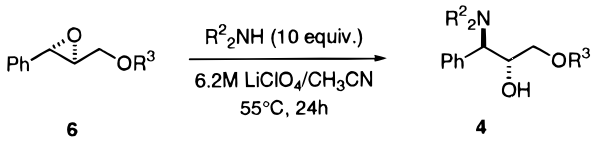
(14) (a) Hanessian, S.; Murray, P. J.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, *26*, 5623−5626. (b) Hanessian, S.; Murray, P. J.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, *26*, 5627−5630. (c) Hanessian, S.; Sahoo, S. P.; Murray, P. J *Tetrahedron Lett.* **1985**, *26*, 5631−5634. (d) Hanessian, S.; Staub, A. P. A. *Tetrahedron Lett.* **1973**, *14*, 3555−3558.

Table 4. Lithium Perchlorate-Induced Regioselective Ring Opening of Epoxy Ethers 6 by Secondary Amines[a]

Epoxyether (6)	Secondary amine	Yield[b] [%]	Aminoalcohol (4)
6-Me		90	 **4d-Me**
6-Bn		98	 **4d-Bn**
6-Bzh		96	 **4d-Bzh**
6-Bzh		94	 **4i-Bzh**
6-Tr		93	 **4d-Tr**
6-Tr		98	 **4h-Tr**
6-Tr		89	 **4i-Tr**
6-Tr	Bu_2NH	93	 **4j-Tr**
6-Tbs		98[c]	 **4h**

[a] All reactions were performed by treating the starting epoxy ether **6** with a 10-fold excess of the corresponding amine in a 6.2 M solution of $LiClO_4$ in acetonitrile at 55 °C for 24 h. [b] Yields are referred to pure isolated material. [c] Product is a 7:1 mixture of regioisomers arising from C-3 (major) and C-2 (minor) attacks.

Scheme 6



6 **4**

of Crotti,[7] which involves the use of 5−10 M $LiClO_4$ in acetonitrile, was selected (Scheme 6).

In this way, the target amino alcohols **4** were obtained in very high yield as shown in Table 4. It is worth noting that, except for the reaction of **6-Tbs** with *N*,*N*,*N*′-trimethylethylenediamine, the processes were completely regioselective and, in all cases, stereospecific.

Comparison of Routes A and B to Amino Alcohols 4 and Further Modification of These Substances. The synthetic sequences represented by routes A and B (Scheme 1) clearly complement to one another in many different aspects. Route A is well suited for the preparation of families of amino alcohols **4** containing a bulky R^3 group, while route B can allow the easy preparation of families of ligands **4** incorporating a common amine residue while varying at will the nature of the protecting group R^3.

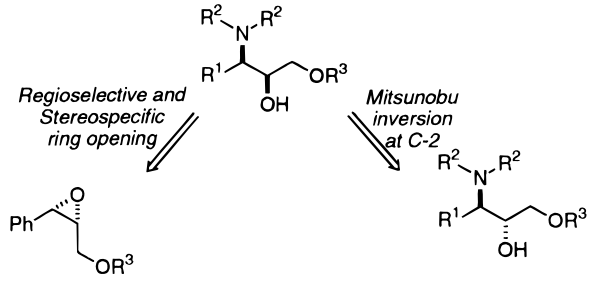
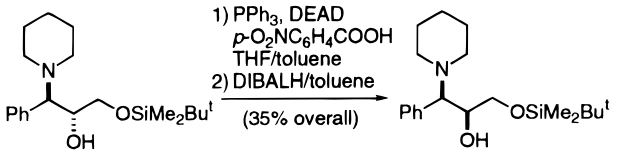


Figure 2.

Scheme 7



4d ***syn*-4d**

Whereas route B is unique in some instances; *i.e.*, when a nonbulky R^3 group has to be chemoselectively introduced, it offers a more subtle advantage in other situations. It is noteworthy that route A is characterized by a highly polar intermediate **5**, while in route B the intermediate epoxy ether **6** exhibits much lower polarity. When an amino alcohol **4** incorporating more than one nitrogen atom in the amino moiety is prepared according to route A (*i.e.*, **4h**, **4h-Tr**, **4i-Bzh**, **4i-Tr**), the chromatographic purification of the corresponding precursors **5**, which are extremely polar substances, can be hardly performed. On the other hand, if the preparation of the same substance is planned according to route B, the only polar species in the sequence is the final product **4**. Since **4** is obtained from **5** in very high yield, purification at this stage is a more convenient alternative.

The nonproblematic example **4d-Tr** has been prepared according to both routes. Overall yield is slightly higher in route A (66 *vs* 61%), but the ease of purification of the intermediate and final product could favor route B even in this case.

In order to understand the factors controlling the catalytic activity of the various ligands under investigation, it seemed interesting to modify, at least in one case, the *anti* arrangement of the substituents at C-2 and C-3. Among the different strategies suitable to achieve this (Figure 2), the Mitsunobu inversion[15] of a preformed *anti* amino alcohol **4** appeared the most promising,[16] since it is known that the Sharpless epoxidation of *Z* allyl alcohols is less efficient than that of the corresponding *E* isomers[5a] and the subsequent ring opening of the intermediate *cis* 1,2-disubstituted epoxides takes place with poor regioselectivity.[7]

Amino alcohol **4d** was selected as the starting material for the C-2 inversion. A Mitsunobu reaction with *p*-nitrobenzoic acid as the nucleophile[15c,16] (Scheme 7) followed by reduction with DIBALH gave *syn*-**4d** in diastereomerically pure form.

Ligand Optimization through the Catalytic Enantioselective Addition of Diethylzinc to Benzaldehyde. The enantioselective addition of diethylzinc and

(15) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Robinson, P. L.; Barry, C. N.; Bass, S. W.; Jarvis, S. E.; Evans, S. A. *J. Org. Chem.* **1983**, *48*, 5396−5398. (c) Coleman, R. S.; Grant, E. B. *Tetrahedron Lett.* **1994**, *36*, 8341−8344.

(16) For related examples see ref 4f,g.

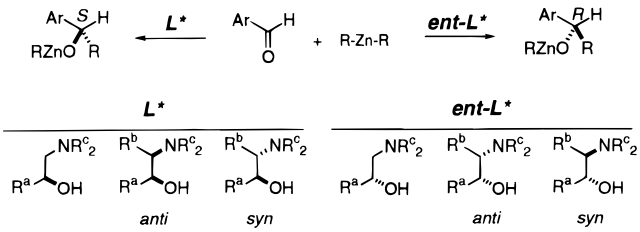


Figure 3.

its congeners to aldehydes mediated by chiral nonracemic amino alcohols represents one of the most studied examples of ligand-accelerated catalysis.[2] From a practical perspective, it is placed among the most powerful methodologies for the production of the ubiquitous secondary alcohols in enantiomerically pure form.[17] Several characteristics of the reaction, such as the very important nonlinear effects,[17–19] autocatalysis phenomena,[20] and the derived amplification of enantiomeric excess, make it attractive from an industrial perspective, provided that sufficiently active catalytic ligands are developed.

Following the pioneering work by Oguni,[21] many different β-amino alcohols have been tested with success as catalytic ligands: They are mostly derived from natural products such as isoborneol, proline, and norephedrine.[17] From the results of these studies, a consistent empirical correlation between the absolute configuration of ligand and product has been established (Figure 3),[17b] and the mechanism of the process has been studied by Noyori from both experimental[17a,b,19a] and theoretical[22] points of view.

As mentioned earlier, the functionalized amino alcohols **4** offer the possibility of systematic variations of steric and electronic characteristics in order to achieve an improved catalytic behavior. As the initial point in our study, we synthesized two limited sets of ligands **4** containing as a common feature a bulky (*tert*-butyldimethylsilyl or trityl) R^3 group (as defined in Figure 1). The first of these sets, characterized by the presence of an acyclic $-NR^2_2$ group, comprises compounds **4g**, **4j-Tr**, and **4h-Tr**, while the second one, incorporating a cyclic dialkylamino residue, comprises **4a**, **4d**, and **4f**.

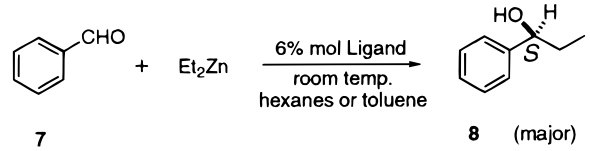
The components of the acyclic set were selected as follows: **4g** and **4j-Tr** represent two extreme situations in terms of steric bulk around the nitrogen atom; moreover, the di-*n*-butylamino substituent has been successfully employed by Soai in norephedrine-derived ligands.[23] On the other hand, **4h-Tr** incorporates the *N,N,N′*-trimethylethylenediamino moiety, a structural motif introduced by Corey in ephedrine-related ligands.[24] All three ligands were studied in the addition of Et_2Zn to benzaldehyde (**7a**) (Scheme 8), employing a 6% molar amount of ligand[25] and performing the reactions at room temperature in hexanes or toluene, as indicated in Table 5. In all instances, the predominantly obtained enantiomer of 1-phenylpropanol (**8a**) had the *S* configuration, in full agreement with the empirical model discussed above.

Table 5. Catalytic Enantioselective Addition to Et_2Zn to Benzaldehyde:[a] Initial Screening

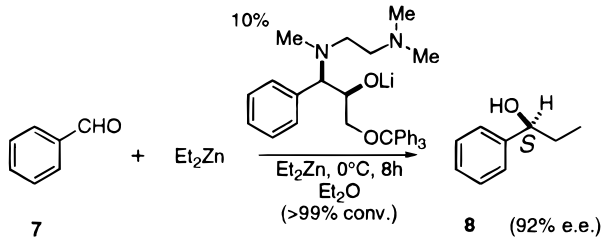
ligand	reaction condns	conversion (%)	selectivity (%)	ee (**8**) (%)
4g	hexanes, 20 h	>99	98	32
4h-Tr	toluene, 4 h	>99	97	84
4j-Tr	toluene, 3 h	>99	98	86
4a	hexanes, 20 h	>99	99	79
4d	hexanes, 3 h	>99	98	89
4f	hexanes, 4 h	>99	99	77

[a] All reactions were performed at room temperature, using a Et_2Zn/C_6H_5CHO/ligand molar ratio of 2.5/1/0.06.

Scheme 8



Scheme 9



While the result with **4g** was mediocre, indicating that steric congestion around the nitrogen atom is negative to catalytic activity and enantioselectivity, much better results were recorded with **4h-Tr** and **4j-Tr**, the later being the most active ligand in this group. Guided by the results reported by Corey,[24] we also explored the use as a catalyst of the lithium salt of **4h-Tr**. Gratifyingly, the ee of 1-phenylpropanol (**8a**) increased to 92% when a 10% molar amount of this lithium salt was used (Scheme 9).

In the study of the set of ligands containing a cyclic amino residue (**4a**, **4d**, **4f**), the amount of catalyst and the reaction conditions employed were the same as in the preceding set; these parameters have been kept constant throughout the present study. It is interesting to note that a piperidino substituent (in **4d**) is optimal for

(17) For reviews on the enantioselective addition of organometallic reagents to carbonyl compounds see: (a) Reference 1a, Chapter 5, pp 255–297. (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69. (c) Soai, K. *Chem. Rev* **1992**, *92*, 833–856.

(18) Bolm, C.; Schlingloff, G.; Harms, K. *Chem. Ber.* **1992**, *125*, 1191–1203.

(19) (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036. (b) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877–7878. (c) Noyori, R. *Science* **1990**, *248*, 1194–1199. (d) Kitamura M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832–4842.

(20) (a) Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun.* **1990**, 982–983. (b) Soai, K.; Hayase, T.; Shimada. C.; Isobe, K. *Tetrahedron: Asymmetry* **1994**, *5*, 789–792. (c) Soai, K.; Hayase, T.; Takai, K. *Tetrahedron: Asymmetry* **1995**, *6*, 637–638. (d) Shibata, T.; Choji, K.; Morioka, H.; Hayase, T.; Soai, K. *J. Chem. Soc., Chem. Commun.* **1996**, 751–752. (e) Shibata, T.; Morioka, H.; Hayase, T.; Choji, K.; Soai, K. *J. Am. Chem. Soc.* **1996**, *118*, 471–472. (e) Shibata, T.; Choji, K.; Hayase, T.; Aizu, Y.; Soai, K. *J. Chem. Soc., Chem. Commun.* **1996**, 1235–1236. (f) Bolm, C.; Bienewald, F.; Seger, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1657–1659.

(21) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823–2824.

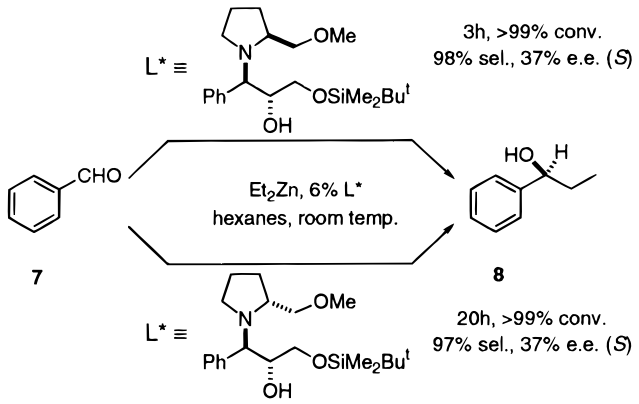
(22) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327–6335.

(23) See, for example: Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264–4268 and references cited therein.

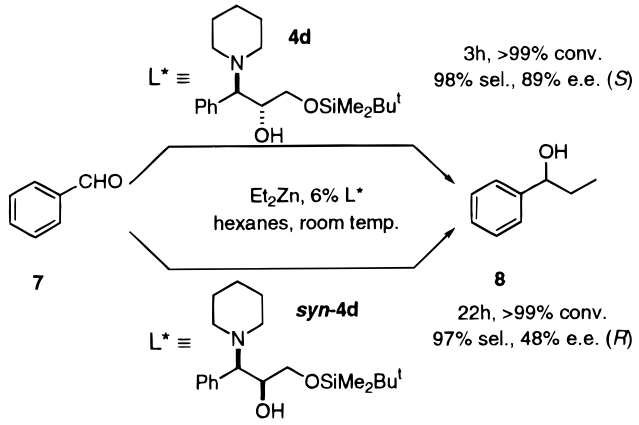
(24) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, 28, 5233–5236.

(25) The optimal amount of ligand was determined for **4d** as follows: Using a 3% molar amount of ligand, and performing the reaction in hexane, conversion was 96% after 21 h and the enantiomeric excess of the resulting alcohol was 84%. With a 6% molar amount of ligand, conversion was >99% after 3 h, and ee was 89%. No further improvement in enantioselectivity was recorded by increasing the amount of ligand employed.

Scheme 10



Scheme 11



enantioselectivity and catalytic activity, while a pyrrolidin-1-yl substituent (in **4a**) provokes a significant decrease in catalytic activity.

Within the same structural pattern, we were also interested in testing the effect of additional chiral centers, located at the amino substituent, on the catalytic efficiency of the ligands. Due to their ready availability, the enantiomeric forms of *O*-methylprolinol were incorporated into ligands **4b** and **4c**. When the activity of these ligands was studied (Scheme 10) under our standard conditions, in no case were we able to detect any improvement in the enantioselectivity of the reaction (a 79% ee is recorded with **4a**, which contains an unsubstituted pyrrolidin-1-yl group). In light of these results, we concentrated our efforts on the structural optimization of ligands containing a six-membered-ring amino substituent.

Although it has been established by Noyori that *anti* β-amino alcohols (which lead to *cis* disubstituted zinc chelates) are in general better ligands than the corresponding *syn* stereoisomers,[17b] we wanted to confirm that the additional alkoxy group present in our ligands did not modify this behavior. To this end, we compared the catalytic activities of **4d** and *syn*-**4d** (Scheme 11) in the standard addition of diethylzinc to benzaldehyde.

In full agreement with the accepted mechanistic pathway of the reaction, the *syn* ligand is less efficient than the *anti* analogue both in terms of turnover and enantioselectivity. Also in agreement with previous experience, the absolute configuration at C-2 in the ligand determines the sense of the enantioselectivity.

With this new parameter in the structure of our target ligands already fixed, we turned our attention to the determination of the optimal protecting group R^3. With this aim, a family of ligands containing the piperidino fragment and different R^3 groups were evaluated. The results are summarized in Table 6.

Table 6. Catalytic Enantioselective Addition of Et_2Zn to Benzaldehyde: Effect of the R^3 Protecting Group

ligand	R^3	reaction condns[b]	conversion (%)	selectivity (%)	ee[c] (%)
5d	H	rt, 21 h, tol	93	72	45
4d-Me	CH_3	rt, 5 h, hex.	>99	99	69
4d	$SiMe_2Bu^t$	rt, 3 h, hex.	>99	98	89
4d-Bp	$SiPh_2Bu^t$	rt, 3 h, hex.	>99	98	90
4d-Bn	CH_2Ph	rt, 5 h, hex.	>99	99	66
4d-Bzh	$CHPh_2$	rt, 3 h, tol	>99	99	88
4d-Tr	CPh_3	rt, 3 h, tol	>99	99	91
4d-Tr	CPh_3	0 °C, 7 h, tol	>99	99	92
4d-Tr	CPh_3	−18 °C, 24 h, tol	98	98	95

[a] A 6% molar amount of ligand was used in all experiments. [b] tol = toluene, hex. = hexanes. [c] (*S*)-1-Phenyl-1-propanol was predominantly obtained in all instances.

Some important conclusions can be drawn from these results. Firstly, in order to achieve practical levels of catalytic activity and enantioselectivity, it is important that the primary hydroxy group be protected, as clearly indicated by the results obtained with **5d**. Secondly, the best enantioselectivities are recorded for the bulkiest protecting groups (**4d-Bp** > **4d**; **4d-Tr** > **4d-Bzh** > **4d-Bn** > **4d-Me**) without appreciable decrease in catalytic activity.

For the best ligand in this series, **4d-Tr**, we have investigated the effect of temperature on enantioselectivity. Interestingly, as the reaction temperature is lowered from room temperature to −18 °C, the enantiomeric excess of the (*S*)-1-phenylpropanol formed increases from 91 to 95% with the turnover of the system being maintained within reasonable limits.

As the final parameter in this optimization, we have tested the effect on enantioselectivity of small variations on the amino substituent keeping constant, however, the presence of a nitrogen-containing six-membered ring. We have summarized in Table 7 the results obtained with ligands **4e** (morpholino substituent), **4i-Bzh** (4-methylpiperazin-1-yl substituent), and **4i-Tr** (4-methylpiperazin-1-yl substituent). For comparison, the results obtained with **4d** and **4d-Tr** have also been included in Table 7.

In agreement with the fact that we are already in an optimal region of the response hypersurface, all ligands in this group exhibit a high catalytic activity and induce a consistently high enantioselectivity in the addition of Et_2Zn to benzaldehyde. Whereas ligand **4e** does not represent any improvement over those containing the piperidino fragment, the presence of a 4-methylpiperazin-1-yl moiety (a cyclic analogue of the *N*,*N*,*N*′-trimethylethylenediamino one) seems to impart interesting characteristics to ligands **4**. In comparing **4i-Bzh** with **4i-Tr**, it is confirmed once again that the bulkiest protecting groups R^3 within an otherwise identical family of ligands are the most convenient for high enantioselectivity. In fact, **4i-Tr** induces the highest enantioselectivity we have been able to observe at room temperature with ligands **4**.

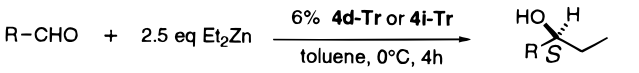
We have carried out two additional studies devoted to the improvement of the enantioselectivity in the reactions with **4i-Tr**. First, we have analyzed the effect of temperature on enantioselectivity by performing reactions at 0 and −18 °C. In this case (*cf.* with **4d-Tr**, above), the enantioselectivity of the reaction is completely inde-

Table 7. Catalytic[a] Enantioselective Addition of Et_2Zn to Benzaldehyde:[b] Effect of the Six-Membered Ring Amino Substituent

Ligand	NR^2_2	OR^3	Reaction Conditions	Conversion [%]	Selectivity [%]	e.e. [%]
4d		$OSiMe_2Bu^t$	3h, hexanes	>99	98	89
4d-Tr		$OCPh_3$	3h, toluene	>99	99	91
4e		$OSiMe_2Bu^t$	3h, hexanes	>99	98	87
4i-Bzh		$OCHPh_2$	3h, toluene	>99	99	87
4i-Tr		$OCPh_3$	3h, toluene	>99	97	92

[a] A 6% molar amount of ligand was used in all cases. [b] All reactions were performed at room temperature and were complete (>99% conversion) after 3 h.

Scheme 12



7b-h **8b-h** (major)

pendent of temperature in the range studied, and this fact can be of practical importance for the potential applications of this ligand.

On the other hand, and keeping in mind the analogy between the 4-methylpiperazin-1-yl and the *N,N,N′*-trimethylethylenediamino moieties, we have also tested the use as a catalyst of the lithium salt of **4i-Tr**. Thus, when a 10% molar amount of this salt was used and the reaction was performed at 0 °C in 1:1 diethyl ether: toluene, the enantioselectivity did not significantly improve (93 *vs* 92%). Accordingly, it appears that the most practical conditions for the use of **4i-Tr** involve working with the neutral ligand at room temperature.

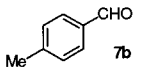
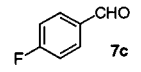
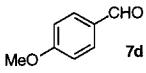
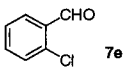
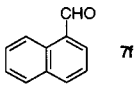
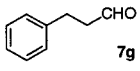
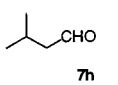
Enantioselective Addition of Diethylzinc to Selected Aldehydes Catalyzed by the Optimized Ligands 4d-Tr and 4i-Tr. As a confirmation of the validity of the fine-tuning process performed on ligands **4**, the optimized ligands, **4d-Tr** and **4i-Tr**, have been used in the addition of diethylzinc to a family of aldehydes (**7b-h**), including both *para*- and *ortho*-substituted aromatic specimens, as well as the generally more problematic aliphatic analogues.[17]

In order to facilitate comparison, all experiments have been performed under identical conditions (Scheme 12). Results on catalyst efficiency (conversion and selectivity) and enantiomeric excess of the resulting 1-substituted 1-propanols (**8b-h**) have been collected in Table 8.

Interestingly, both ligands exhibit a good profile of enantioselectivity over the range of studied aldehydes. Not surprisingly, the best results are obtained with *p*-substituted benzaldehydes (**7b-d**). However, in contrast with many previously reported ligands that are catalytically active in this particular process, the ee's recorded with *ortho*-substituted benzaldehydes (**7e,f**) or, even, with aliphatic ones (**7g,h**) remain high.

As a general trend, **4d-Tr** behaves as a slightly more active ligand than **4i-Tr**, the most important differences occurring with aldehydes **7d** and **7f**. When catalytic activity and enantioselectivity are jointly considered,

Table 8. Catalytic Enantioselective Addition of Et_2Zn to Aldehydes[a] (7b−h) Leading to Alcohols 8b−h,[b] Mediated by Ligands 4d-Tr and 4i-Tr

	Ligand	
Starting Aldehyde	**4d-Tr**	**4i-Tr**
 **7b**	Conversion: >99% Selectivity: 98% e.e. **8b**: 92%	Conversion: 95% Selectivity: 97% e.e. **8b**: 95%
 **7c**	Conversion: >99% Selectivity: 99% e.e. **8c**: 93%	Conversion: 96% Selectivity: 99% e.e. **8c**: 94%
 **7d**	Conversion: 99% Selectivity: 96% e.e. **8d**: 91%	Conversion: 72% Selectivity: 98% e.e. **8d**: 96%
 **7e**	Conversion: >99% Selectivity: 93% e.e. **8e**: 87%	Conversion: 97% Selectivity: 93% e.e. **8e**: 87%
 **7f**	Conversion: 99% Selectivity: 91% e.e. **8f**: 82%	Conversion: 48% Selectivity: 89% e.e. **8f**: 80%
 **7g**	Conversion: >99% Selectivity: 96% e.e. **8g**: 86%	Conversion: >99% Selectivity: 91% e.e. **8g**: 86%
 **7h**	Conversion: >99% Selectivity: 98% e.e. **8h**: 85%	Conversion: >99% Selectivity: 87% e.e. **8h**: 80%

[a] All reactions were performed as indicated in Scheme 12. [b] The *S* enantiomer is preferentially obtained in all cases.

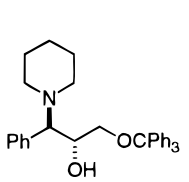
ligand **4i-Tr** turns out to be the best choice for *p*-substituted benzaldehydes, whereas **4d-Tr** would be preferable in all other situations.

Conclusions

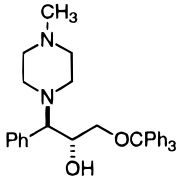
In summary, we have developed a family of new chiral ligands, (1*R*,2*R*)-1-(dialkylamino)-1-phenyl-3-(R-oxy)-2-

propanols, *based on non-natural starting materials*. The molecular architecture of these ligands, built from widely varying fragments grafted in a controlled manner on a chiral skeleton that, in turn, arises from the enantioselective epoxidation of an allyl alcohol, allows a gradual variation of steric/electronic characteristics that is key to the fine tuning of catalytic properties.

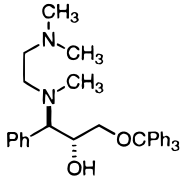
We have employed a well-established enantioselective process, *i.e.*, the amino alcohol-promoted addition of diethylzinc to benzaldehyde, to iteratively optimize the structural characteristics of the ligands for this particular process. As a result of this study, we have identified the steric bulk of the R-oxy group and the specification of the dialkylamino substituent as a nitrogen-containing six-membered ring as the key parameters for high catalytic activity and enantioselectivity. Whereas the steric bulk of the R-oxy group could be important in shifting the dimer/monomer equilibrium of the ethylzinc alkoxide derived from the ligand toward the reactive monomeric form, the results of theoretical (AM1) calculations on the commonly admitted transition states of the reaction suggest that interactions between the methylene groups α to nitrogen (in ligands bearing a six-membered nitrogen-containing ring) with the ethyl group being transferred from zinc to carbonyl are responsible for the high enantiofacial selectivity observed in these cases.[26] Two optimized ligands arising from this analysis, **4d-Tr** and **4i-Tr**, offer particular interest, allowing us to perform the enantioselective addition of Et_2Zn to benzaldehyde with ee's in the range 91−95%. Significantly, in both cases the addition reaction can be performed at room temperature without significant decrease, if any, in the enantioselectivity. Closely related to **4i-Tr**, the acyclic ligand **4h-Tr** also possesses practical applicability, as its lithium salt efficiently induces the reference addition to proceed with 92% ee. In addition, ligands **4d-Tr** and **4i-Tr** have been shown to possess general applicability in the enantioselective addition of Et_2Zn to a variety of aldehydes covering *p*-substituted benzaldehydes (91−96% ee), *o*-substituted benzaldehydes (82−87% ee), and aliphatic benzaldehydes (80−86% ee).



4d-Tr



4i-Tr



4h-Tr

We are currently applying the iterative process of ligand design/fine tuning of catalytic properties to related reactions catalyzed by amino alcohols. The corresponding results will be reported in due course.

Experimental Section

General Methods. General experimental aspects have been published elsewhere.[4a] (2*S*,3*S*)-2,3-Epoxy-3-phenylpropanol, **1a**, was prepared according to the procedure described by Sharpless; *et al.*;[5a] (2*S*)-2-(methoxymethyl)pyrrolidine and (2*R*)-2-(methoxymethyl)pyrrolidine were prepared according to the procedure described by Enders *et al.*[27]

Regioselective Ring Opening of (2*S*,3*S*)-2,3-Epoxy-3-phenylpropanol by Secondary Amines in the Presence of $Ti(O^iPr)_4$. (2*R*,3*R*)-3-Phenyl-3-(pyrrolidin-1-yl)-1,2-propanediol (5a). To a solution of **1a** (250 mg, 1.66 mmol) in CH_2Cl_2 (12 mL) were added pyrrolidine (210 μL, 2.52 mmol) and $Ti(O^iPr)_4$ (740 μL, 2.51 mmol) under N_2 at room temperature. After 5 h of stirring at room temperature, a 10% solution of NaOH in brine (10 mL) was added, and vigorous stirring continued for another 24 h. The mixture was filtered through Celite and the residue washed with CH_2Cl_2 (10 mL). The aqueous solution was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were dried and concentrated *in vacuo*. The residual oil was recrystallized from Et_2O to give 313 mg (85%) of **5a** as white crystals: mp 95 °C; $[\alpha]^{23}_D = -65.8$ (c = 1.0 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26−7.33 (m, 5H), 4.23 (d × d × d, 1H, J = 6.6, 5.7, 5.1 Hz), 3.48 (d × d, 1H, J = 11.9, 5.1 Hz), 3.43 (d, 1H, J = 5.7 Hz), 3.38 (d × d, 1H, J = 11.9, 6.6 Hz), 2.93 (br s, 2H, OH), 2.46−2.59 (m, 4H), 1.70−1.75 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.4 (C), 129.3 (CH), 128.2 (CH), 127.8 (CH), 71.9 (CH), 70.7 (CH), 66.0 (CH_2), 51.4 (CH_2), 22.9 (CH_2); IR (KBr) 3506,3267, 3089, 3060, 3027, 2973, 2952, 2937, 2881, 2786, 2732, 1142, 1075, 1024, 772, 696 cm^{-1}; MS (EI) m/z 221 (M^+, 0), 160 ($M - C_2H_5O_2^+$, 100). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.51; H, 8.77; N, 6.29.

(2*R*,3*R*)-3-[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]-3-phenyl-1,2-propanediol (5b). Compound **1a** (250 mg, 1.66 mmol), CH_2Cl_2 (12 mL), (2*S*)-2-(methoxymethyl)pyrrolidine (290 μL, 2.52 mmol), and $Ti(O^iPr)_4$ (735 μL, 2.49 mmol) were treated as described for **5a** during 5 h. The reaction mixture was quenched with a 10% solution of NaOH in brine (10 mL) as described for **5a** to give 355 mg (80%) of **5b** as an oil after chromatography using hexane:EtOAc (40:60) as eluent: $[\alpha]^{23}_D = -61.8$ (c = 1.0 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.24−7.39 (m, 5H), 4.24 (d × d × d, 1H, J = 9.3, 5.4, 4.2 Hz), 4.08 (d, 1H, J = 9.3 Hz), 3.85 (d × d, 1H, J = 11.1, 4.2 Hz), 3.69 (d × d, 1H, J = 11.1, 5.4 Hz), 3.42 (s, 3H), 3.40−3.50 (m, 2H), 2.81−3.01 (m, 2H), 2.22−2.31 (m, 1H), 2.10 (br s, 2H, OH), 1.24−1.67 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 134.2 (C), 129.9 (CH), 128.3 (CH), 127.8 (CH), 76.4 (CH_2), 69.7 (CH), 67.9 (CH), 66.4 (CH_2), 59.1 (CH), 58.7 (CH_3), 48.1 (CH_2), 27.2 (CH_2), 23.0 (CH_2); IR (film) 3396, 3106, 3087, 3062, 3029, 2927, 2875 2832, 1452, 1096, 1198, 708, 758 cm^{-1}; MS (EI) m/z 265 (M^+, 0), 204 ($M - C_2H_5O_2^+$, 100).

(2*R*,3*R*)-3-[(2*R*)-2-(Methoxymethyl)pyrrolidin-1-yl]-3-phenyl-1,2-propanediol (5c). Compound **1a** (250 mg, 1.66 mmol), CH_2Cl_2 (12 mL), (2*R*)-2-(methoxymethyl)pyrrolidine (290 μL, 2.52 mmol). and $Ti(O^iPr)_4$ (735 μL, 2.49 mmol) were treated as described for **5a** during 8 h. The reaction mixture was quenched with a 10% solution of NaOH in brine (10 mL) as described for **5a** to give 350 mg (79%) of **5c** as an oil after chromatography using hexane:EtOAc (20:80) as eluent. The residual oil was recrystallized from hexane:EtOAc (80:20) to give 318 mg (72%) of **5c** as pale brown crystals: mp 61 °C; $[\alpha]^{23}_D = -9.7$ (c = 1.0 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29−7.40 (m, 5H), 4.26 (d × d × d, 1H, J = 6.6, 5.7, 4.1 Hz), 3.67 (d, 1H, J = 5.7 Hz), 3.48 (d × d, 1H, J = 11.1, 5.1 Hz), 3.41 (d × d, 1H, J = 11.1, 6.6 Hz), 3.18 (s, 3H), 3.04−3.17 (m, 4H), 2.70−2.78 (m, 1H), 1.62−1.78 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.4 (C), 130.0 (CH), 128.3 (CH), 128.1 (CH), 75.3 (CH_2), 71.6 (CH), 70.6 (CH), 65.3 (CH_2), 59.1 (CH), 58.7 (CH_3), 54.1 (CH_2), 28.2 (CH_2), 23.4 (CH_2); IR (KBr) 3417, 3352, 3062, 3033, 2975, 2941, 2927, 2912, 2883, 2846, 2829, 2813, 2734, 1117, 1102, 1070, 1040, 743, 714 cm^{-1}; MS (EI) m/z 265 (M^+, 0), 204 ($M - C_2H_5O_2^+$, 100). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.86; H, 8.78; N, 5.31.

(2*R*,3*R*)-3-Phenyl-3-piperidino-1,2-propanediol (5d). Compound **1a** (1.0 g, 6.66 mmol), CH_2Cl_2 (40 mL), piperidine (985 μL, 9.96 mmol), and $Ti(O^iPr)_4$ (2.95 mL, 9.96 mmol) were treated as described for **5a** during 4 h. The reaction mixture was quenched with a 10% solution of NaOH in brine (40 mL) as described for **5a** to give 1.42 g (91%) of **5d** as a white solid after recrystallization from hexane:Et_2O (2:1): mp 96.5 °C; $[\alpha]^{23}_D = +11.7$ (c = 1.3 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.22−7.40 (m, 5H), 5.35 (br s, 1H, OH), 4.34 (d × d × d, 1H, J = 9.3, 7.5, 4.8 Hz), 3.84 (d × d, 1H, J = 10.8, 4.8 Hz), 3.73

(26) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. To be published.

(27) Enders, D.; Fey, P.; Kipphardt, H. *Org. Synth.* **1987**, *65*, 173−182.

(d × d, 1H, J = 10.8, 7.5 Hz), 3.59 (d, 1H, J = 9.3 Hz), 2.51−2.53 (br s, 2H), 2.30 (br s, 2H), 1.70 (br s, 1H, OH), 1.51−1.60 (m, 4H), 1.29−1.34 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 133.2 (C), 129.7 (CH), 128.4 (CH), 128.2 (CH), 75.7 (CH), 67.4 (CH_2), 67.1 (CH), 51.6 (CH_2), 25.9 (CH_2), 23.9 (CH_2); IR (KBr) 3544, 3286, 3064, 3029, 2993, 2933, 2852, 2792, 2751, 1451, 1123, 1088, 1063, 1026, 754, 708, 698 cm^{-1}; MS (EI) m/z 235 (M^+, 0.1), 174 ($M - C_2H_5O_2^+$, 100). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.48; H, 9.09; N, 5.93.

(2*R*,3*R*)-3-Morpholino-3-phenyl-1,2-propanediol (5e). Compound **1a** (250 mg, 1.66 mmol), CH_2Cl_2 (10 mL), morpholine (220 μL, 2.52 mmol), and Ti(O^{i}Pr)$_4$ (735 μL, 2.49 mmol) were treated as described for **5a** during 5 h. The reaction mixture was quenched with a 10% solution of NaOH in brine (10 mL) as described for **5a** to give 345 mg (87%) of **5e** as a white solid after recrystallization from hexane:EtOAc (2:1): mp 103 °C; $[\alpha]^{23}_D$ = −23.8 (c = 1.1 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.24−7.42 (m, 5H), 4.34 (m, 1H), 3.66−3.70 (m, 5H), 3.63 (d × d, 1H, J = 10.5, 5.1 Hz), 3.49 (d, 1H, J = 7.5 Hz), 2.43−2.55 (m, 4H), 2.02 (br s, 1H, OH), 1.59 (br s, 1H, OH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 133.6 (C), 129.6 (CH), 128.5 (CH), 128.4 (CH), 73.7 (CH), 68.2 (CH), 66.7 (CH_2), 66.2 (CH_2), 50.9 (CH_2); IR (KBr) 3442, 2815, 1497, 1449, 1117, 872, 777, 719 cm^{-1}; MS (EI) m/z 237 (M^+, 0.1), 176 ($M - C_2H_5O_2^+$, 100). Anal. Calcd for $C_{13}H_{19}NO_3 \cdot 1/3H_2O$: C, 64.18; H, 8.15; N, 5.76. Found: C, 64.12; H, 8.39; N, 5.80.

(2*R*,3*R*)-3-(Azepan-1-yl)-3-phenyl-1,2-propanediol (5f). Compound **1a** (750 mg, 4.99 mmol), CH_2Cl_2 (25 mL), hexamethyleneimine (840 μL, 7.45 mmol), and Ti(O^{i}Pr)$_4$ (2.20 mL, 7.46 mmol) were treated as described for **5a** during 8 h. The reaction mixture was quenched with a 10% solution of NaOH in brine (30 mL) as described for **5a** to give 1.13 g (91%) of **5f** as a white solid after recrystallization from Et_2O: mp 94 °C; $[\alpha]^{23}_D$ = +17.5 (c = 1.0 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26−7.38 (m, 5H), 4.27 (d × d × d, 1H, J = 9.0, 6.6, 5.1 Hz), 3.83 (d × d, 1H, J = 10.9, 5.1 Hz), 3.75 (d × d, 1H, J = 10.9, 6.6 Hz), 3.74 (d, 1H, J = 9.0 Hz), 2.73 (d × t, 2H, J = 12.7, 6.4 Hz), 2.52 (d × t, 2H, J = 12.7, 6.4 Hz), 1.80 (br s, 2H, OH), 1.50−1.61 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 135.0 (C), 129.3 (CH), 128.3 (CH), 127.9 (CH), 75.2 (CH), 68.0 (CH), 67.5 (CH_2), 53.3 (CH_2), 28.5 (CH_2), 26.3 (CH_2); IR (KBr) 3384, 3226, 3087, 3060, 3025, 3002, 2966, 2931, 2885, 2854, 1451, 1059, 1022, 762, 702 cm^{-1}; MS (EI) m/z 249 (M^+, 0), 188 ($M - C_2H_5O_2^+$, 100). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.33; H, 9.41; N, 5.62.

(2*R*,3*R*)-3-(Diisopropylamino)-3-phenyl-1,2-propanediol (5g). Compound **1a** (650 mg, 4.33 mmol), CH_2Cl_2 (20 mL), diisopropylamine (910 μL, 6.49 mmol), and Ti(O^{i}Pr)$_4$ (1.91 mL, 6.47 mmol) were treated as described for **5a** during 7 h. The reaction mixture was quenched with a 10% solution of NaOH in brine (20 mL) as described for **5a** to give **5g** as an oil after chromatography using hexane:EtOAc (20:80−40:60) as eluent. The oil was recrystallized from hexane:Et_2O (10:1) to give 155 mg (14%) of **5g** as a white solid: mp 114 °C; $[\alpha]^{23}_D$ = −51.9 (c = 1.0 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26−7.38 (m, 5H), 4.16 (d × d × d, 1H, J = 9.6, 5.7, 5.4 Hz), 3.90 (d, 1H, J = 9.6 Hz), 3.83 (d × d, 1H, J = 10.9, 5.4 Hz), 3.74 (d × d, 1H, J = 10.9, 5.7 Hz), 3.33 (h, 2H, J = 6.6 Hz), 1.75 (br s, 2H, OH), 1.14 (d, 6H, J = 6.6 Hz), 0.80 (d, 6H, J = 6.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.7 (C), 129.9 (CH), 128.5 (CH), 127.5 (CH), 70.7 (CH), 65.9 (CH_2), 62.6 (CH), 46.4 (CH), 21.4 (CH_3), 23.6 (CH_3); IR (KBr) 3282, 3195, 3031, 2981, 2966, 2914, 2869, 1452, 1395, 1383, 1102, 1082, 1061, 1036, 722, 698 cm^{-1}; MS (EI) m/z 251 (M^+, 0), 190 ($M - C_2H_5O_2^+$, 100). Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.25; N, 5.34. Found: C, 71.67; H, 10.02; N, 5.57.

(2*R*,3*R*)-3-[[[2-(Dimethylamino)ethyl]methyl]amino]-3-phenyl-1,2-propanediol (5h). Compound **1a** (1.0 g, 6.66 mmol), CH_2Cl_2 (40 mL), *N*,*N*,*N*′-trimethylethylenediamine (1.27 mL, 9.99 mmol), and Ti(O^{i}Pr)$_4$ (2.95 mL, 9.99 mmol) were treated as described for **5a** during 8 h. The reaction mixture was quenched with a 10% solution of NaOH in brine (40 mL) as described for **5a** to give 1.172 mg (70%) of **5h** as an oil after chromatography using hexane:EtOAc (40:60), EtOAc and EtOAc:EtOH (90:10) as eluents: $[\alpha]^{23}_D$ = −46.2 (c = 1.1 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.22−7.37 (m, 5H), 4.22 (d × d × d, 1H, J = 9.6, 1.8, 1.8 Hz), 4.20 (br s, 2H, OH), 4.07 (d × d, 1H, J = 11.7, 1.8 Hz), 3.83 (d, 1H, J = 9.6 Hz), 3.67 (d × d, 1H, J = 11.7, 1.8 Hz), 2.99−3.11 (m, 2H), 2.33 (s, 6H), 2.14−2.45 (m, 4H), 2.05 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 133.8 (C), 129.7 (CH), 128.1 (CH), 127.5 (CH), 70.8 (CH), 64.2 (CH_2), 63.4 (CH), 55.5 (CH_2), 50.4 (CH_2), 44.2 (CH_3), 38.4 (CH_3); IR (film) 3359, 3106, 3087, 3062, 3029, 2942, 2860, 2821, 2794, 1452, 1366, 1102, 1072, 1042, 752, 704 cm^{-1}; MS (EI) m/z 252 (M^+, 0), 191 ($M - C_2H_5O_2^+$, 10), 194 ($M - C_3H_8N^+$, 100).

Selective protection of the primary hydroxy group in 5a−h as a silyl ether.

(2*R*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-phenyl-3-(pyrrolidin-1-yl)-2-propanol (4a). A solution of **5a** (440 mg, 1.99 mmol), *tert*-butyldimethylsilyl chloride (330 mg, 2.19 mmol), and imidazole (299 mg, 4.39 mmol) in DMF (18 mL) was heated at 65 °C for 24 h under N_2. The reaction mixture was cooled to room temperature, and Et_2O (18 mL) and brine (18 mL) were added. The aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organic extracts were dried and concentrated *in vacuo*. The residual oil was chromatographed using hexane:EtOAc (90:10−80:20) as eluent to give 529 mg (79%) of **4a** as a colorless oil: $[\alpha]^{23}_D$ = −19.7 (c = 1.0 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.27−7.34 (m, 5H), 4.15 (d × d × d, 1H, J = 6.6, 6.3, 3.9 Hz), 3.38 (d × d, 1H, J = 9.9, 6.3 Hz), 3.33 (d, 1H, J = 3.9 Hz), 3.20 (d × d, 1H, J = 9.9, 6.6 Hz), 3.14 (br s, 1H, OH), 2.60−2.63 (m, 2H), 2.42−2.46 (m, 2H), 1.74−1.78 (m, 4H), 0.88 (s, 9H), 0.00 (s, 3H), −0.02 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 138.0 (C), 129.3 (CH), 127.8 (CH), 127.3 (CH), 71.6 (CH), 71.2 (CH), 64.3 (CH_2), 52.4 (CH_2), 25.9 (CH_3), 23.2 (CH_2), 18.2 (C), −5.5 (CH_3); IR (film) 3454, 3064, 3031, 2956, 2858, 2804, 1115, 757, 702 cm^{-1}; MS (CI, NH_3) m/z 336 ($C_{19}H_{33}NO_2Si \cdot H^+$, 100).

(2*R*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-3-phenyl-2-propanol (4b). A solution of **5b** (567 mg, 2.14 mmol), *tert*-butyldimethylsilyl chloride (354 mg, 2.35 mmol), and imidazole (320 mg, 4.71 mmol) in DMF (20 mL) was heated at 65 °C for 24 h under N_2. A workup identical to the one described for **4a** followed by chromatography using hexane:EtOAc (90:10) as eluent yielded 615 mg (76%) of **4b** as a colorless oil: $[\alpha]^{23}_D$ = −42.4 (c = 1.1 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33−7.35 (m, 5H), 4.19 (d × d × d, 1H, J = 7.2, 6.3, 6.0 Hz), 3.87 (d, 1H, J = 7.2 Hz), 3.53−3.63 (m, 2H), 3.46 (d × d, 1H, J = 9.3, 6.3 Hz), 3.40 (s, 3H), 3.28 (d × d, 1H, J = 9.3, 6.0 Hz), 2.76−3.09 (m, 2H), 2.32−2.40 (m, 1H), 1.45−1.76 (m, 4H), 0.91 (s, 9H), 0.05, 0.07 (s, 3H+3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.3 (C), 130.0 (CH), 127.7 (CH), 127.2 (CH), 76.8 (CH_2), 71.0 (CH), 67.0 (CH), 65.0 (CH_2), 59.0 (CH + CH_3), 49.8 (CH_2), 28.0 (CH_2), 25.9 (CH_3), 23.3 (CH_2), 18.3 (C), −5.4 (CH_3); IR (film) 3458, 3029, 2929, 2858, 1117, 778, 704 cm^{-1}; MS (CI, NH_3) m/z 380 ($C_{21}H_{37}NO_3Si \cdot H^+$, 100).

(2*R*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-[(2*R*)-2-(methoxymethyl)pyrrolidin-1-yl]-3-phenyl-2-propanol (4c). A solution of **5c** (425 mg, 1.60 mmol), *tert*-butyldimethylsilyl chloride (265 mg, 1.76 mmol), and imidazole (241 mg, 3.54 mmol) in DMF (15 mL) was heated at 65 °C for 24 h under N_2. A workup identical to the one described for **4a** followed by chromatography using hexane:EtOAc (80:20) as eluent yielded 520 mg (85%) of **4c** as a colorless oil: $[\alpha]^{23}_D$ = +9.7 (c = 1.1 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.27−7.39 (m, 5H), 4.18 (d × d × d, 1H, J = 6.3, 4.2, 3.6 Hz), 3.66 (d, 1H, J = 4.2 Hz), 3.44 (d × d, 1H, J = 10.0, 3.6 Hz), 3.27 (d × d, 1H, J = 10.0, 6.3 Hz), 3.05−3.18 (m, 2H), 3.12 (s, 3H), 2.95−3.05 (m, 2H), 2.64−2.73 (m, 1H), 1.63−1.74 (m, 4H), 0.86 (s, 9H), 0.02 (s, 3H), −0.05 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 137.8 (C), 130.1 (CH), 127.8 (CH), 127.5 (CH), 75.9 (CH_2), 72.0 (CH), 69.6 (CH), 64.5 (CH_2), 59.0 (CH), 58.6 (CH_3), 53.6 (CH_2), 28.2 (CH_2), 25.8 (CH_3), 23.5 (CH_2), 18.2 (C), −5.5 (CH_3); IR (film) 3440, 3029, 2956, 2929, 2858, 1115, 778, 704 cm^{-1}; MS (CI, NH_3) m/z 380 ($C_{21}H_{37}NO_3Si \cdot H^+$, 100).

(2*R*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-phenyl-3-piperidino-2-propanol (4d). A solution of **5d** (783 mg, 3.33 mmol), *tert*-butyldimethylsilyl chloride (551 mg, 3.65 mmol), and imidazole (500 mg, 7.34 mmol) in DMF (30 mL) was heated at 65 °C for 14 h under N_2. A workup identical to the one described for **4a** followed by chromatography using hexane:

EtOAc (90:10−80:20) as eluent yielded 889 mg (76%) of **4d** as a colorless oil: $[\alpha]^{23}_D = -9.3$ ($c = 1.0$ in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29−7.32 (m, 5H), 4.29 (d × d × d, 1H, J = 6.6, 6.0, 4.8 Hz), 3.62 (d × d, 1H, J = 9.9, 6.0 Hz), 3.55 (d × d, 1H, J = 9.9, 4.8 Hz), 3.48 (d, 1H, J = 6.6 Hz), 3.04 (br s, 1H, OH), 2.43 (br s, 4H), 1.57−1.59 (m, 4H), 1.34−1.40 (m, 2H), 0.90 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 134.5 (C), 129.8 (CH), 127.9 (CH), 127.5 (CH), 71.6 (CH), 69.5 (CH), 64.7 (CH_2), 51.9 (CH_2), 25.90 (CH_2), 25.91 (CH_3), 24.3 (CH_2), 18.3 (CH_2), −5.5, −5.4 (CH_3); IR (film) 3448, 3064, 3029, 2932, 2858, 2805, 1252, 1113, 778, 702 cm^{-1}; MS (CI, NH_3) m/z 350 ($C_{20}H_{35}NO_2Si{\cdot}H^+$, 100).

(2*R*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-morpholino-3-phenyl-2-propanol (4e). A solution of **5e** (1.19 g, 5.01 mmol), *tert*-butyldimethylsilyl chloride (830 mg, 5.51 mmol), and imidazole (753 mg, 11.06 mmol) in DMF (45 mL) was heated at 65 °C for 24 h under N_2. A workup identical to the one described for **4a** followed by chromatography using hexane:EtOAc (90:10−80:20) as eluent yielded 1.31 g (74%) of **4e** as a colorless oil: $[\alpha]^{23}_D = -10.4$ ($c = 1.0$ in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.27−7.31 (m, 5H), 4.23 (d × d × d, 1H, J = 6.0, 5.7, 5.4 Hz), 3.68 (t, 4H, J = 5.1 Hz), 3.51 (d × d, 1H, J = 9.9, 6.0 Hz), 3.43 (d × d, 1H, J = 9.9, 5.4 Hz), 3.40 (d, 1H, J = 5.7 Hz), 2.84 (br s, 1H, OH), 2.38−2.48 (m, 4H), 0.86 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 135.3 (C), 129.7 (CH), 128.1 (CH), 127.8 (CH), 71.4 (CH), 69.2 (CH), 67.0 (CH_2), 64.5 (CH_2), 51.3 (CH_2), 25.9 (CH_3), 18.2 (C), −5.4 (CH_3), −5.5 (CH_3); IR (film) 3460, 3064, 3029, 2956, 2858, 1119, 1005, 778, 704 cm^{-1}; MS (CI, NH_3) m/z 352 ($C_{19}H_{33}NO_3Si{\cdot}H^+$, 100).

(1*R*,2*R*)-1-(Azepan-1-yl)-3-[(*tert*-butyldimethylsilyl)-oxy]-1-phenyl-2-propanol (4f). A solution of **5f** (500 mg, 2.00 mmol), *tert*-butyldimethylsilyl chloride (332 mg, 2.20 mmol), and imidazole (302 mg, 4.44 mmol) in DMF (20 mL) was heated at 65 °C for 24 h under N_2. A workup identical to the one described for **4a** followed by chromatography using hexane:Et_2O (97:3) as eluent yielded 518 mg (71%) of **4f** as a colorless oil: $[\alpha]^{23}_D = -3.5$ ($c = 1.2$ in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25−7.30 (m, 5H), 4.17 (d × d × d, 1H, J = 7.8, 5.7, 4.8 Hz), 3.64 (d, 1H, J = 7.8 Hz), 3.63−3.72 (m, 2H), 2.75 (br s, 1H, OH), 2.50−2.70 (m, 4H), 1.54 (br s, 8H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 137.3 (C), 129.3 (CH), 127.8 (CH), 127.1 (CH), 70.41 (CH), 70.38 (CH_2), 65.2 (CH_2), 52.6 (CH_2), 29.2 (CH_2), 26.8 (CH_2), 25.9 (CH_3), 18.3 (C), −5.3 (CH_3), −5.4 (CH_3); IR (film) 3570, 3442, 3087, 3064, 3029, 2929, 2858, 1463, 1452, 1117, 1075, 1061, 778, 702 cm^{-1}; MS (CI, NH_3) m/z 364 ($C_{21}H_{37}NO_2Si{\cdot}H^+$, 100).

(2*R*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-(diisopropylamino)-3-phenyl-2-propanol (4g). A solution of **5g** (175 mg, 0.70 mmol), *tert*-butyldimethylsilyl chloride (115 mg, 0.76 mmol), and imidazole (105 mg, 1.54 mmol) in DMF (7 mL) was heated at 65 °C for 24 h under N_2. A workup identical to the one described for **4a** followed by chromatography using hexane:Et_2O (99:1) as eluent yielded 133 mg (52%) of **4g** as a colorless oil: $[\alpha]^{23}_D = -39.8$ ($c = 0.9$ in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25−7.46 (m, 5H), 4.10 (d × d × d, 1H, J = 8.5, 6.7, 3.7 Hz), 3.88 (d, 1H, J = 8.5 Hz), 3.86 (d × d, 1H, J = 10.0, 3.7 Hz), 3.64 (d × d, 1H, J = 10.0, 6.7 Hz), 3.31 (h, 2H J = 6.5 Hz), 2.30 (br s, 1H, OH), 1.08 (d, 6H J = 6.5 Hz), 0.91 (s, 9H), 0.80 (d, 6H, J = 6.5 Hz), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.1 (C), 129.8 (CH), 127.9 (CH), 126.7 (CH), 71.8 (CH), 65.9 (CH_2), 60.3 (CH), 46.1 (CH), 25.9 (CH_3), 23.9 (CH_3), 21.5 (CH_3), 18.3 (C), −5.3 (CH_3), −5.4 (CH_3); IR (film) 3571, 3064, 3031, 2962, 2931, 2860, 1464, 1115, 778, 702 cm^{-1}; MS (CI, NH_3) m/z 366 ($C_{21}H_{39}NO_2Si{\cdot}H^+$, 100).

(2*R*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-[[[2-(dimethylamino)ethyl]methyl]amino]-3-phenyl-2-propanol (4h). A solution of **5h** (480 mg, 1.90 mmol), *tert*-butyldimethylsilyl chloride (315 mg, 2.09 mmol), and imidazole (286 mg, 4.20 mmol) in DMF (18 mL) was heated at 65 °C for 24 h under N_2. A workup to the one described for **4a** followed by chromatography using hexane:EtOAc (50:50−30:70), EtOAc, and EtOAc:EtOH (90:10) as eluents yielded 460 mg of a mixture of **4h** and **5h** (8:1) as a colorless oil: ^{13}C-NMR for **5h** (50 MHz, $CDCl_3$) δ 136.4 (C), 129.7 (CH), 127.8 (CH), 127.3 (CH), 70.4 (CH), 70.2 (CH_2), 65.0 (CH), 57.9 (CH_2), 52.2 (CH_2), 45.8 (CH_3), 40.0 (CH_3), 25.9 (CH_3), 18.5 (C), −5.4 (CH_3); MS (CI, NH_3) m/z 367 ($C_{20}H_{38}N_2O_2Si{\cdot}H^+$, 100) for **4h**, 253 ($C_{14}H_{24}N_2O_2{\cdot}H^+$, 7) for **5h**.

(2*R*,3*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-3-phenyl-3-piperidino-2-propanol (4d-Bp). A solution of **5b** (200 mg, 0.85 mmol), *tert*-butyldiphenylsilyl chloride (240 μL, 0.94 mmol), and imidazole (127 mg, 1.87 mmol) in DMF (10 mL) was heated at 65 °C for 24 h under N_2. A workup identical to the one described for **4a** followed by chromatography using hexane:EtOAc (95:5−90:10) as eluent yielded 400 mg (99%) of **4d-Bp** as a colorless oil: $[\alpha]^{23}_D = -10.3$ ($c = 1.0$ in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60−7.70 (m, 4H), 7.22−7.41 (m, 11H), 4.28 (d × d × d, 1H, J = 7.7, 6.0, 4.7 Hz), 3.78 (d × d, 1H, J = 10.2, 6.0 Hz), 3.69 (d × d, 1H, J = 10.2, 4.7 Hz), 3.49 (d, 1H, J = 7.7 Hz), 2.70 (br s, 1H, OH), 2.28 (t, 4H, J = 5.0 Hz), 1.41−1.47 (m, 4H), 1.26−1.33 (m, 2H), 1.06 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 135.9 (C), 135.53 (CH), 135.47 (CH), 133.34 (C), 133.28 (C), 129.6 (CH), 129.5 (CH), 127.7 (CH), 127.6 (CH), 127.2 (CH), 71.3 (CH), 69.7 (CH), 65.6 (CH_2), 51.5 (CH_2), 26.8 (CH_3), 26.3 (CH_2), 24.5 (CH_2), 19.2 (CH); IR (film) 3575, 3450, 3072, 2933, 2858, 2805, 1472, 1452, 1113, 1067, 741, 702 cm^{-1}; MS (CI, NH_3) m/z 474 ($C_{30}H_{39}NO_2Si{\cdot}H^+$, 100).

Selective Protection of the Primary Hydroxyl Group in 5d as a Trityl Ether: (1*R*,2*R*)-1-Phenyl-1-piperidino-3-(triphenylmethoxy)-2-propanol (4d-Tr). A solution of **5d** (300 mg, 1.27 mmol) and triphenylmethyl chloride (426 mg, 1.53 mmol) in pyridine (12 mL) was heated at 90 °C for 12 h under N_2. The solvent was removed *in vacuo*, and the residual oil was chromatographed using firstly hexane:Et_2O (90:10) as eluent to separate the excess of tritylating agent and finally hexane:EtOAc (80:20) to give 443 mg (73%) of **4d-Tr** as white crystals: mp 150 °C; $[\alpha]^{23}_D = +3.1$ ($c = 1.1$ in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40−7.43 (m, 6H), 7.17−7.29 (m, 14H), 4.33 (d × d × d, 1H, J = 7.2, 6.3, 4.8 Hz), 3.46 (d, 1H, J = 7.2 Hz), 3.27 (d × d, 1H, J = 9.6, 6.3 Hz), 3.04 (d × d, 1H, J = 9.6, 4.8 Hz), 2.78 (br s, 1H, OH), 2.23−2.30 (br s, 4H), 1.41−1.48 (m, 4H), 1.28−1.33 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 144.1 (C), 136.1 (C), 129.4 (CH), 128.6 (CH), 127.74 (CH), 127.70 (CH), 127.2 (CH), 126.9 (CH), 86.7 (C), 71.7 (CH), 68.8 (CH), 65.6 (CH_2), 51.7 (CH_2), 26.3 (CH_2), 24.5 (CH_2); IR (KBr) 3357, 3056, 3033, 2966, 2929, 2879, 2861, 2807, 1597, 1491, 1449, 1094, 1079, 764, 754, 702 cm^{-1}; MS (CI, NH_3) m/z 478 ($C_{33}H_{35}NO_2{\cdot}H^+$, 100). Anal. Calcd for $C_{33}H_{35}NO_2$: C, 82.98; H, 7.39; N, 2.93. Found: C, 83.10; H, 7.46; N, 2.97.

Protection of the Hydroxy Group in 1a with R^3X Reagents. (2*S*,3*S*)-2-(methoxymethyl)-3-phenyloxirane (6-Me). A solution of **1a** (1.0 g, 6.66 mmol) in DMF (7 mL) was added *via canula* to a suspension of sodium hydride (231 mg, *ca.* 7.7 mmol) in DMF (8 mL) at −20 °C under N_2. The mixture was stirred for 20 min, and methyl iodide (540 μL, 8.66 mmol) was syringed into the mixture. After being stirred for 4 h at −20 °C, the mixture was allowed to reach room temperature and stirred for another hour. MeOH (25 mL) and brine (25 mL) were added. The aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried and concentrated *in vacuo*. The residual oil was chromatographed using hexane:Et_2O (90:10−70:30) as eluent to give 995 mg (91%) of **6-Me** as an oil: $[\alpha]^{23}_D = -43.9$ ($c = 1.0$ in $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.25−7.33 (m, 5H), 3.79 (d, 1H, J = 2.2 Hz), 3.77 (d × d, 1H, J = 11.6, 2.8 Hz), 3.53 (d × d, 1H, J = 11.6, 5.6 Hz), 3.44 (s, 3H), 3.20 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 136.8 (C), 128.4 (CH), 128.2 (CH), 125.6 (CH), 72.1 (CH_2), 60.9 (CH), 59.2 (CH_3), 55.7 (CH); IR (film) 3031, 2989, 2931, 2883, 2829, 1605, 1499, 1463, 1436, 1378, 1138, 1117, 752, 698 cm^{-1}; MS (EI) m/z 164 (M^+, 1), 121 (100).

Preparation of (2*S*,3*S*)-2-(Benzyloxymethyl)-3-phenyloxirane (6-Bn) Using Benzyl Bromide as Protecting Reagent. Compound **1a** (380 mg, 2.53 mmol) in DMF (5 mL), sodium hydride (88 mg, *ca.* 2.9 mmol) in DMF (3 mL), and benzyl bromide (300 μL, 2.54 mmol) were treated as described for **6-Me** to give 558 mg (91%) of **6-Bn** as an oil after chromatography using hexane:Et_2O (90:10) as eluent: $[\alpha]^{23}_D = -36.1$ ($c = 0.9$ in $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.28−7.37 (m, 10H), 3.85 (d × d, 1H, J = 11.6, 2.8 Hz), 3.78 (d, 1H,

J = 2.2 Hz), 3.61 (d × d, 1H, J = 11.6, 5.2 Hz), 3.24 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 137.8 (C), 136.8 (C), 128.42 (CH), 128.39 (CH), 128.2 (CH), 127.7 (CH), 125.6 (CH), 73.2 (CH_2), 69.8 (CH_2), 61.1 (CH), 55.8 (CH); IR (film) 3064, 3031, 2860, 1605, 1497, 1455, 1102, 743, 698 cm^{-1}; MS (CI, NH_3) m/z 258 ($C_{16}H_{16}O_2{\cdot}H{\cdot}NH_3^+$, 100).

Preparation of (2*S*,3*S*)-2-(Benzyloxymethyl)-3-phenyloxirane (6-Bn) Using Benzyl Chloride as Protecting Reagent. Compound **1a** (200 mg, 1.33 mmol) in DMF (2 mL), sodium hydride (52 mg, *ca.* 1.7 mmol) in DMF (2 mL) and benzyl chloride (190 μL, 1.40 mmol) were treated as described, using benzyl bromide as the protecting reagent and stirring 36 h at −20 °C, to give 262 mg (82%) of **6-Bn**. This compound was spectroscopically identical to the one obtained using benzyl bromide as reagent.

(2*S*,3*S*)-2-[(Diphenylmethoxy)methyl]-3-phenyloxirane (6-Bzh). Compound **1a** (1.0 g, 6.66 mmol) in DMF (7 mL), sodium hydride (231 mg, *ca.* 7.7 mmol) in DMF (8 mL), and benzhydryl bromide (2.06 g, 8.32 mmol) were treated as described for **6-Me**, stirring 22 h at 0 °C, to give 1.440 g (68%) of **6-Bzh** as an oil after chromatography, using hexane:Et_2O (98:2) as eluent. One hundred mg of the oil was recrystallized from hexane to give analytically pure white crystals: mp 62 °C; $[\alpha]^{23}_D$ = −30.9 (c = 1.1 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.21−7.40 (m, 15H), 3.82 (d × d, 1H, J = 11.5, 3.0 Hz), 3.75 (d, 1H, J = 2.1 Hz), 3.62 (d × d, 1H, J = 11.5, 5.1 Hz), 3.26 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.73 (C), 141.67 (C), 136.9 (C), 128.4 (CH), 128.2 (CH), 127.6 (CH), 127.5 (CH), 127.0 (CH), 126.9 (CH), 125.7 (CH), 83.9 (CH), 68.6 (CH_2), 61.3 (CH), 55.9 (CH); IR (KBr) 3087, 3062, 3029, 3004, 2861, 1601, 1586, 1495, 1453, 1096, 1079, 741, 702, 695 cm^{-1}; MS (CI, NH_3) m/z 334 ($C_{22}H_{20}O_2{\cdot}NH_4^+$, 59), 317 ($C_{22}H_{20}O_2{\cdot}H^+$, 17), 167 (100). Anal. Calcd for $C_{22}H_{20}O_2$: C, 83.51; H, 6.38. Found: C, 83.64; H, 6.43.

Preparation of (2*S*,3*S*)-3-Phenyl-2-[(triphenylmethoxy)methyl]oxirane (6-Tr) Using Chlorotriphenylmethane and Sodium Hydride as Protecting Reagents. Compound **1a** (250 mg, 1.66 mmol) in DMF (3 mL), sodium hydride (60 mg, *ca.* 2.0 mmol) in DMF (2 mL), and chlorotriphenylmethane (466 mg, 1.67 mmol) in DMF (4 mL) were treated as described for **6-Me**, stirring 72 h at 0 °C, to give 83 mg (13%) of **6-Tr** as an oil after chromatography, using hexane:Et_2O (99:1) as eluent. This oil was recrystallized from hexane to give analytically pure white crystals: mp 120 °C; $[\alpha]^{23}_D$ = −32.4 (c = 1.0 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.21−7.50 (m, 20H), 3.78 (d, 1H, J = 1.8 Hz), 3.45 (d × d, 1H J = 10.2, 2.4 Hz), 3.21−3.29 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.8 (C), 137.1 (C), 128.6 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.1 (CH), 125.7 (CH), 86.8 (C), 64.2 (CH_2), 61.3 (CH), 56.1 (CH); IR (KBr) 3064, 3023, 2925, 2869, 1595, 1489, 1468, 1447, 1109, 1094, 1078, 762, 751, 700 cm^{-1}; MS (CI, NH_3) m/z 410 ($C_{28}H_{24}O_2{\cdot}H^+$, 1), 243 (100). Anal. Calcd for $C_{28}H_{24}O_2$: C, 85.68; H, 6.16. Found: C, 85.62; H, 6.16.

Preparation of (2*S*,3*S*)-3-Phenyl-2-(triphenylmethoxymethyl)oxirane (6-Tr) Using Chlorotriphenylmethane, 4-(Dimethylamino)pyridine, and Pyridine as Reagents. Compound **1a** (250 mg, 1.66 mmol), chlorotriphenylmethane (487 mg, 1.75 mmol), and DMAP (20 mg, 0.16 mmol) in pyridine (10 mL) were stirred for 90 min at 90 °C under N_2. Et_2O (25 mL) was added, and the mixture was washed with HCl 10% (3 × 30 mL) and H_2O (2 × 25 mL). The solvent was removed *in vacuo*, and the residual oil was chromatographed using hexane:Et_2O (99:1) as eluent to give 293 mg (45%) of **6-Tr** as an oil that was recrystallized afterwards from hexane. This compound was spectroscopically identical to the one obtained using chlorotriphenylmethane and sodium hydride as reagents.

Preparation of (2*S*,3*S*)-3-Phenyl-2-[(triphenylmethoxy)methyl]oxirane (6-Tr) Using *N*-(Triphenylmethyl)pyridinium Tetrafluoroborate. 1a (250 mg, 1.66 mmol) and *N*-triphenylmethylpyridinium tetrafluoroborate (750 mg, 1.83 mmol) in acetonitrile (4 mL) were stirred for 24 h at room temperature under N_2. Et_2O (15 mL) was added, and the precipitate was filtered out. The solvent was removed *in vacuo*, and the residual oil was chromatographed using hexane:Et_2O (99:1) as eluent to give 433 mg (66%) of **6-Tr** as an oil that was recrystallized afterwards from hexane. This compound was spectroscopically identical to the one obtained using chlorotriphenylmethane and sodium hydride as reagents.

(2*S*,3*S*)-3-Phenyl-2-[(*tert*-butyldimethylsilyl)oxy]oxirane (6-Tbs). A solution of **1a** (500 mg, 3.33 mmol), *tert*-butyldimethylsilyl chloride (552 mg, 3.66 mmol), and imidazole (499 mg, 7.32 mmol) in DMF (30 mL) was stirred at room temperature for 12 h under N_2. Et_2O (25 mL) and a saturated NH_4Cl solution (25 mL) were added. The aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organic extracts were dried and concentrated *in vacuo*. The residual oil was chromatographed using hexane:Et_2O (99:1) as eluent to give 695 mg (79%) of **6-Tbs** as a colorless oil: $[\alpha]^{23}_D$ = −28.5 (c = 1.3 in $CHCl_3$) (lit.[28] $[\alpha]^{23}_D$ = −26.8 (c = 1.04 g in MeOH)); spectroscopic data were in agreement with the those already described for **6-Tbs**.[28]

Lithium Perchlorate-Induced Regioselective Ring Opening of Epoxy Ethers 6 by Secondary Amines. (2*R*,3*R*)-1-Methoxy-3-phenyl-3-piperidinopropan-2-ol (4d-Me). Piperidine (990 μL, 10 mmol) was syringed into a mixture of **6-Me** (164 mg, 1 mmol) and $LiClO_4$ (1.65 g, 15.5 mmol) in acetonitrile (2.5 mL) at 55 °C under N_2. After the mixture was stirred for 24 h at 55 °C, H_2O (20 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried and concentrated *in vacuo*. The residual oil was chromatographed using hexane:EtOAc (90:10−80:20) as eluent to give 234 mg (94%) of **4d-Me** as a colorless oil that was afterwards recrystallized from hexane:Et_2O to give 224 mg (90%) of **4d-Me** as white crystals: mp 69 °C; $[\alpha]^{23}_D$ = −39.1 (c = 1.0 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.27−7.31 (m, 5H), 4.39 (d × d × d, 1H, J = 7.2, 6.3, 3.6 Hz), 3.31 (s, 3H), 3.32 (d, 1H, J = 6.3 Hz), 3.31 (d × d, 1H, J = 9.6, 3.6 Hz), 3.16 (d × d, 1H, J = 9.6, 7.2 Hz), 2.92 (br s, 1H, OH), 2.30−2.40 (m, 4H), 1.50−1.57 (m, 4H), 1.33−1.40 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 136.4 (C), 129.3 (CH), 127.9 (CH), 127.4 (CH), 75.2 (CH_2), 71.8 (CH), 68.4 (CH), 59.0 (CH_3), 51.9 (CH_2), 26.3 (CH_2), 24.5 (CH_2); IR (KBr) 3422, 3064, 3027, 2981, 2937, 2802, 1096, 704, 751 cm^{-1}; MS (CI, NH_3) m/z 250 ($C_{15}H_{23}NO_2{\cdot}H^+$, 1), 174 (100). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.17; H, 9.41; N, 5.56.

(2*R*,3*R*)-1-(Benzyloxy)-3-phenyl-3-piperidinopropan-2-ol (4d-Bn). Compound **6-Bn** (240 mg, 1.0 mmol), $LiClO_4$ (1.65 g, 15.5 mmol), and piperidine (990 μL, 10 mmol) in acetonitrile (2.5 mL) were treated as described for **4d-Me** during 24 h. The workup was identical to the one described for **4d-Me** to give 318 mg (98%) of **4d-Bn** as an oil after chromatography using hexane:EtOAc (90:10−80:20) as eluent: $[\alpha]^{23}_D$ = −5.7 (c = 1.0 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.29−7.35 (m, 10H), 4.43−4.53 (m, 3H), 3.35−3.46 (m, 3H), 2.95 (br s, 1H, OH), 2.32−2.40 (m, 4H), 1.50−1.58 (m, 4H), 1.24−1.41 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 138.2 (C), 136.3 (C), 129.4 (CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 73.3 (CH_2), 72.7 (CH_2), 71.7 (CH), 68.5 (CH), 51.8 (CH_2), 26.3 (CH_2), 24.5 (CH_2); IR (film) 3454, 3087, 3064, 3029, 2933, 2856, 2805, 1113, 1028, 700, 751 cm^{-1}; MS (CI, NH_3) m/z 326 ($C_{21}H_{27}NO_2{\cdot}H^+$, 100).

(2*R*,3*R*)-1-(Diphenylmethoxy)-3-phenyl-3-piperidinopropan-2-ol (4d-Bzh). Compound **6-Bzh** (250 mg, 0.79 mmol), $LiClO_4$ (1.30 g, 12.2 mmol), and piperidine (780 μL, 7.9 mmol) in acetonitrile (2 mL) were treated as described for **4d-Me** during 24 h. The workup was identical to the one described for **4d-Me** to give 305 mg (96%) of **4d-Bzh** as an oil after chromatography using hexane:EtOAc (80:20) as eluent: $[\alpha]^{23}_D$ = −3.8 (c = 1.0 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.22−7.32 (m, 15H), 5.31 (s, 1H), 4.55 (m, 1H), 3.40−3.49 (m, 3H), 2.80 (br s, 1H, OH), 2.34−2.35 (m, 4H), 1.50−1.57 (m, 4H), 1.33−1.40 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 142.2 (C), 142.1 (C), 136.2 (C), 129.5 (CH), 128.31 (CH), 128.30 (CH), 127.9 (CH), 127.4 (CH), 127.3 (CH), 126.9 (CH), 84.1 (CH), 71.6 (CH), 71.3 (CH_2), 68.7 (CH), 51.8 (CH_2), 26.3 (CH_2), 24.5 (CH_2);

(28) Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. *Tetrahedron* **1991**, *47*, 6983−6998.

IR (film) 3448, 3087, 3062, 3029, 2931, 2856, 1094, 1073, 1030, 743, 702 cm^{-1}; MS (CI, NH_3) *m/z* 402 ($C_{27}H_{31}NO_2 \cdot H^+$, 100).

(2*R*,3*R*)-1-(Diphenylmethoxy)-3-(4-methylpiperazin-1-yl)-3-phenylpropan-2-ol (4i-Bzh). Compound **6-Bzh** (455 mg, 1.44 mmol), $LiClO_4$ (2.37 g, 22.3 mmol), and 4-methylpiperazine (1.6 mL, 14.4 mmol) in acetonitrile (3.6 mL) were treated as described for **4d-Me** during 24 h. The workup was identical to the one described for **4d-Me** to give 565 mg (94%) of **4i-Bzh** after chromatography using hexane:EtOAc (50:50) as eluent. This material solidified upon standing: $[\alpha]^{23}_D$ = +3.5 (*c* = 0.9 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25−7.30 (m, 15H), 5.26 (s, 1H), 4.41−4.47 (m, 1H), 3.42 (d, *J* = 6.5 Hz, 1H), 3.31−3.40 (m, 2H), 2.67 (br s, 1H, OH), 2.40−2.42 (br s, 8H), 2.24 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 142.0 (C), 141.9 (C), 135.9 (C), 129.5 (CH), 128.3 (CH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 126.9 (CH), 84.1 (CH), 71.1 (CH_2), 71.0 (CH), 68.4 (CH), 55.3 (CH_2), 50.4 (CH_2), 45.8 (CH_3); IR (KBr) 3421, 3087, 3062, 3029, 2935, 2875, 2798, 2695, 1452, 1144, 1107, 1072, 758, 742, 702 cm^{-1}; MS (CI, NH_3) *m/z* 417 ($C_{27}H_{32}N_2O_2 \cdot H^+$, 100). Anal. Calcd for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 6.72. Found: C, 77.63; H, 7.84; N, 6.63.

(1*R*,2*R*)-1-Phenyl-1-piperidino-3-(triphenylmethoxy)-2-propanol (4d-Tr). Compound **6-Tr** (455 mg, 1.16 mmol), $LiClO_4$ (1.91 g, 17.99 mmol), and piperidine (1.15 mL, 11.62 mmol) in acetonitrile (3 mL) were treated as described for **4d-Me** during 24 h. The workup was identical to the one described for **4d-Me** to give 520 mg (93%) of **4d-Tr** as an oil after chromatography using hexane:Et_2O (90:10) as eluent. This oil was recrystallized in hexane:Et_2O to give 481 mg (86%) of **4d-Tr** as analytically pure white crystals. This compound was spectroscopically identical to the one obtained by selective tritylation of the primary hydroxyl group in **5d**.

(1*R*,2*R*)-1-[[[2-(Dimethylamino)ethyl]methyl]amino]-1-phenyl-3-(triphenylmethoxy)propan-2-ol (4h-Tr). Compound **6-Tr** (525 mg, 1.33 mmol), $LiClO_4$ (2.21 g, 20.8 mmol), and *N*,*N*,*N*′-trimethylethylenediamine (1.7 mL, 13.4 mmol) in acetonitrile (4.0 mL) were treated as described for **4d-Me** during 24 h. The workup was identical to the one described for **4d-Me** to give 650 mg (98%) of **4h-Tr** as a vitreous material after chromatography using EtOAc as eluent: $[\alpha]^{23}_D$ = +0.7 (*c* = 1.0 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35−7.39 (m, 6H), 7.16−7.27 (m, 14H), 4.24 (d × d × d, 1H, *J* = 6.3, 6.0, 5.7 Hz), 4.13 (br s, 1H, OH), 3.53 (d, 1H, *J* = 5.7 Hz), 3.13 (d × d, 1H, *J* = 9.4, 6.3 Hz), 2.88 (d × d, 1H, *J* = 9.4, 6.0 Hz), 2.38−2.51 (m, 4H), 2.23 (s, 6H), 2.17 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.9 (C), 136.5 (C), 129.6 (CH), 128.5 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 126.8 (CH), 86.6 (C), 70.7 (CH), 69.5 (CH), 65.5 (CH_2), 57.5 (CH_2), 51.5 (CH_2), 45.5 (CH_3), 40.3 (CH_3); IR (KBr) 3409, 3087, 3058, 3025, 2939, 2858, 2821, 1447, 1073, 1032, 772, 749, 704 cm^{-1}; MS (CI, NH_3) *m/z* 495 ($C_{38}H_{38}N_2O_2 \cdot H^+$, 42), 253 (100).

(1*R*,2*R*)-1-(4-Methylpiperazin-1-yl)-1-phenyl-3-(triphenylmethoxy)propan-2-ol (4i-Tr). Compound **6-Tr** (500 mg, 1.27 mmol), $LiClO_4$ (2.10 g, 19.7 mmol), and 4-methylpiperazine (1.4 mL, 12.8 mmol) in acetonitrile (3.2 mL) were treated as described for **4d-Me** during 24 h. The workup was identical to the one described for **4d-Me** to give 559 mg (89%) of **4i-Tr** as an amorphous solid after chromatography using hexane:EtOAc (50:50−0:100) as eluent: $[\alpha]^{23}_D$ = −7.5 (*c* = 0.9 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36−7.40 (m, 6H), 7.14−7.29 (m, 14H), 4.30 (d × d × d, 1H, *J* = 6.0, 5.7, 5.1 Hz), 3.44 (d, 1H, *J* = 5.7 Hz), 3.15 (d × d, 1H, *J* = 9.6, 6.0 Hz), 2.94 (d × d, 1H, *J* = 9.6, 5.1 Hz), 2.40−2.43 (br s, 8H), 2.31 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.9 (C), 135.6 (C), 129.3 (CH), 128.6 (CH), 128.0 (CH), 127.7 (CH), 127.5 (CH), 126.9 (CH), 86.8 (C), 80.0 (CH), 68.5 (CH), 65.3 (CH_2), 55.2 (CH_2), 50.0 (CH_2), 45.6 (CH_3); IR (KBr) 3448, 3087, 3060, 3031, 2935, 2883, 2811, 1449, 1144, 1115, 1079, 762, 748, 704 cm^{-1}; MS (CI, NH_3) *m/z* 493 ($C_{33}H_{36}N_2O_2 \cdot H^+$, 19), 251 (100).

(1*R*,2*R*)-1-(Di-*n*-butylamino)-1-phenyl-3-(triphenylmethoxy)propan-2-ol (4j-Tr). Compound **6-Tr** (150 mg, 0.38 mmol), $LiClO_4$ (0.63 g, 5.92 mmol), and di-*n*-butylamine (640 μL, 3.8 mmol) in acetonitrile (1 mL) were treated as described for **4d-Me** during 24 h. The workup was identical to the one described for **4d-Me** to give 187 mg (94%) of **4j-Tr** as an oil after chromatography using hexane:EtOAc (80:20) as eluent. The oil was further recrystallized in hexane to give analytically pure white crystals: mp 81 °C; $[\alpha]^{23}_D$ = −23.7 (*c* = 0.9 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42−7.46 (m, 6H), 7.22−7.31 (m, 14H), 4.38 (d × d × d, 1H, *J* = 7.5, 7.3, 4.2 Hz), 3.65 (d, 1H, *J* = 7.5 Hz), 3.34 (d × d, 1H, *J* = 9.6, 4.2 Hz), 3.16 (d × d, 1H, *J* = 9.6, 7.3 Hz), 2.62 (br s, 1H, OH), 2.05−2.43 (m, 4H), 0.98−1.30 (m, 8H), 0.80 (t, 6H, *J* = 7.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 144.0 (C), 136.2 (C), 129.5 (CH), 128.7 (CH), 127.8 (CH), 127.7 (CH), 127.1 (CH), 126.9 (CH), 86.7 (C), 69.7 (CH), 66.6 (CH_2) 65.5 (CH), 49.9 (CH_2), 29.8 (CH_2), 20.4 (CH_2), 14.1 (CH_3); IR (KBr) 3587, 3483, 3162, 3087, 3060, 3029, 3002, 2958, 2931, 2871, 2861, 2817, 1491, 1466, 1449, 1074, 773, 762, 746, 702 cm^{-1}; MS (CI, NH_3) *m/z* 522 ($C_{36}H_{43}NO_2 \cdot H^+$, 100). Anal. Calcd for $C_{36}H_{43}NO_2$: C, 82.88; H, 8.31; N, 2.68. Found: C, 82.98; H, 8.46; N, 2.70.

(2*R*,3*R*)-1-[(*tert*-butyldimethylsilyl)oxy]-3-[[[2-(dimethylamino)ethyl]methyl]amino]-3-phenylpropan-2-ol (4h). Compound **6-Tbs** (312 mg, 1.18 mmol), $LiClO_4$ (1.94 g, 18.3 mmol), and *N*,*N*′,*N*′-trimethylethylenediamine (1.5 mL, 11.8 mmol) in acetonitrile (3.0 mL) were treated as described for **4d-Me** during 24 h. The residual oil after removal of the solvents was distilled *in vacuo* (Kugelrohr apparatus, 150−160 °C, 0.3 Torr) to give 424 mg (98%) of a 7:1 mixture of **4h** and its regioisomer.

Mitsunobu Inversion at C-2 of the *Anti* Amino Alcohol 4. 4-Nitrobenzoic Acid (1*S*,2*R*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2-phenyl-2-piperidinoethyl Ester. A solution of **4d** (358 mg, 1.02 mmol), PPh_3 (1.32 g, 5.04 mmol), and 4-nitrobenzoic acid (750 mg, 1.02 mmol) in toluene (9 mL) and THF (9 mL) under N_2 was cooled at −20 °C. DEAD (795 μL, 5.04 mmol) was syringed into the solution. The mixture was stirred at −20 °C for 3 h, allowed to reach room temperature, and stirred for another 14 h at room temperature. The solvents were removed *in vacuo*, and the residual oil was chromatographed using hexane:EtOAc (95:5) as eluent to give 340 mg (67%) of 4-nitrobenzoic acid (1*S*,2*R*)-1-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-phenyl-2-piperidinoethyl ester as a colorless oil: $[\alpha]^{23}_D$ = −41.7 (*c* = 1.0 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20−8.31 (m, 4H), 7.26−7.43 (m, 5H), 6.15 (d, 1H, *J* = 9.0 Hz), 3.55 (m, 2H), 3.14 (d × d × d, 1H, *J* = 6.6, 6.0, 4.8 Hz), 3.04 (br s, 1H, OH), 2.42 (br s, 4H), 1.55−1.58 (m, 4H), 1.33−1.38 (m, 2H), 0.85 (s, 9H), −0.07 (s, 3H), 0.00 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.5 (C), 150.5 (C), 139.5 (C), 136.0 (C), 130.6 (CH), 127.9 (CH), 127.7 (CH), 127.1 (CH), 123.5 (CH), 75.4 (CH), 69.9 (CH), 59.6 (CH_2), 51.6 (CH_2), 26.7 (CH_2), 25.8 (CH_3), 24.7 (CH_2), 18.0 (C), −5.5 (CH_3), −5.4 (CH_3); IR (film) 3035, 2932, 1728, 1609, 1530, 1472, 1270, 1102, 1015, 776, 698 cm^{-1}; MS (CI, NH_3) *m/z* 495 ($C_{27}H_{38}N_2O_5Si \cdot H^+$, 100).

Preparation of (2*S*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-phenyl-3-piperidinopropan-2-ol (*syn*-4d). To a solution 4-nitrobenzoic acid (1*S*,2*R*)-1-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-phenyl-2-piperidinoethyl ester (157 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) at −20 °C under N_2 was added DIBALH 1 M in hexanes (2.5 mL, 2.5 mmol) dropwise. The mixture was stirred at −20 °C for 19 h. Brine (20 mL) and CH_2Cl_2 (30 mL) were added carefully, and the mixture was stirred vigorously. The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried and concentrated *in vacuo*. The residual oil was chromatographed using hexane:EtOAc (95:5) as eluent to give 58 mg (53%) of syn-**4d**: $[\alpha]^{23}_D$ = −5.6 (*c* = 1.1 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.23−7.38 (m, 5H), 5.04 (br s, 1H), 3.68−3.81 (m, 2H), 2.81−2.87 (m, 1H), 2.67−2.75 (br s, 4H), 1.60 (br s, 4H), 1.41−1.47 (m, 2H), 0.89 (s, 9H), 0.02 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 142.4 (C), 127.9 (CH), 126.9 (CH), 126.0 (CH), 71.5 (CH), 70.8 (CH), 60.2 (CH_2), 52.5 (CH_2), 26.3 (CH_2), 25.7 (CH_3), 24.2 (CH_2), 18.0 (C), −5.61 (CH_3), −5.63 (CH_3); IR (film) 3433, 3064, 3031, 2931, 2858, 1526, 1453, 1096, 778, 700 cm^{-1}; MS (CI, NH_3) *m/z* 350 ($C_{20}H_{35}NO_2Si \cdot H^+$, 100).

General Procedure for the Enantioselective Amino Alcohol-Catalyzed Addition of Diethylzinc to Aldehydes. To a solution of the chiral catalyst (0.06 mmol, 6 mol %) in hexane or 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 (2.5 mL of a 1 M hexanes solution, 2.5 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). The combined organic extracts were dried and concentrated *in vacuo*. The enantiomeric excesses were determined from the crude mixture by GC analyses. Conditions of GC analyses: β-DEX or α-DEX 120 column, 30 m length, 0.25 mm internal 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-(*p*-tolyl)-propanol: β-DEX 120 column, 120 °C, t_R *R* isomer 48.1 min, t_R *S* isomer 51.9 min. For 1-(4-methoxyphenyl)propanol: β-DEX 120 column, 135 °C, t_R *R* isomer 65.3 min, t_R *S* isomer 68.1 min. For 1-(4-fluorophenyl)propanol: β-DEX 120 column, 112 °C, t_R *R* isomer 53.1 min, t_R *S* isomer 58.8 min. For 1-(2-chlorophenyl)propanol: β-DEX 120 column, 135 °C, t_R *R* isomer 45.8 min, t_R *S* isomer 50.2 min. For 1-(1-naphthyl)-propanol: β-DEX 120 column, 160 °C, t_R *S* isomer 96.5 min, t_R *R* isomer 101.1 min. For 1-phenyl-3-pentanol: α-DEX 120 column, 115 °C, t_R *R* isomer 74.4 min, t_R *S* isomer 75.6 min. For 5-methyl-3-hexanol: α-DEX 120 column, 65 °C, t_R *R* isomer 14.7 min, t_R *S* isomer 15.2 min.

In order 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,[29] (*S*)-1-(*p*-tolyl)propanol,[30] (*S*)-1-(4-methoxyphenyl)propanol,[30] (*R*)-1-(4-fluorophenyl)propanol,[31] (*R*)-1-(1-naphthyl)propanol,[32] (*S*)-1-phenyl-3-pentanol,[33] and (*S*)-5-methyl-3-hexanol[34]).

General Procedure for the Enantioselective Amino Alcohol-Catalyzed Addition of Diethylzinc to Benzaldehyde Using the Lithium Salt of 4h-Tr or 4i-Tr. A solution of **4h-Tr** or **4i-Tr** (0.1 mmol) in Et_2O (4 mL) at −78 °C was treated with *n*-BuLi (65 μL of a 1.6 M solution in Et_2O, 0.1 mmol) under N_2. The solution was stirred for 10 min, and then benzaldehyde (100 μL, 1 mmol) and diethylzinc (2.5 mL of a 1 M hexanes solution, 2.5 mmol) were added. The reaction mixture was warmed to 0 °C and stirred for 8 h at 0 °C. Quenching and determination of the ee. of the product was performed as described above.

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Supporting Information Available: ^{13}C NMR spectra of compounds **5b,h**, **4a−g**, **4h/5h** (8:1 mixture), **4d-Bp**, **6-Me**, **6-Bn**, **4d-Bn**, **4d-Bzh**, **4h-Tr**, **4i-Tr**, ***syn*-4d** (*p*-nitrobenzoate), and ***syn*-4d** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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