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Modular Amino Alcohol Ligands Containing Bulky Alkyl Groups as Chiral Controllers for Et_2Zn Addition to Aldehydes: Illustration of a Design Principle

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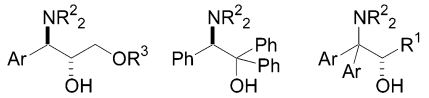
A new family of enantiomerically pure (1*S*,2*R*)-1-alkyl-2-(dialkylamino)-3-(R-oxy)-1-propanols containing a very bulky alkyl substituent (*tert*-butyl or 1-adamantyl) on their hydrocarbon chains has been synthesized from the corresponding enantiopure epoxy alcohols, arising from the catalytic Sharpless epoxidation, by protection of the primary hydroxy group and subsequent regioselective ring opening of the epoxide by a secondary cyclic amine (C-2 attack). The performance of these amino alcohols as ligands for the catalytic enantioselective addition of diethylzinc to benzaldehyde has been studied, with enantioselectivities of 92−96% being recorded. The best performing ligands, those with a bulky R-oxy group, also depict a convenient activity and selectivity profile in the addition of Et_2Zn to a representative family of aldehydes. An anomalous structure/enantioselectivity relationship of some ligands in the *tert*-butyl series has been studied using PM3 calculations, and conclusions have been drawn on the possible effects of including in modular designs structural fragments giving rise to a variety of rotameric transition states.

Introduction

Addition of organometallic reagents to carbonyl compounds is one of the most common and fundamental reactions for the formation of carbon−carbon bonds.[1] In particular, the amino alcohol-catalyzed dialkylzinc addition to aldehydes has been extensively studied, allowing the preparation of chiral secondary alcohols in high enantiomeric purities.[2] Furthermore, this reaction has become a classical test when designing new ligands for asymmetric catalysis.

Chiral β-amino alcohols are often prepared from the corresponding α-amino acids or from other natural products such as ephedrine. However, enantiomerically pure amino alcohols of synthetic origin are becoming increasingly important. In the past few years, we have reported the synthesis of three new families of β-amino alcohols through the regioselective and stereospecific ring opening of epoxides arising from the Sharpless[3] (**1**)[4] and Jacobsen[5] (**2** and **3**)[6] epoxidations. The main advantage of these ligands is their modular construction and, thus, the easy modification of their structures at any step of the synthesis. This characteristic is important for the fine-tuning of the catalytic activity and for a deeper understanding of the structural effects in the addition reaction outcome.



1 **2** **3**

In all these families of amino alcohols, aryl groups are important structural elements: not only do they direct the ring opening of the precursor epoxides but probably their π-systems participate in important interactions in the catalysis event.

Besides ligands where aromatic systems are important structural elements (for instance, those derived from ephedrine, taddol, and 1,1′-binaphthyl) an alternative, rather successful approach to catalytic ligands has relied on the use as stereodifferentiating elements of simple yet bulky alkyl groups, like isopropyl (as in the case of valine) or *tert*-butyl (as in the case of *tert*-leucine). In the absence

(1) (a) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; John Wiley & Sons: New York, 1994; pp 255−297. (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 46−49. (c) Soai, K. *Chem. Rev.* **1992**, *92*, 833−856.

(2) For some leading references, see: (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; pp 255−297.

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

(4) (a) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970−4982. (b) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773−8776. (c) Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902−7911.

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

(6) (a) Solà, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A.; Álvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1998**, *63*, 7078−7082. (b) Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 3969−3974. (c) Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synthesis* **2000**, 165−176.

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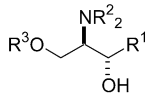
of π-systems, the action mode of these groups in directing reactivity should be mostly,[7] or even exclusively, of steric nature.[8]

To see whether this approach could also be applied to amino alcohol ligands arising from the ring opening of synthetic epoxides, we decided to prepare epoxy alcohols incorporating a bulky, tertiary group as a substituent of the oxirane ring and submit them to the ring opening/protection sequences already used for the preparation of **1**. In this case, however, precedents due to Crotti[9] indicate that the ring-opening process would take place at the less hindered position, C2, leading to amino alcohols of type **4**.



R^1: bulky substituent

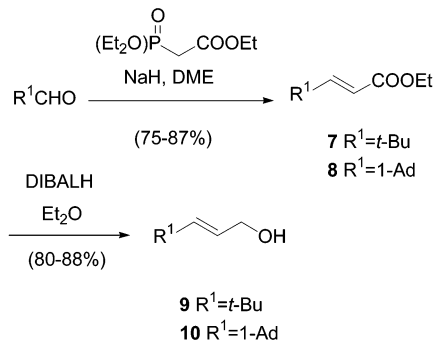
4

We report here how amino alcohols **4** can be efficiently prepared following the same strategies that were applied to the synthesis of family **1**[4] (ring opening plus selective primary hydroxyl protection, or otherwise, initial hydroxyl protection followed by epoxide opening) by simply changing the nature of the starting epoxide. The ligands synthesized in this manner have been successfully optimized and applied to the highly enantioselective diethylzinc addition to aldehydes, completing the study of the catalytic activity of all four regioisomeric families of β-amino alcohols (**1**−**4**).

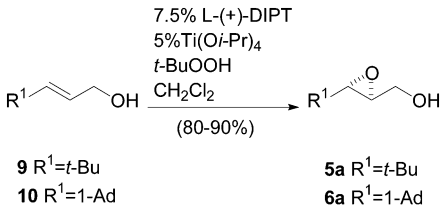
Results and Discussion

The starting epoxy alcohols were chosen taking into account the results obtained by Crotti in the lithium perchlorate-induced regioselective ring opening of epoxides.[9] Racemic *O*-benzyl epoxy alcohols usually react at the C3 position under Crotti's conditions, except when very bulky substituents (i.e., *tert*-butyl) are bonded to that carbon. In this case, harder reaction conditions are needed and the ring opening takes place at the less hindered position, C2.[9c] With these precedents in mind, we chose 3-*tert*-butylepoxypropanol **5a** and 3-(1-adamantyl)epoxypropanol **6a**, which looked suitable for our purposes. (*E*)-3-*tert*-Butyl-2-propen-1-ol (**9**) and (*E*)-3-(1-adamantyl)-2-propen-1-ol (**10**), the substrates for Sharpless epoxidation, were prepared starting from commercially available pivalaldehyde and from 1-(adamantyl)-carbaldehyde, respectively. This last aldehyde was obtained in 72% overall yield, starting from commercial 1-(adamantyl)carboxylic acid, by reduction to the corresponding alcohol with $LiAlH_4$[10] and subsequent selective oxidation using bleach in the presence of TEMPO.[11] Both aldehydes were subjected to the highly stereoselective Wadsworth−Horner−Emmons olefination followed by reduction with DIBALH (Scheme 1). In both cases, this procedure is amenable to a multigram scale and takes place with good overall yield.

SCHEME 1



SCHEME 2



Both allyl alcohols were epoxidized under catalytic Sharpless conditions (Scheme 2), and the corresponding epoxy alcohols (**5a**[12] and **6a**) were isolated in 90 and 80% yields, respectively. The enantiomeric excess of **5a** was 96% according to the DSC (Differential Scanning Calorimetry)[13] of its trityl derivative (**5d**), and the enantiomeric excess of **6a** was 94% determined by HPLC of its acetyl derivative.[14] Since epoxy alcohol **6a** is a crystalline solid, its ee could be raised to 98% after one recrystallization from hexanes.

For the selective protection of the primary hydroxyl group (Scheme 3), epoxy alcohols **5a** and **6a** were subjected to a variety of protection schemes that have been summarized in Table 1.

For the regioselective and stereospecific ring opening of epoxides with secondary amines, Crotti's procedure,[9] which involves the use of 5−10 M $LiClO_4$ in acetonitrile, was selected. Compounds **11a**−**e** and **12a**−**c**, where the nitrogen atom in the dialkylamino residue is a part of a

(7) The importance of steric effects in the diarylhydroxymethyl group present in many successful ligands has been stressed: Braun, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 519−522.

(8) For a recent example, see: Nugent, W. A. *Org. Lett.* **2002**, *4*, 2133.

(9) (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.

(10) Della, E. W.; Pigou, P. E. *J. Am. Chem. Soc.* **1984**, *106*, 1085−1092.

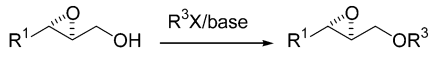
(11) Anelli, P. L.; Biffi, C. B.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.

(12) (a) Schweiter, M. J.; Sharpless, K. B. *Tetrahedron Lett.* **1985**, *26*, 2543−2546. (b) Konoike, T.; Hayashi, T.; Araki, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1559−1566.

(13) *Enantiomers, Racemates and Resolutions*; Jacques, J., Collet, A., Wilen, S. H., Eds.; John Wiley & Sons: New York, 1981; pp 151−159.

(14) Racemic epoxide was acetylated under standard conditions. Conditions of its HPLC analysis: Chiralcel-OD column, 25 cm, eluent = hexane/propan-2-ol (99:1); flow rate = 0.3 mL/min; t_R of enantiomers = 25 and 28 min.

SCHEME 3



5a R^1=*t*-Bu
6a R^1=1-Ad

5b-d R^1=*t*-Bu
6b-c R^1=1-Ad

TABLE 1. Protection of 5a and 6a with R^3X Reagents

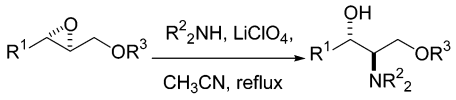
epoxy alcohol	reaction conditions	R^3	epoxyether	yield (%)
5a	NaH, CH_3I, DMF	Me	**5b**	90
5a	NaH, $PhCH_2Br$, DMF	Bn	**5c**	99
5a	$(Ph_3C\text{-pyr})BF_4$, CH_3CN	Tr	**5d**	66
6a	NaH, CH_3I, DMF	Me	**6b**	99
6a	NaH, $PhCH_2Br$, DMF	Bn	**6c**	92

TABLE 2. Lithium Perchlorate-Induced Ring Opening of Epoxides with Secondary Amines

epoxide	R	amine	product	yield (%)
5a	H	piperidine	**11a**	86
5b	Me	piperidine	**11b**	56
5c	Bn	piperidine	**11c**	85
5d	Tr	piperidine	**11d**	0[a]
5c	Bn	pyrrolidine	**11e**	99
6a	H	piperidine	**12a**	98
6b	Me	piperidine	**12b**	77
6c	Bn	piperidine	**12c**	70

[a] Recovery of **5d** = 95%.

SCHEME 4



5 R^1=*t*-Bu
6 R^1=1-Ad

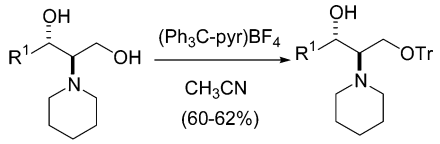
11 R^1=*t*-Bu
12 R^1=1-Ad

ring, were selected as targets bearing in mind the excellent catalytic results provided by this type of amino residue in ligand **1**.[4a,b] The results of these reactions have been summarized in Table 2. With trilylated epoxy alcohol **5d**, no reaction was detected at all, probably due to its important hindrance at both oxirane carbons. Methylated epoxy alcohol **5b** reacted poorly with piperidine, barely giving a 56% yield of the corresponding *β*-amino alcohol **11b**. Even though the reaction was carried out in a sealed pressure tube, its high volatility may have been crucial for the observed yield decrease.

To prepare *β*-amino alcohols with bulky protecting hydroxy groups, a different strategy was envisaged. Epoxy alcohols **5a** and **6a** were first submitted to the regioselective ring opening by a secondary amine, and the resulting amino diols **11a** and **12a**, respectively, were then protected. For the introduction of the trityl group, the best reaction conditions involved the use of 1.1 equiv of *N*-(triphenylmethyl)pyridinium tetrafluororborate in acetonitrile at room temperature (Scheme 5). The *tert*-butyldimethylsilyl ether **11f** was prepared in 82% yield under standard conditions (Scheme 6).

As an initial estimate of their performance, amino alcohols **11** and **12** were tested as ligands in the enantioselective addition of diethylzinc to benzaldeyde (**13a**) in toluene solution.[15] All experiments were performed at

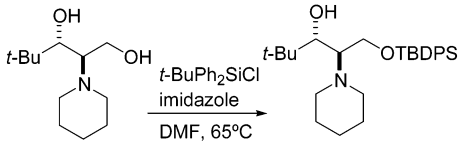
SCHEME 5



11a R^1=*t*-Bu
12a R^1=1-Ad

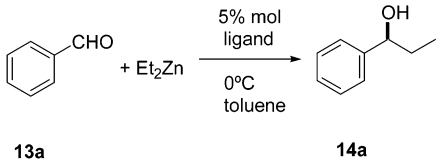
11d R^1=*t*-Bu
12d R^1=1-Ad

SCHEME 6



11a **11f**

SCHEME 7



13a **14a**

TABLE 3. Screening of Ligands in the Catalytic Enantioselective Addition of Diethylzinc to Benzaldehyde

entry	ligand	conversion[a] (%)	selectivity[b] (%)	ee[c] (%)
1	**11a**	48	95	48 (*S*)
2	**11b**	71	>99	94 (*S*)
3	**11c**	65	99	88 (*S*)
4	**11d**	>99	99	95 (*S*)
5	**11e**	30	96	49 (*S*)
6	**11f**	>99	99	92 (*S*)
7	**12a**	21	70	5 (*S*)
8	**12b**	30	96	15 (*S*)
9	**12c**	39	97	35 (*S*)
10	**12d**	>99	98	96 (*S*)

[a] Determined by integration of residual **13a** in front of all new products in the gas chromatogram of the reaction crude. [b] Determined by integration of **14a** (both enantiomers) in front of all new products in the gas chromatogram of the reaction crude. [c] Determined by GC on a *β*-DEX 120 column.

0 °C for 5 h, using a 5% molar amount of ligand and 2 equiv of 1 M diethylzinc solution in hexanes (Scheme 7). Results on the catalyst efficiency (conversion and selectivity) and the enantiomeric excess of the resulting (*S*)-1-phenylpropanol have been collected in Table 3. As we had previously disclosed for the regioisomeric amino alcohols **1**,[4] a bulky protecting group (R^3) at the primary hydroxyl is needed to achieve an efficient process. When ligands containing a *tert*-butyl group (**11a**−**f**) were used, an increase in the conversion as well as in the enantioselectivity was observed when the size of the primary hydroxyl protecting group was increased (entries 1−4 and 6 in Table 3). However, the O-benzylated ligand **11c**

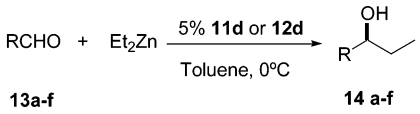
(15) For some recent work, see: (a) Kang, J.; Lee, J. W.; Kim, J. I. *J. Chem. Soc., Chem. Commun.* **1994**, 2009−2010. (b) Kang, J.; Kim, D. S.; Kim, J. I. *Synlett* **1994**, 842−844. (c) Qiu, J.; Guo, C.; Zhang, X. *J. Org. Chem.* **1997**, *62*, 2665−2668. (d) Zhang, F. Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651−3655. (e) Huang, W. S.; Hu, Q. S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364−1365.

TABLE 4. Additions of Diethylzinc to Several Aldehydes Using 5 Mol % 11d or 12d

		ligand **11d**			ligand **12d**		
entry	starting aldehyde	conversion[a] (%)	selectivity[b] (%)	ee[c] (%)	conversion[a] (%)	selectivity[b] (%)	ee[c] (%)
1	benzaldehyde (**13a**)	>99	99	95	>99	98	96
2	*p*-tolualdehyde (**13b**)	>99	99	94	99	98	97
3	*m*-tolualdehyde (**13c**)	99	98	96			
4	*o*-tolualdehyde (**13e**)	99	96	92	97	95	95
5	1-naphthaldehyde (**13f**)				99	94	84
6	*n*-heptanal (**13g**)	99	98	72			
7	(*E*)-α-methylcinnamaldehyde (**13h**)	99	98	96	87	99	96

[a] Determined by integration of residual **13** in front of all new products in the gas chromatogram of the reaction crude. [b] Determined by integration of **14** (both enantiomers) in front of all new products in the gas chromatogram of the reaction crude. [c] Determined by GC on a β-DEX 120 column.

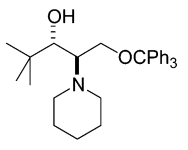
SCHEME 8



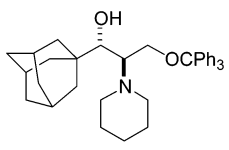
showed a slightly odd result (entry 3) since the resulting ee (88%) is lower than that obtained by the O-methylated ligand **11b** (entry 2), which offers the second highest ee (94%) in this group of ligands, or the O-tritylated ligand **11d** (entry 4, 95% ee), which is the optimal one. As in the previously studied family of amino alcohols **1**,[4] the ligand containing the pyrrolidinyl module (**11e**) did not provide particularly good results (entry 5).

When ligands containing the 1-adamantyl group were tested (entries 7−10), the previously mentioned effect of the steric hindrance of R^3 was even clearer; all three studied parameters (conversion, selectivity, and ee) increase with the size of the protecting group. Catalyst **12d** eventually afforded (*S*)-1-phenyl-1-propanol in excellent yield and 96% ee, the highest detected among all of the new compounds.

The best performing ligands resulting from this preliminary screening, **11d** and **12d**, were subsequently employed to induce enantioselective addition of diethylzinc to a representative family of aromatic aldehydes (**13b**−**f**) (Scheme 8and Table 4). The enantiomeric purity of the resulting (*S*)-alcohols (**14b**−**f**) was quite high in most of the cases. As previously described,[15c,e] *o*-tolualdehyde and 1-naphthaldehyde, the more congested substrates, tend to experience dialkylzinc addition with comparatively lower enantioselectivity than other aromatic substrates.[16] The reaction of one aliphatic aldehyde **13g** showed poor enantioselectivity. Finally, we tested the addition to an α,β-unsaturated aldehyde, α-methylcinnamaldehyde, and gratifyingly enough, for both ligands the enantiomeric purity of the resulting alcohol was very high.



11d



12d

It is noteworthy that all these β-amino alcohols follow Noyori's empirical rule on the dependence of the sense of enantioselectivity on the absolute configuration of the carbon supporting the hydroxyl group on the ligand.[17] It is also necessary to point out that the ligands used were not completely enantiopure, since (2*S*,3*S*)-3-*tert*-butyl-2,3-epoxypropanol (**5a**) was a liquid of 96% enantiomeric purity; all of its derived amino alcohols, **11a**−**f**, were oils as well, and none of them could be recrystallized to increase their ee. Catalysts containing the 1-adamantyl group, **12a**−**d**, had 98% enantiomeric purities (the same as the starting epoxy alcohol) since it was not possible to recrystallize any of them. In this sense, and bearing in mind that the bulky nature of the catalyst should probably reduce the importance of the nonlinear effects[18] operating in the studied reaction, enantioselectivities recorded with the optimal ligands are within the limit of the catalysts.

As already mentioned, modular design is important in catalysis since it allows the separate optimization of molecular fragments and, in successful cases, the application of optimized molecular modules to new families of ligands. In our work on the design of enantiopure, stereodefined 3-aryl-1-alkoxy-3-amino-2-propanols as multipurpose ligands, we have repeatedly observed that both enantioselectivity and catalytic activity increase with the steric bulk of the 1-alkoxy module. This is the case for the diethylzinc addition to aldehydes[4] and imines,[19] the transfer hydrogenation of ketones,[20] and the asymmetric allylic alkylation[21] (via the derived bis-oxazolines), and in this way, the use of bulky alkoxy groups in these ligands has become a *design principle* among us.

When we analyze the results obtained with ligands **12a**−**d**, it is evident that the forementioned principle fully applies: the highest catalytic activity and enantioselectivity are recorded with **12d**. However, as indicated above, this principle breaks for the family of ligands **11b**−**d**, where either the most or the least bulky substituents (methyl in **11b** and trityl in **11d**) lead to better results than a substituent of intermediate bulk like benzyloxy (in **11c**). To justify this apparently odd behavior, we decided to perform a theoretical study of the

(16) Interestingly, ligand families **2** and **3** are complementary in this respect (see ref 6)

(17) See ref 1a, pp 265−266.

(18) Recent review: (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922. (b) Buono, F.; Walsh, P. J.; Blackmond, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 13653.

(19) Jimeno, C.; Readdy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 3157.

(20) Pastó, M.; Riera, A.; Pericàs, M. A. *Eur. J. Org. Chem.* **2002**, 2337−2341.

(21) Pericàs, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gómez, M.; Jiménez, F.; Muller, G.; Rocamora, M. *Chem. Eur. J.* **2002**, *8*, 18.

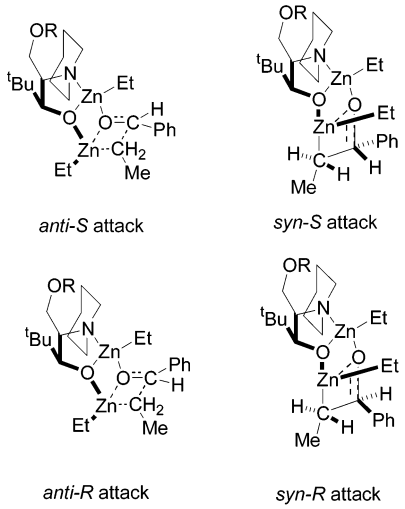


FIGURE 1. Diastereomeric transition states for the diethylzinc addition to benzaldehyde mediated by ligands **11b**−**d**.

TABLE 5. Relative Energies (kcal/mol) of the Most Stable Conformers of the Diastereomeric Transition States with Ligands 11b−d

	R:Me, **11b**	R:Bn, **11c**	R:Tr, **11d**
anti-(*S*)	**0**	**0**	**0**
anti-(*R*)	**8.114**	**7.455**	13.462
syn-(*S*)	12.897	not found	13.222
syn-(*R*)	8.655	8.059	**11.461**

geometries and relative energies of the diastereomeric transition states involved in the diethylzinc addition to benzaldehyde promoted by **11b**−**d**.

The stereochemical outcome of the reaction could be explained considering the relative energies of the four diastereomeric transition states (*anti*-(*S*), *syn*-(*S*), *anti*-(*R*), *syn*-(*R*)) despicted in Figure 1, which according to the pioneering work of Noyori[22] should be those determining the enantioselectivity of the reaction.

The geometries and relative energies of these four species were calculated at the PM3 level[23] (Table 5), which in previous instances has been shown to provide satisfactory results for the considered chemistry. In all cases, conformational isomerism arising from both the inversion of the piperidinyl ring and the rotation of the transferred ethyl group was thoroughly investigated. This leads to a maximum of six conformers for each diastereomeric TS. In addition, rotation of the benzyl group was also investigated in all TSs involving ligand **11c**, leading to a maximum of 18 conformational isomers for each basic TS.

In so doing, we were pleased to find that the sense of enantioselectivity induced by the three ligands **11b**−**d** was correctly predicted (*anti*-(*S*) is the most favorable TS in all cases), and for every ligand the predicted gap between the TSs for *S* and *R* attacks is in reasonable agreement with the observed ee of the resulting alcohols. In effect, comparing the TS energies makes it clear that the bigger the energy gap between the most stable TS

TABLE 6. Relative Energies (kcal/mol) with Respect to the More Stable Conformer of the *anti*-(*R*) and *anti*-(*S*) Transition States for Ligand 11c

	anti-(*S*)	*anti*-(*R*)
conformer 1 (tube)	0	2.844
conformer 2 (ball and wire)	0.222	1.82
conformer 3 (wire)	0.533	0

(*anti*-(*S*) for all of them) and the next lowest energy TS (*anti*-(*R*) for **11b**, *anti*-(*R*) for **11c**, and *syn*-(*R*) for **11d**), the better the observed enantioselectivity. Very interestingly, the present calculations succeed in predicting that both **11b** and **11d** are better ligands than **11c** (R = Bn).

In Figure 2 we present for ligands **11b**−**d** the optimized structures of the most stable diastereomeric transition states (*anti*-(*S*)) in the addition process separately and in superimposed form.[24] A closer inspection evidences an important geometric characteristic at the level of the OR protecting group that could explain the different energetic gaps that we have obtained for every ligand. In this sense, despite the long distance between the alkoxy group and the site where the bond-forming process takes place (more than 8 Å), the OR protecting group represents a structural element of the ligand located in a *stereoinducing region spatially congruent with the site of chemistry*.[25]

Ligand **11c** shows a fundamental difference from ligands **11b** and **11d**: whereas for the latter ligands no isomerism arises from the rotation of the alkoxy group, in the case of **11c**, up to three accessible conformations must be considered. Thus, in **11c** the benzyl group may rotate to avoid unfavorable steric interactions between the phenyl and the *tert*-butyl group or the piperidinyl ring, and it is the most stable conformation arising from this process, which has to be considered (Figure 3). In so doing, we found that the rotation of the benzyl group in the *anti*-(*S*) TS structures gives rise to energy differences of 0.53 kcal/mol, while in the *anti*-(*R*) TS structures, the energetic differences between the most and the least stable conformer are much more important and are up to 2.84 kcal/mol (Table 6).

We have present in Scheme 9 the calculated energy differences between transition states, which are responsible for the enantioselectivity in reactions mediated by **11b** and **11c**. It is most interesting to observe that the energy differences originated by the rotation of the benzyl group can exert a dramatic influence on enantioselectivity. Thus, depending on rotamer transition state availability, the energy gap responsible for the enantioselectivity could range from 6.92 to 10.30 kcal/mol in **11c** (compare with 8.11 kcal/mol in the case of **11b**). Therefore, even though the benzyl protecting group is bulkier than methyl, ligand **11c** is not so selective due to the conformational flexibility of the benzyl group, which provides a mechanism for energy relaxation and modulate the energies of the TSs.

Thus, the present theoretical study shows that conformationally flexible ligands give rise to rotameric TSs that

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

(23) (a) Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998. (b) Goldfuss, B.; Steigelmann, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77.

(24) For a similar superimposition analysis of TSs in the fenchone-based catalysts in dialkylzinc additions to benzaldehyde, see: Goldfuss, B.; Steigelmann, M.; Rominger, F. *Eur. J. Org. Chem.* **2000**, 1785−1792.

(25) Lipkowitz, K. B.; D'Hue, C. A.; Sakamoto, T.; Stack, J. N. *J. Am. Chem. Soc.* **2002**, *124*, 14255.

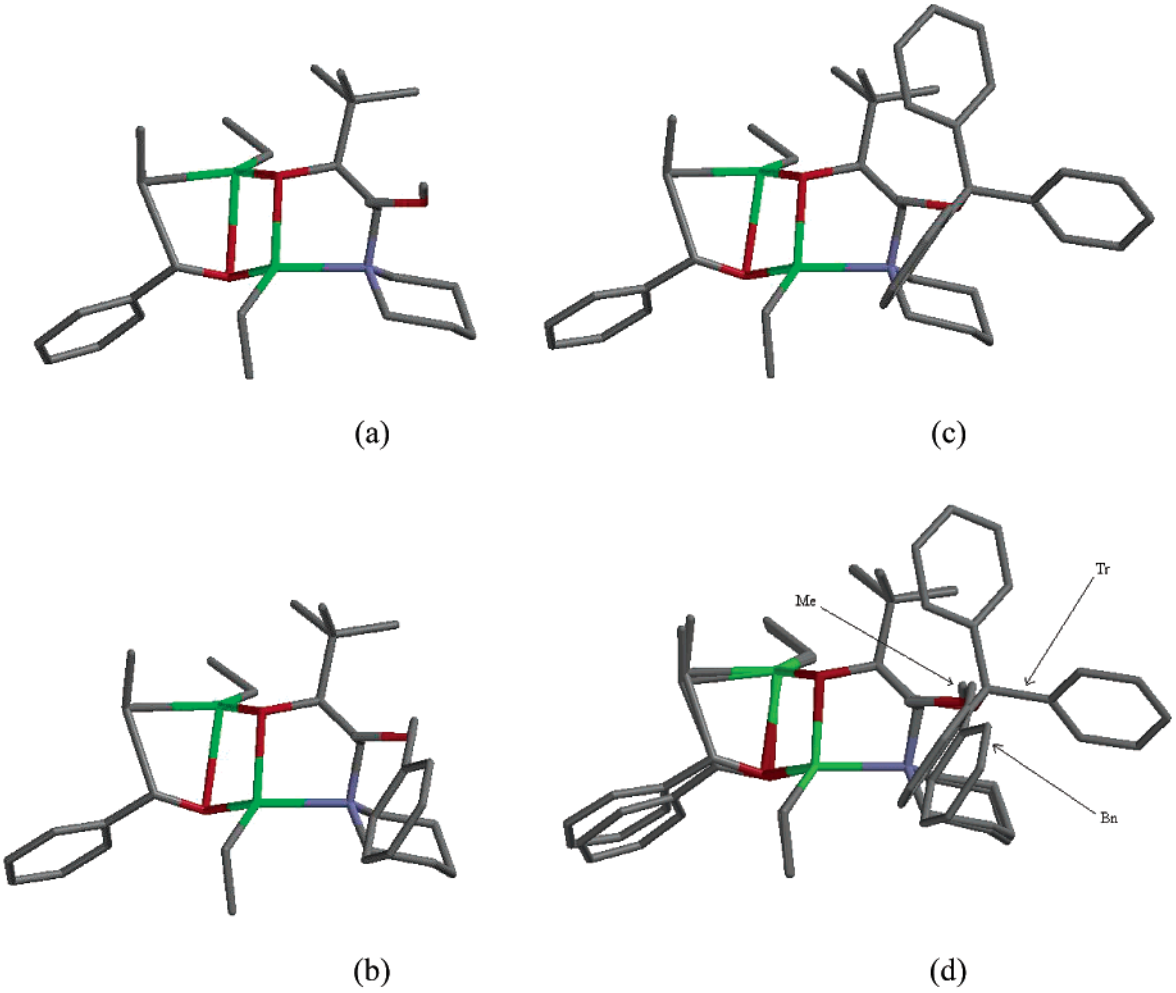
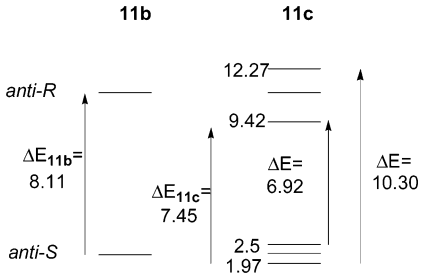


FIGURE 2. (a) *anti*-(*S*) TS for **11b**. (b) *anti*-(*S*) TS for **11c**. (c) *anti*-(*S*) TS for **11d**. (d) Superposition of the *anti*-(*S*) TSs for **11b**−**d** (hydrogen atoms have been omitted for clarity; N = blue, O = red, Zn = green).

SCHEME 9. Representation of the Conformer TS Energies



might decrease the energetic gap between the TS related with the enantioselectivity of the processes for which they have been designed.

Conclusions

In summary, the synthesis of chiral *β*-amino alcohols containing a bulky alkyl substituent from enantiomerically enriched (2*S*,3*S*)-2,3-epoxy-3-alkylpropanols has led to the development of a new family of ligands for the enantioselective addition of diethylzinc to aldehydes. Our synthetic strategy based on the protection of the primary hydroxyl and the epoxide ring opening with secondary amines allows a variation of steric/electronic characteristics that is key to the fine-tuning of catalytic properties. Two optimized ligands, **11d** and **12d**, offer particular potential, allowing us to perform the enantioselective addition of Et_2Zn to aromatic aldehydes with very high ees.

On the other hand, the theoretical analysis of the addition of diethylzinc to benzaldehyde mediated by ligands **11b**−**d** provides an excellent explanation for the observed enantioselectivities and rules in favor of a cautious use of conformationally flexible ligand fragments that might diminish the energetic gap between the TSs that determine the enantioselectivity of the catalytic process. This observation represents an important warning that should be considered in the design of new and more efficient ligands.

Experimental Section

General Methods. Optical rotations were measured at room temperature (23 °C) (concentration in g/100 mL). Melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were recorded using NaCl film or KBr pellet techniques. ^{1}H NMR were recorded at 200 or 300 MHz (s = singlet, d = doublet, t = triplet, m = multiplet, b = broad). ^{13}C NMR were recorded at 50.3 or 75.4 MHz. Carbon multiplicities have been assigned by distortionless

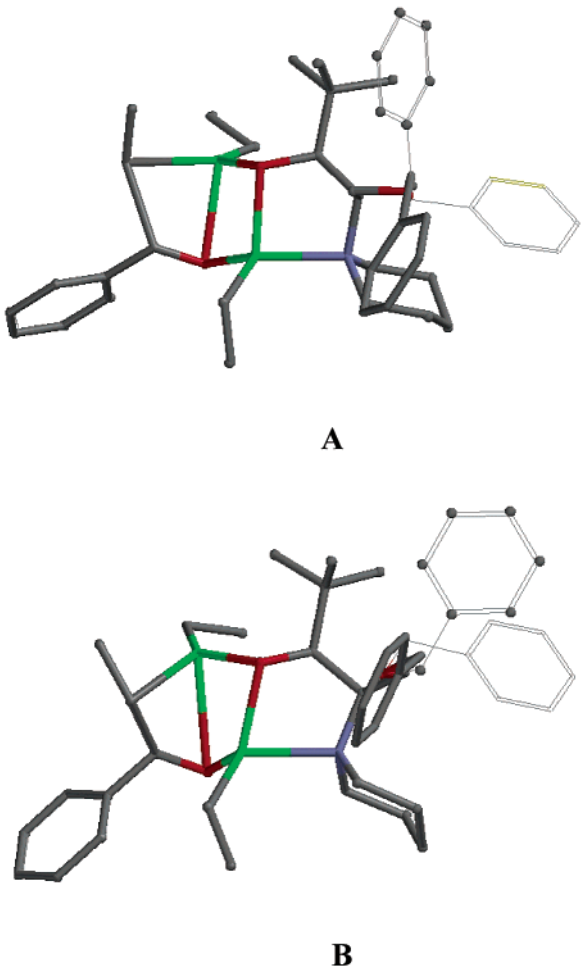


FIGURE 3. Superposition of the conformer TSs for **11c**. **A**, *anti*-(*S*); **B**, *anti*-(*R*) (hydrogen atoms have been omitted for clarity; N = blue, O = red, and Zn = green).

enhancement by polarization transfer (DEPT) experiments. High-resolution mass spectra (CI) were measured by the Unidade de Espectrometria de Masas, Universidade de Santiago de Compostela. Elemental analyses were performed by the Servei de Microanàlisi del CSIC de Barcelona. Chromatographic separations were carried out using Et_3N-pretreated (2.5% v/v) SiO_2 (70−230 mesh), eluting (unless otherwise stated) with hexanes−ethyl acetate mixtures of increasing polarity.

(2*S*,3*S*)-3-(1-Adamantyl)-2,3-epoxypropan-1-ol, 6a. The same procedure described above for the preparation of **5a** was followed, using the following amounts of reagents: allylic alcohol **10** (1.7 g, 8.84 mmol), $Ti(O^iPr)_4$ (130 μL, 0.44 mmol), L-(+)-DIPT (130 μL, 0.66 mmol), TBHP 5.4 M in isooctane (3.9 mL, 17.6 mmol), and 4 Å MS (0.56 g) in anhydrous CH_2Cl_2 (97 mL). A workup identical to the one described for **5a** followed by chromatography using hexane/EtOAc as the eluent afforded 1.44 g (80% yield) of **6a**. The enantiomeric purity of the product was determined to be 94% (determined by HPLC of its acetyl derivative; Chiralcel OD, 0.3 mL/min, hexane/*i*-PrOH (99/1), λ = 220 nm). After recrystallization from hexanes, ee increased to 98% (determined by DSC): mp 52−53 °C, $[\alpha]_D$ = −14.5 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53−1.74 (m, 12H), 1.98 (m, 3H), 2.60 (d, *J* = 2 Hz, 1H), 3.11 (m, 1H), 3.58 (m, 1H), 3.90 (m, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 27.9 (CH), 32.1 (C), 36.9 (CH_2), 36.9 (CH_2), 38.6 (CH_2), 54.1 (CH), 62.3 (CH_2), 64.0 (CH); IR (KBr) 3502, 2904, 1453, 1343, 1077, 1026, 888 cm^{-1}; MS (CI, NH_3) *m*/*z* 227 ($C_{13}H_{20}O_2$·H^+ + 18, 100), 226 ($C_{13}H_{20}O_2$ + 18, 91); Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.37; H, 9.95.

(2*S*,3*S*)-3-*tert*-Butyl-2-methoxymethyloxirane, 5b. A solution of **5a** (2.0 g, 15.36 mmol) in DMF (16 mL) was added via cannula to a suspension of sodium hydride (804 mg, ca. 18.43 mmol) in DMF (18 mL) at −20 °C, under N_2. The mixture was stirred at −20 °C for 20 min, and methyl iodide (1.2 mL, 19.97 mmol) was added via syiringe into the mixture. The mixture was stirred for 3 h, allowing it to warm to room temperature. MeOH (25 mL) and brine (40 mL) were added. The aqueous solution was extracted with Et_2O (3 × 60 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated carefully in vacuo (water bath at 0 °C) due to the high volatility of the product. The residual oil was chromatographed on silica gel, eluting with pentane/ether mixtures of increasing polarity. Compound **5b** (1.0 g, 90% yield) was isolated as an oil: $[\alpha]_D$ −4.2 (*c* 2.64, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 9H), 2.63 (d, *J* = 3 Hz, 1H), 3.01 (m, 1H), 3.36 (dxd, *J* = 11 Hz, *J*′ = 5 Hz, 1H), 3.40 (s, 3H), 3.65 (dxd, *J* = 11 Hz, *J*′ = 3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7 (CH_3), 30.5 (C), 53.7 (CH), 59.0 (CH_3), 63.6 (CH), 72.9 (CH_2); IR (film) 2950, 1440, 1350, 1205, 1110, 875 cm^{-1}; MS (CI, NH_3) *m*/*z* 162 ($C_8H_{16}O_2^+$ + 18, 74), 91 (100).

(2*S*,3*S*)-2-Benzyloxymethyl-3-*tert*-butyloxirane, 5c. The same procedure described above for **5b** was followed using the following amounts of reagents: epoxy alcohol **5a** (2.0 g, 15.36 mmol) in DMF (16 mL), NaH (804 mg, ca. 18.43 mmol) in DMF (16 mL), and benzyl bromide (2.4 mL, 19.97 mmol). After one workup identical to the one described for **5b** and purification by column chromatography eluting with hexane/ether (from 100/0 to 90/10), **5c** was isolated in quantitative yield as a dense oil: $[\alpha]_D$ −4.3 (*c* 0.77, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (s, 9H), 2.60 (d, *J* = 2 Hz, 1H), 3.04 (m, 1H), 3.40 (dxd, *J* = 11 Hz, *J*′ = 6 Hz, 1H), 3.70 (dxd, *J* = 11 Hz, *J*′ = 3H, 1H), 4.54 (m, 2H), 7.31 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.6 (CH_3), 30.4 (C), 53.8 (CH), 63.5 (CH), 70.6 (CH_2), 72.9 (CH_2), 127.4 (CH), 127.5 (CH), 128.1 (CH), 137.8 (C); IR (film) 3031, 2960, 2869, 1455, 1364, 1104, 737 cm^{-1}; MS (CI, NH_3) *m*/*z* 238 ($C_{14}H_{20}O_2^+$ + 18, 100); HRMS (CI) calcd for $C_{14}H_{20}0_2$·H^+ 221.1541, found 221.1522.

(2*S*,3*S*)-3-*tert*-Butyl-2-triphenylmethoxymethyloxirane, 5d. Epoxy alcohol **5a** (265 mg, 2.03 mmol) and *N*-triphenylmethylpyridinium tetrafluoroborate (1.5 g, 3.65 mmol) in acetonitrile (5 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 purified by chromatography using hexane/Et_2O (from 100/0 to 90/10) to give 655 mg (87%) of **5d** as a solid. Recrystallization from hexane increased the product's ee from 96 to 99% (determined by DSC): mp 104−106 °C; $[\alpha]_D$ +6.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (s, 9H), 2.60 (d, *J* = 2 Hz, 1H), 3.02−3.27 (m, 3H), 7.22−7.49 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.8 (CH_3), 30.6 (C), 54.0 (CH), 64.2 (CH), 65.1 (CH_2), 86.6 (C), 127.0 (CH), 127.8 (CH), 128.7 (CH), 143.9 (C); IR (KBr) 3070, 2960, 1451, 1364, 1214, 1070, 903, 791 cm^{-1}; MS (CI, NH_3) *m*/*z* 390 ($C_{26}H_{28}O_2^+$ + 18, 1), 243 (CPh_3^+, 100). Anal. Calcd for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 83.82; H, 7.71.

(2*S*,3*S*)-3-(1-Adamantyl)-2-methoxymethyloxirane, 6b. The same procedure described above for **5b** was followed using the following amounts of reagents: epoxy alcohol **6a** (200 mg, 0.960 mmol), NaH (54 mg, ca. 1.248 mmol), and MeI (97 μL, 1.560 mmol) in anhydrous DMF (2 mL). After the usual workup and purification by flash chromatography, **6b** was obtained in quantitative yield: $[\alpha]_D$ −15.3 (*c* 1.38, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.54 (m, 6H), 1.70 (m, 6H), 1.98 (m, 3H), 2.48 (d, *J* = 2 Hz, 1H), 3.10 (m, 1H), 3.34 (dxd, *J* = 11 Hz, *J*′ = 6 Hz, 1H), 3.39 (s, 3H), 3.62 (dxd, *J* = 11 Hz, *J*′ = 3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9 (CH), 32.1 (C), 36.9 (CH_2), 38.5 (CH_2), 52.4 (CH), 59.0 (CH_3), 64.0 (CH), 73.2 (CH_2); IR (film) 2906, 2850, 1453, 1198, 1121, 893 cm^{-1}; MS (CI, NH_3) *m*/*z* 240 ($C_{14}H_{22}O_2^+$ + 18, 100), 223 ($C_{14}H_{22}O_2$·H^+, 3).

(2*S*,3*S*)-3-(1-Adamantyl)-2-benzyloxymethyloxirane, 6c. The same procedure described above for **5b** was followed using the following amounts of reagents: epoxy alcohol **6a** (160 mg, 0.768 mmol), NaH (50 mg, ca. 0.998 mmol), and benzyl bromide (165 μL, 1.152 mmol) in anhydrous DMF (2 mL). After the usual workup and purification by column chromatography, 211 mg (92% yield) of **6c** was isolated as an oil: $[\alpha]_D$ −10.4 (*c* 1.47, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (m, 6H), 1.67 (m, 6H), 1.97 (m, 3H), 2.47 (d, J = 2 Hz, 1H), 3.13 (m, 1H), 3.42 (dxd, J = 13 Hz, J' = 6 Hz, 1H), 3.70 (dxd, J = 13 Hz, J' = 3 Hz, 1H), 4.56 (m, 2H), 7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.9 (CH), 32.1 (C), 36.8 (CH_2), 38.5 (CH_2), 52.5 (CH), 64.0 (CH), 70.9 (CH_2), 73.0 (CH_2), 127.5 (CH), 127.6 (CH), 128.2 (CH) 137.9 (C); IR (film) 3050, 2906, 2850, 1453, 1100, 893, 735 cm^{-1}; MS (CI, NH_3) *m*/*z* 316 ($C_{20}H_{26}O_2^+$ + 18, 100), 299 ($C_{20}H_{26}O_2{\cdot}H^+$, 7).

(1*S*,2*R*)-1-*tert*-Butyl-2-piperidino-1,3-propandiol, 11a. Piperidine (7.6 mL, 76.8 mmol) was added via syringe into a mixture of **5a** (1.0 g, 7.68 mmol) and $LiClO_4$ (12 g, 115.2 mmol) in acetonitrile (20 mL) under N_2. The resulting mixture was heated at reflux. After 24 h, the solution was cooled to room temperature, and water (40 mL) was added. The solution was extracted with CH_2Cl_2 (3 × 30), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residual crude was purified by column chromatography using hexane/EtOAc as the eluent to give 1.42 g (86% yield) of **11a** as a dense oil: $[\alpha]_D$ +18.0 (*c* 1.18, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.57 (m, 6H), 2.51 (m, 6H), 3.44 (d, J = 5 Hz, 1H), 3.79 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.1 (CH_2), 26.0 (CH_3), 26.7 (CH_2), 34.2 (C), 54.7 (CH_2), 61.0 (CH_2), 66.3 (CH), 81.5 (CH); IR (film) 3408, 2939, 1443, 1391, 1279, 1119, 897 cm^{-1}; MS (EI) *m*/*z* 128 ($C_5H_{10}NC^+HCH_2OH$, 29), 98 ($C_5H_{10}NC^+H_2$, 100); HRMS (CI) calcd for $C_{12}H_{25}NO_2{\cdot}H^+$ 216.1963, found 216.1963.

(1*S*,2*R*)-1-*tert*-Butyl-3-methoxy-2-piperidino-1-propanol, 11b. The same procedure described above for **11a** was followed, except that the reaction was carried out in a selaed tube, using the following amounts of reagents: epoxy ether **5b** (700 mg, 4.85 mmol), $LiClO_4$ (8.9 g, 83.2 mmol), and piperidine (5.5 mL, 55.5 mmol) in acetonitrile (20 mL). After 5 days at reflux, the reaction was quenched and treated as described for **11a** to give 625 mg (56% yield) of **11b**: $[\alpha]_D$ −23.8 (*c* 1.10, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.49 (m, 6H), 2.45 (m, 2H), 2.65 (m, 3H), 3.33 (s, 3H), 3.47 (m, 1H), 3.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7 (CH_2), 26.2 (CH_3), 26.5 (CH_2), 35.4 (C), 50.8 (CH_2), 58.8 (CH_3), 64.4 (CH), 70.7 (CH_2), 78.7 (CH); IR (film) 3487, 2933, 2805, 1457, 1364, 1106 cm^{-1}; EM (EI) *m*/*z* 184 (^{t}BuCHOHC$^+$HNC$_5$H$_{10}$, 27), 142 ($C_5H_{10}NC^+HCH_2OCH_3$, 100); HRMS (CI) calcd for $C_{13}H_{27}NO_2{\cdot}H^+$ 230.2120, found 230.2107.

(1*S*,2*R*)-3-Benzyloxy-1-*tert*-butyl-2-piperidino-1-propanol, 11c. The same procedure described above for **11a** was followed, using the following amounts of reagents: epoxy ether **5c** (600 mg, 2.72 mmol), $LiClO_4$ (4.3 g, 40.8 mmol), and piperidine (2.7 mL, 27.2 mmol) in dry acetonitrile (10 mL). After 4 days at reflux, the reaction was quenched and treated as described for **11a** to give 705 mg (85% yield) of **11c** as a dense oil: $[\alpha]_D$ −15.4 (*c* 1.25, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.48 (m, 6H), 2.42 (m, 2H), 2.68 (m, 2H), 2.86 (d, J = 9 Hz, 1H), 3.45 (m, 1H), 3.73 (d, J = 6 Hz, 2H), 4.51 (s, 2H), 7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.8 (CH_2), 26.2 (CH_3), 26.7 (CH_2), 35.5 (C), 50.8 (CH_2), 64.5 (CH), 68.2 (CH_2), 73.3 (CH_2), 78.9 (CH), 127.5 (CH), 127.6 (CH), 128.3 (CH), 137.8 (C); IR (film) 3494, 2934, 1455, 1362, 1090, 1003, 735 cm^{-1}; MS (EI) *m*/*z* 306 ($C_{19}H_{31}NO_2{\cdot}H^+$, 1), 218 ($C_5H_{10}NC^+$-$HCH_2OCH_2Ph$, 58), 184 (^{t}BuCHOHC$^+HNC_5H_{10}$, 24), 91 ($PhCH_2^+$, 100); HRMS (CI) calcd for $C_{19}H_{31}NO_2{\cdot}H^+$ 306.2433, found 306.2418.

(1*S*,2*R*)-3-Benzyloxy-1-*tert*-butyl-2-pyrrolidino-1-propanol, 11e. The same procedure described above for **11a** was followed, using the following amounts of reagents: epoxy ether **5c** (500 mg, 2.27 mmol), $LiClO_4$ (3.6 g, 34.05 mmol), and pyrrolidine (1.9 mL, 22.70 mmol) in dry acetonitrile (15 mL). After 4 days at reflux, the reaction was quenched and treated as described for **11a** to give **11e** in quantitative yield: $[\alpha]_D$ +5.0 (*c* 1.16, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.92 (m, 4H), 3.10 (m, 2H), 3.42 (m, 2H), 3.66 (s, 1H), 3.70−3.90 (m, 2H), 4.52 (s, 2H), 7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.1 (CH_2), 26.2 (CH_3), 35.2 (C), 45.5 (CH_2), 47.3 (CH_2), 51.4 (CH_2), 64.2 (CH), 68.0 (CH_2), 73.7 (CH_2), 77.5 (CH), 127.9 (CH), 128.0 (CH), 128.4 (CH), 137.1 (C); IR (film) 3429, 2956, 1625, 1455, 1098 cm^{-1}; MS (CI, NH_3) *m*/*z* 292 ($C_{18}H_{29}NO_2{\cdot}H^+$, 100); HRMS (CI) calcd for $C_{18}H_{29}NO_2{\cdot}H^+$ 292.2276, found 292.2280.

(1*S*,2*R*)-1-*tert*-Butyl-2-piperidino-3-triphenylmethoxy-1-propanol, 11d. The same procedure described above for **5d** was followed, using the following amounts of reagents: **11a** (520 mg, 2.41 mmol) and *N*-triphenylmethylpyridinium tetrafluoroborate (1.43 g, 3.48 mmol) in dry acetonitrile (10 mL). After column chromatography, 635 mg (60% yield) of **11d** was obtained: $[\alpha]_D$ −56.4 (*c* 1.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73 (s, 9H), 1.32 (m, 2H), 1.45 (m, 4H), 2.05 (m, 2H), 2.34 (m, 4H), 3.48 (m, 1H), 3.63 (d, J = 5 Hz, 1H), 7.10−7.60 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9 (CH_2), 25.9 (CH_2), 26.7 (CH_3), 35.4 (C), 54.9 (CH_2), 61.0 (CH_2), 69.8 (CH), 84.2 (CH), 87.2 (C), 126.9 (CH), 127.5 (CH), 129.2 (CH), 144.9 (C); IR (film) 3460, 3090, 2939, 1490, 1450,1219, 1115, 1048 cm^{-1}; MS (FAB+) *m*/*z* 458.3 ($C_{31}H_{39}NO_2{\cdot}H^+$, 14), 242.9 ($C^+Ph_3$, 100); HRMS (CI) calcd for $C_{31}H_{39}NO_2{\cdot}H^+$ 458.3059, found 458.3052.

(1*S*,2*R*)-1-*tert*-Butyl-3-*tert*-butyldiphenylsilyloxy-2-piperidino-1-propanol, 11f. A solution of **11a** (500 mg, 2.32 mmol), *tert*-butyldiphenylsilyl chloride (700 mg, 2.55 mmol), and imidazole (348 mg, 5.10 mmol) in anhydrous DMF (30 mL) was heated at 65 °C for 24 h under N_2. The reaction mixture was cooled to room temperatue, and Et_2O (20 mL) and brine (20 mL) were added. The aqueous layer was extracted with ether (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residual oil was purified by flash chromatography, affording 860 mg (82% yield) of **11f** as a dense oil: $[\alpha]_D$ −37.2 (*c* 4.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (s, 9H), 1.03 (s, 9H), 1.28 (m, 2H), 1.40 (m, 4H), 2.13 (m, 2H), 2.28 (m, 2H), 2.41 (dxd, J = 13 Hz, J' = 3 Hz, 1H), 2.62 (dxd, J = 13 Hz, J' = 7 Hz, 1H), 3.43 (d, J = 5 Hz, 1H), 3.78 (m, 1H), 7.30−7.80 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3 (C), 23.9 (CH_2), 25.8 (CH_2), 26.6 (CH_3), 27.0 (CH_3), 34.9 (C), 55.0 (CH_2), 63.8 (CH_2), 69.7 (CH), 85.2 (CH), 127.4 (CH), 127.6 (CH), 129.5 (CH), 129.7 (CH), 133.5 (CH), 134.3 (C), 135.8 (CH), 135.9 (CH); IR (film) 3107, 3072, 2936, 1474, 1428, 1113 cm^{-1}; MS (CI, NH_3) *m*/*z* 455 ($C_{28}H_{43}$-$NO_2Si{\cdot}H^+$ + 1, 35), 454 ($C_{28}H_{43}NO_2Si{\cdot}H^+$, 100); HRMS (CI) calcd for $C_{28}H_{43}NO_2Si{\cdot}H^+$ 454.3141, found 454.3140.

(1*S*,2*R*)-1-(1-Adamantyl)-2-piperidino-1,3-propandiol, 12a. The same procedure described above for **11a** was followed, using the following amounts of reagents: **6a** (200 mg, 0.96 mmol), piperidine (1.1 mL, 10.4 mmol), and $LiClO_4$ (1.7 g, 14.4 mmol) in dry acetonitrile (3 mL). After 24 h at reflux, the reaction was quenched and treated as described for **11a** to give 278 mg (98% yield) of **12a** as a dense oil: $[\alpha]_D$ +16.4 (*c* 0.98, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45−1.68 (m, 18H), 1.97 (m, 3H), 2.75 (m, 4H), 3.10 (b s, 2H), 3.29 (d, J = 5 Hz, 1H), 3.37 (m, 1H), 3.50 (m, 1H), 3.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5 (CH_2), 25.2 (CH_2), 28.3 (CH), 36.2 (C), 37.1 (CH_2), 38.6 (CH_2), 54.7 (CH_2), 60.9 (CH_2), 65.4 (CH), 82.2 (CH); IR (film) 3481, 2904, 2850, 1453, 1098, 623 cm^{-1}; MS (EI) *m*/*z* 98 ($C_5H_{10}NC^+H_2$, 100); HRMS (CI) calcd for $C_{18}H_{31}NO_2$ − H_2O 275.2249, found 275.2259.

(1*S*,2*R*)-1-(1-Adamantyl)-3-methoxy-2-piperidino-1-propanol, 12b. The same procedure described above for **11a** was followed, using the following amounts of reagents: **6b** (160 mg, 0.72 mmol), piperidine (1 mL, 10.1 mmol), and $LiClO_4$ (770 mg, 7.20 mmol) in dry acetonitrile (4 mL). After 4 days at reflux, the reaction was quenched and treated as described for **11a** to give 170 mg (77% yield) of **12b**: $[\alpha]_D$ −5.5 (*c* 1.40, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40−1.68 (m, 18H), 1.98

(m, 3H), 2.40−2.80 (m, 6H), 3.22 (m, 1H), 3.33 (s, 3H), 3.60 (d, J = 5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.7 (CH_2), 26.6 (CH_2), 28.4 (CH), 37.2 (C), 37.3 (CH_2), 38.1 (CH_2), 50.7 (CH_2), 58.8 (CH_3), 62.9 (CH), 70.8 (CH_2), 78.7 (CH); IR (film) 3477, 2904, 2848, 1451, 1345, 1306, 1106 cm^{-1}; MS (EI) m/z 262 ($C_{10}H_{15}CHOHC^+HNC_5H_{10}$, 25), 142 ($C_5H_{10}NC^+HCH_2$-$OCH_3$, 100); HRMS (CI) calcd for $C_{19}H_{33}NO_2 \cdot H^+$ 308.2589, found 308.2599.

(1*S*,2*R*)-1-(1-Adamantyl)-3-benzyloxy-2-piperidino-1-propanol, 12c. The same procedure described above for **11a** was followed, using the following amounts of reagents: **6c** (200 mg, 0.67 mmol), piperidine (1 mL, 10.1 mmol), and $LiClO_4$ (710 mg, 6.70 mmol) in dry acetonitrile (4 mL). After 4 days at reflux, the reaction was quenched and treated as described for **11a** to give 180 mg (70% yield) of **12c**: $[\alpha]_D$ −3.1 (*c* 0.69, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40−1.62 (m, 18H), 1.72 (m, 3H), 2.50−2.70 (m, 5H), 2.82 (m, 1H), 3.27 (m, 1H), 3.70 (d, J = 6 Hz, 1H), 4.51 (s, 2H), 7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7 (CH_2), 26.6 (CH_2), 28.3 (CH), 37.1 (C), 37.2 (CH_2), 38.0 (CH_2), 50.7 (CH_2), 63.1 (CH), 68.2 (CH_2), 73.2 (CH_2), 78.8 (CH), 127.5 (CH), 137.9 (C); IR (film) 3489, 3050, 2906, 2848, 1453, 1362, 1075 cm^{-1}; MS (CI, NH_3) m/z 384 ($C_{25}H_{37}$-$NO_2 \cdot H^+$, 27), 383 ($C_{25}H_{37}NO_2^+$, 100); HRMS (CI) calcd for $C_{25}H_{37}NO_2 \cdot H^+$ 384.2902, found 384.2901.

(1*S*,2*R*)-1-(1-Adamantyl)-2-piperidino-3-triphenylmethoxy-1-propanol, 12d. The same procedure described above for **5d** was followed, using the following amounts of reagents: **12a** (360 mg, 1.23 mmol) and *N*-triphenylmethylpyridinium tetrafluoroborate (1.0 g, 2.46 mmol) in dry acetonitrile (10 mL). After purification by flash chromatography, 410 mg (62% yield) of compound **12d** was obtained: $[\alpha]_D$ −27.2 (*c* 1.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25−1.58 (m, 18H), 1.82 (m, 3H), 2.03 (m, 4H), 2.33 (d, J = 5 Hz, 1H), 3.48 (m, 3H), 7.21−7.53 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9 (CH_2), 25.9 (CH_2), 28.4 (CH), 37.2 (CH_2), 37.4 (C), 38.4 (CH_2), 54.8 (CH_2) 61.1 (CH_2), 68.5 (CH), 84.5 (CH), 87.1 (C), 126.9 (CH), 127.4 (CH), 129.2 (CH), 144.9 (C); IR (film) 3200, 3058, 2902, 1490, 1266, 1048 cm^{-1}; MS (CI, NH_3) m/z 536 (M + 1, 41%), 535 (M^+, 100%). HRMS (CI) calcd for $C_{37}H_{45}NO_2$ 535.3450, found 535.3451.

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Supporting Information Available: Experimental procedures for the preparation of 1-adamantylcarbaldehyde and compounds **5a** and **7**−**10** and for the enantioselective addition of diethylzinc to aldehydes, as well as Cartesian coordinates and energies of transition states **14**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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