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Structural Optimization of Enantiopure 2-Cyclialkylamino-2-aryl-1,1-diphenylethanols as Catalytic Ligands for Enantioselective Additions to Aldehydes

Sergi Rodríguez-Escrich,[†] Katamreddy Subba Reddy,[‡] Ciril Jimeno,[†] Gisela Colet,[†] Carles Rodríguez-Escrich,[†] Lluís Solà,[†] Anton Vidal-Ferran,[†,§] and Miquel A. Pericàs*[,†,‡]

Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, E-43007 Tarragona, Spain, Department of Organic Chemistry, University of Barcelona, E-08028 Barcelona, Spain, and Catalan Institution for Research and Advanced Studies (ICREA), E-08010 Barcelona, Spain

mapericas@iciq.es

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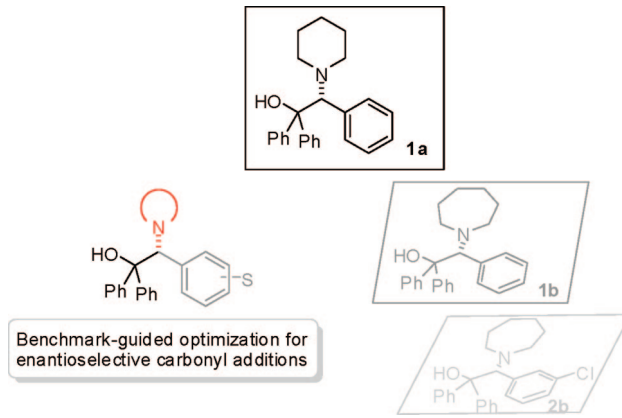

The structural optimization of a family of modular, enantiopure β-amino alcohol ligands with a common 2-amino-2-aryl-1,1-diphenylethanol skeleton, whose stereogenicity was introduced through the Jacobsen epoxidation of 1,1-diphenyl-2-arylethylenes, has led to the identification of a small set of optimal catalysts with enhanced activity and enantioselectivity in the addition of alkylzinc and arylzinc reagents to aldehydes. Criteria for the discrimination between apparently analogous, highly enantioselective ligands are proposed.

Introduction

Amino alcohols are among the most useful ligands for asymmetric catalysis because either on their own or in the form of their derivatives (oxazaborolidines, bis(oxazolines), phosphinooxazolines) they can effectively act as catalysts for a great variety of enantioselective reactions. However, many of them are still obtained from natural products, and fine-tuning of their structures for optimal catalytic behavior is not always easy.[1]

In response to this difficulty, the synthesis of new ligands based on achiral precursors and involving processes amenable to parallel synthesis appears as a most convenient alternative. Within this approach, exploration of diversity space by means of small, focused ligand libraries becomes straightforward and the subsequent, benchmark-guided structural optimization results are accelerated.

Some years ago, we proposed the synthesis of modular β-amino alcohol ligands from synthetic yet enantiopure epoxides prepared through the Sharpless[2] or Jacobsen[3] epoxidations. Work in this field has led to the preparation of four regioisomeric families of ligands, as depicted in Figure 1. The absolute stereochemistry of these molecules is fixed in the preparation

[†] Institute of Chemical Research of Catalonia.
[‡] University of Barcelona.
[§] ICREA.

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

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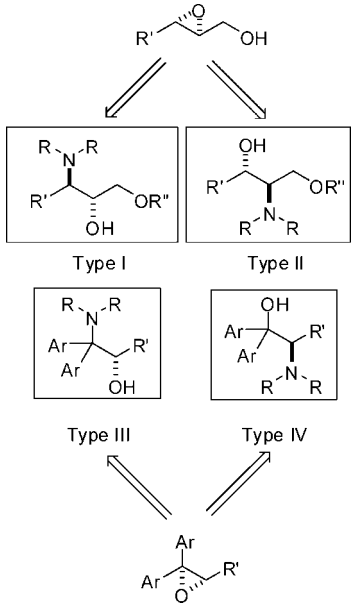


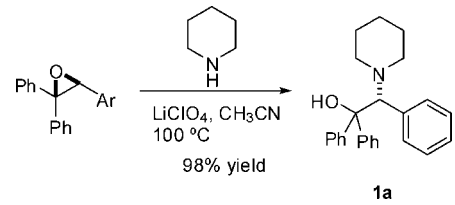
FIGURE 1. Structural types of β-amino alcohols developed at our research group from enantiopure Sharpless (Types I and II) and Jacobsen (Types III and IV) epoxides.

of the precursor epoxides and can be predictably selected. Then, regioselective and stereospecific ring opening with amines yields the enantiopure amino alcohols. In this way, type I[4] and II[5] ligands are prepared via Sharpless epoxidation, whereas type III[6] and IV[7] ligands stem from Jacobsen epoxidation. All of them are fully modular and possess the following common features of structural diversity: the skeletal groups (Ar and R′), coming from the starting olefins, the dialkylamino groups, arising from epoxide ring-opening steps, and in the cases of type I and II ligands, the *O*-protecting group R″.

The role of the different modules in the control of catalytic activity and enantioselectivity has been analyzed for type I and type II ligands in detail, with the finding that important catalytic characteristics can be traced to the nature of the dialkylamino substituent and to the steric bulk of the alkoxy group.[4,5,8] Second-generation ligands arising from type I amino alcohols, such as bis(oxazolines), oxazaborolidines, amino thiols, and imino alcohols (Schiff bases), have also been prepared in our group and successfully submitted to structural optimization for application in a variety of catalytic enantioselective reactions.[9]

2-Piperidino-1,1,2-triphenylethanol, **1a**[10] (Scheme 1), a type IV ligand synthesized in our group, turned out to be one of the most successful catalysts for the highly enantioselective addition of alkylzinc[7] and arylzinc[9i] reagents to aldehydes. It is, in fact, one of the readily available β-amino alcohol structures, since it can be prepared in two simple steps from commercially available

SCHEME 1. Preparation of 2-Piperidino-1,1,2-triphenylethanol, 1a



1a

triphenylethylene: Jacobsen epoxidation followed by regioselective and stereospecific ring opening of the enantiopure triphenyloxirane[11] with piperidine yields the desired amino alcohol in a straightforward manner. Initial efforts devoted to the optimization of the amino moiety were circumscribed to cyclic, six-membered amines using the enantioselective ethylation of aldehydes[7a] as a benchmark reaction. Working on the enantioselective methylation of aldehydes,[7b] it could also be established that **1a** was a far more active catalyst as compared to structural analogs containing acyclic dialkylamino substituents.[7b] However, no systematic approach had been tackled so far concerning an in-depth optimization of the structure of amino alcohols analogous to **1a** for catalytic applications.

Given the interest in **1a** for catalytic enantioselective arylation,[9j] we decided to undertake a systematic exploration of variations in its structure that could lead to even more efficient and enantioselective ligands. Bearing in mind the parallelism recorded so far in the catalytic activity displayed by **1a** in ethylation, methylation, and arylation, we decided to use the experimentally simpler ethylation reaction as a benchmark for the optimization process.

The optimization procedure followed has been represented in Figure 2. It is based in preserving the diphenylcarbinol moiety, whose beneficial characteristics in catalysis are well-known,[12] while sequentially exploring the influence of the amino and the skeletal aryl moieties. The best hits obtained by this procedure will be eventually fine-tuned, focusing on the amino moiety.

This project involved as a requisite the synthesis by Jacobsen epoxidation of a full set of new 2-aryl-1,1-diphenylethylene oxides with aryl groups covering a wide range of electronic and steric diversity.

Herein we report on the different stages of this structural optimization process and on analysis methods for the discrimination between ligands of similar, very high efficiency.

Results and Discussion

Jacobsen Epoxidation of 1,1-Diphenyl-2-arylethylenes. To ensure that a maximum of electronic and steric diversity was

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(8) Jimeno, C.; Vidal-Ferran; A.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 3895.

(9) (a) Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902. (b) Jimeno, C.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1999**, *40*, 777. (c) Jimeno, C.; Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 3157. (d) Pastó, M.; Riera, A.; Pericàs, M. A. *Eur. J. Org. Chem.* **2002**, 2337. (e) Jimeno, C.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synlett* **2001**, 1155. (f) Pericàs, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gómez, M.; Jiménez, F.; Muller, G.; Rocamora, M. *Chem. Eur. J.* **2002**, *8*, 4164. (g) Fontes, M.; Verdaguer, X.; Solà, L.; Vidal-Ferran, A.; Reddy, K. S.; Riera, A.; Pericàs, M. A. *Org. Lett.* **2002**, *4*, 2381. (h) Ferrer, S.; Pastó, M.; Rodríguez, B.; Riera, A.; Pericàs, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1747. (i) Rodríguez, B.; Pastó, M.; Jimeno, C.; Pericàs, M. A. *Tetrahedron: Asymmetry* **2006**, *17*, 151. (j) Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532. (k) Popa, D.; Puigjaner, C.; Gómez, M.; Benet-Buchholz, J.; Vidal-Ferran, A.; Pericàs, M. A. *Adv. Synth. Cat.* **2007**, *349*, 2265.

(10) Ligand **1a** is now commercially available from Aldrich and Acros.

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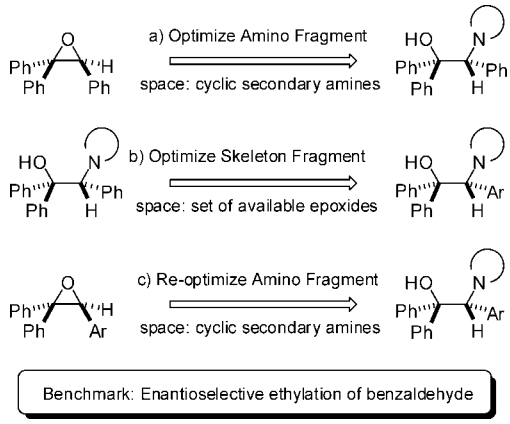
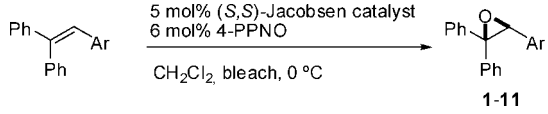


FIGURE 2. Benchmark-guided synthesis of amino alcohol ligands.

SCHEME 2. Jacobsen Epoxidation of Trisubstituted Olefins with Different Stereoelectronic Modulation in One Aromatic Ring (Ar) and a Fixed Diphenylmethylene Moiety[a]



[a] See details in Table 1.

TABLE 1. Jacobsen Epoxidation of Trisubstituted Olefins

compound	Ar substituent	yield (%)[a]	ee (%)[b]
1[c]	Ph	97	92 (>99)
2	*m*-ClC_6H_4	77	88 (>99)
3	*o*-ClC_6H_4	95	83 (>99)
4	*p*-$NO_2C_6H_4$	>99	96 (>99)
5[d]	*p*-FC_6H_4	93	93 (>99)
6[d]	*p*-$MeOC_6H_4$	92	90 (>99)
7	2-Naphthyl	96	94 (>99)
8	CH_3	27	95 (>99)
9	*p*-$CH_3C_6H_4$	75	94 (>99)
10	*m*-$CH_3C_6H_4$	76	84 (>99)
11	*o*-$CH_3C_6H_4$	53	77 (>99)

[a] Isolated yield. [b] Determined by HPLC with a chiral stationary phase. In parentheses is the ee after recrystallization from hexanes. [c] See ref 7a. [d] See ref 7c.

found in the triarylethylene skeleton of the target ligands, a family of known olefins[13] containing a diphenylmethylene subunit and accommodating different electron-donating and electron-withdrawing groups in the third aryl moiety were selected. The presence in the starting olefins of a diphenylmethylene moiety plays a double role for the purposes of this investigation: Besides being the ultimate source of the diphenylcarbinol moiety in the target amino alcohols, the symmetrical substitution at one of the alkene termini suppresses stereochemical problems at the olefination and epoxidation steps. After submitting this set of trisubstituted alkenes to Jacobsen epoxidation using standard conditions (Scheme 2),[14] we were able to isolate the corresponding oxiranes in excellent yields and high enantioselectivities (Table 1) in a multigram scale. It is important to point out that in all cases, the epoxide could be

(13) All olefins used as substrates in the present study are known compounds. See Supporting Information for synthetic details and references.

(14) (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296. (c) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (d) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. II, pp 649−678.

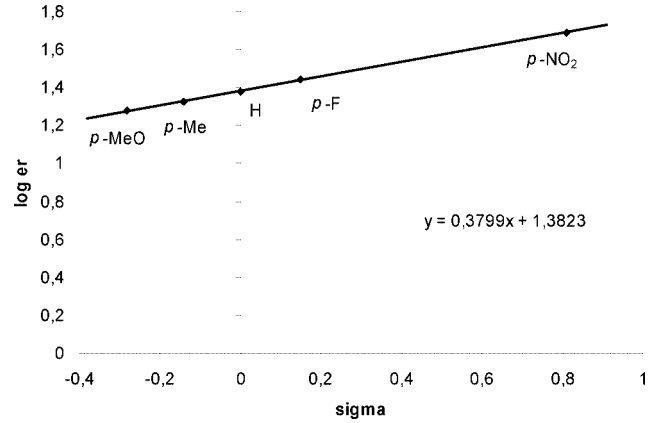


FIGURE 3. Hammett plot of the Jacobsen epoxidation of *para*-substituted 1,1-diphenyl-2-arylethylenes.

obtained in ≥99% ee, either after the reaction or (for compounds **2**, **3**, **10**, and **11**) by simple recrystallization from hexanes (Table 1).

When we analyzed the results obtained for the epoxidation of a set of electronically diverse triarylethylenes, we realized that we might be able to correlate the enantioselectivity of the catalytic reaction (in the form of enantiomeric ratio of the epoxides before recrystallization) with the structure of the trisubstituted olefin/epoxide. A Hammett plot of the log of the ratio of epoxide enantiomers against σ_p values of the *para* substituents in epoxides **1**, **4**, **5**, **6**, and **9** gave a perfect linear fit, with slope $\rho = 0.38$ (Figure 3). Electron-withdrawing substituents in the alkene favor the epoxidation and give higher enantioselectivities than the electron-donating ones. The linearity of the Hammett plot ultimately indicates that the variation of the enantioselectivity throughout the considered series of olefins reflects changes in the relative energies of the corresponding transition states induced by the electronic nature of the *para* substituent in the aryl group.

Previous studies of electronic effects on the Jacobsen epoxidation were restricted to the catalyst itself.[15] Jacobsen et al. analyzed the effect of the substituents on the salicylaldehyde moiety of the salen ligand and showed linear free-energy correlations for several olefin substrates. For a given substrate, the enantioselectivity achieved with the different catalysts displayed a linear relationship with the Hammett parameter σ_p of the substituent on the *para* position of the phenoxy group in the salen moiety. Electron-donating substituents stabilize the Mn(V) oxo complex, generating a relatively milder oxidant which, according to the Hammond postulate, transfers oxygen to the alkene via a more product-like transition state. Later transition states favor a smaller separation between substrate and catalyst and facilitate a better differentiation of the diastereomeric transition states, thus leading to higher degrees of enantioselectivity.[15] A recent report has complemented those studies by establishing quantitative correlations between modified Hammett parameters ($\sigma+$) with the electronic properties of the catalyst and the transition state geometries,[16] but to our knowledge there are no previous quantitative correlations between the enantioselectivity of the reaction and the electronic properties of the substrate olefins.[17,18]

As expected, the electronic effects described in the literature for a series of catalysts (electron-donating substituents increase the efficiency of the catalyst) are opposite to what we observe in the triarylethylenes (electron-withdrawing substituents favor

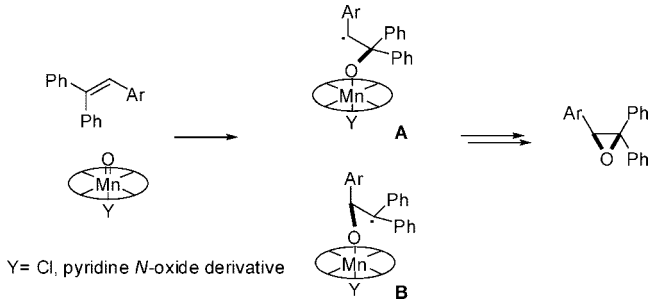


FIGURE 4. Radical pathways for the formation of triarylethylene oxides by Jacobsen epoxidation.

the epoxidation and lead to higher enantioselectivities). This is in accordance with the reactivity-selectivity principle, since the more electron-poor the oxidizing agent (or the more electron-rich the alkene) the more reactive the system will be, with the consequent erosion in the enantioselectivity of the process. As far as the magnitude of these effects is concerned, the electronic effects of the substituents on the alkene are less pronounced than those produced by the substituents on the catalyst. A lower ρ value is observed in our case ($\rho = 0.38$) for the whole substrate series with the standard Jacobsen catalyst compared with the ρ value which is reported for isochromene with a series of catalysts ($\rho = -1.37$).[15] This ultimately reflects that enantioselectivities (ranging from 92% to >99% ee) are not so dramatically affected along the alkene series, while the selectivity displayed by the catalyst is much more strongly dependent on the nature of the *para* substituent in the catalyst structure (22−96% ee for isochromene[15a]).

As it has been mentioned already, the linearity in the Hammett plot indicates that, in our case, the changes in enantioselectivity should arise from changes in the electronic character of the relevant transition states. Given the nonsymmetric substitution of the olefin substrates in the present study, two possible monoradicals, namely, **A** and **B**, may arise (see Figure 4). Our working hypothesis was based in the assumption that the bis-benzylic radical **B** would be preferentially formed, and therefore the ee of the process would be governed by the first elementary step, that is, the radical combination of the manganese oxide to the monosubstituted end of the olefin. Considering that the manganese atom suffers a global two-electron reduction, the olefin has to contribute with one electron to this first step. Consequently, electron-donating substituents will render more reactive olefins which add to the manganese oxo complex in earlier transition states, thus affording lower levels of enantioselectivity. On the other hand, electron-withdrawing groups attenuate the reactivity of the olefin, which as a result reacts through later transition states affording higher enantioselectivities.

Preparation of Amino Alcohols. Ring opening of the epoxides was carried out using Crotti's conditions.[19] The nature of the prepared amino alcohols, i.e., the different combinations

SCHEME 3. Epoxide Opening with Secondary Amines To Afford β-Amino Alcohols

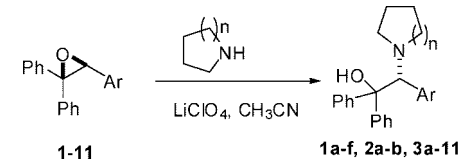
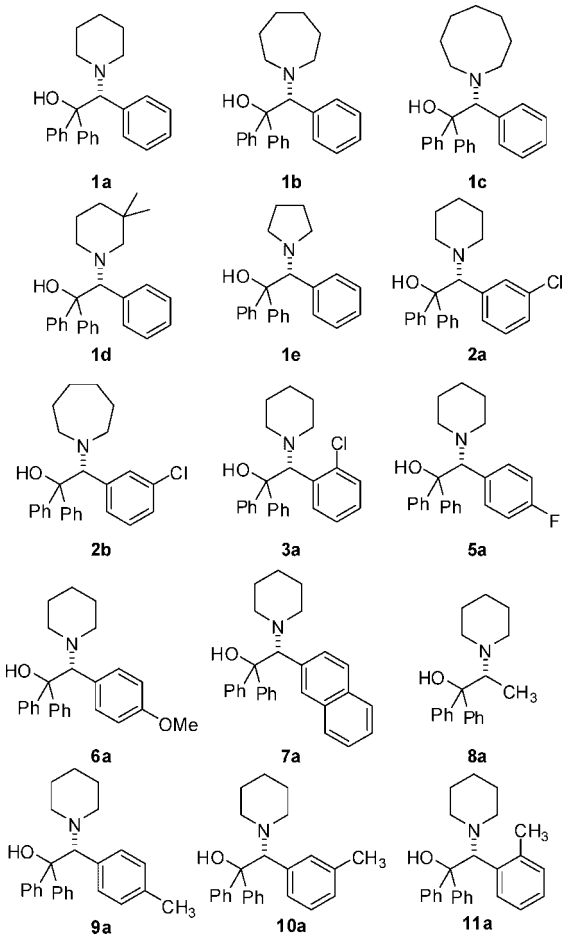


CHART 1. Amino Alcohols Synthesized by Ring Opening of Epoxides 1−11



of epoxide with cyclic amines, was dictated by the progress of the optimization process. Several cyclic secondary amines (pyrrolidine, piperidine, 3,3-dimethylpiperidine, hexamethyleneimine, and heptamethyleneimine) were used (Scheme 3). The overrepresentation of piperidine-containing amino alcohols reflects the results of the optimization process (see below), in agreement with what is observed in the β-amino alcohol catalysts previously designed by us.[4,7] Despite its potential interest,[4b] no α-substituted amines could be evaluated in the optimization process because of their lack of reactivity in the ring-opening reaction.

We have depicted the structures of the β-amino alcohols synthesized in the course of this work in Chart 1 (amino alcohols are designated by the same number as their parent epoxides and a letter that indicates the cyclialkylamino fragment in their structures).

The absolute configuration of the amino alcohols depicted in Chart 1 was assigned as follows: For those derived from triphenylethylene oxide (**1a−e**), the configuration is deduced

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(16) Cavallo, L.; Jacobsen, H. *J. Org. Chem.* **2003**, *68*, 6202.

(17) For the Hammett correlation ($\sigma+$) to relative epoxidation rates of styrenes by a chiral ruthenium-porphyrin catalyst, see: Zhang, R.; Yu, W.-Y.; Wong, K.-Y.; Che, C.-M. *J. Org. Chem.* **2001**, *66*, 8145.

(18) For a qualitative correlation of enantioselectivity with the electronic properties of the substrate in the epoxidation of styrenes catalyzed by a chiral dioxirane, see: Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5794.

TABLE 2. Preparation of Amino Alcohol by $LiClO_4$-Mediated Ring Opening of Triarylethylene Oxides with Secondary Amines

compound	amino group	yield (%)[a]
1a[b]	piperidino	98
1b	hexamethyleneimino	90
1c	heptamethyleneimino	18
1d	3,3-dimethylpiperidino	99
1e	pyrrolidino	91
2a	piperidino	72
2b	hexamethyleneimino	72
3a	piperidino	9
4a	piperidino	0
5a	piperidino	93
6a	piperidino	75
7a	piperidino	63
8a	piperidino	97
9a	piperidino	93
10a	piperidino	66
11a	piperidino	43

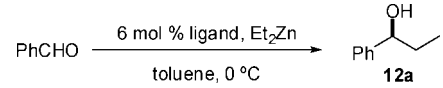
[a] Isolated yield. [b] See ref 7a.

from the known configuration (*S*) of the epoxide obtained with the (*S,S*)-enantiomer of the Jacobsen catalyst and assuming that the ring opening of the epoxide takes place with inversion of configuration, as confirmed by X-ray diffraction of **1a**.[7a] In all other cases, configurations have been assigned by assuming that the epoxidation of 2-aryl-1,1-diphenylethenes with the (*S,S*)-enantiomer of the Jacobsen catalyst leads to the corresponding *S* epoxides, as predicted by the empirical model developed by Jacobsen,[11] and that the ring opening of the epoxides with the cyclic, secondary amines employed in this study takes place with inversion of configuration. It is to be noted that the sign of the enantioselectivity observed in carbonyl additions mediated by amino alcohols **1a−f**, **2a,b**, and **3a−11a** is fully consistent with the assigned configurations.

Epoxide ring-opening reactions proceeded generally in good to excellent yields (Table 2), except for epoxide **4**, which proved reluctant to react. In spite of harsh reaction conditions being explored, the ring-opening product **4a** could not be detected in the reaction crudes. Lower yields were obtained when epoxides with *ortho* substituents were used, and therefore amino alcohols **3a** (*o*-Cl) and **11a** (*o*-CH_3) were isolated in only 9% and 43% yield, respectively. When a specially hindered amine such as heptamethyleneimine was used in combination with epoxide **1**, amino alcohol **1c** was obtained in a low 18% as well. All other examples, though, account for the usefulness of the ring-opening process, which takes place with total regioselectivity and inversion of the configuration at the stereocenter where the amine attack takes place.

Benchmark-Guided Optimization of Ligands: Catalytic Enantioselective Additions of $ZnEt_2$. As already mentioned, the choice of amino alcohol ligands in this study was driven by the sequential optimization process that took place as outlined in the Introduction (see Figure 2). In the first optimization step triphenylethylene oxide was opened with several cyclic amines to generate ligands **1a−1e**, and the resulting amino alcohols were benchmarked for enantioselectivity in the ethylation of benzaldehyde. Since **1a** turned out to be the optimal ligand in this test, analogues of this structure where the nonphenyl aryl group was systematically varied with respect to electronic and steric effects (**2a−11a**) were prepared and evaluated. This process converged again on **1a** as the optimal combination of triarylethylene skeleton and cyclialkylamino fragment. Finally, the structural features of the second best hit in the first optimization step (**1b**) were combined with those of the second best hit in the second optimization step (**2a**), and amino alcohol **2b** was prepared. The catalytic profile displayed by these ligands in the diethylzinc addition to benzaldehyde (benchmark reaction) is illustrated in Table 3. The conditions involved the use of 6 mol % of ligand in toluene at 0 °C.

TABLE 3. Diethylzinc Additions to Benzaldehyde Catalyzed by Amino Alcohols 1a−11a (Data for Optimal Ligands Appear Bold)



ligand	conversion (%)[a]	selectivity (%)[a]	ee (%)[a]
1a[b]	**99**	**99**	**98**
1b	**100**	**100**	**98**
1c	100	99	92
1d	100	99	95
1e	99	99	81
2a	99	99	96
2b	**100**	**99**	**98**
3a	94	98	69
5a	95	96	96
6a	99	93	95
7a	94	88	71
8a	99	99	86
9a	92	96	94
10a	99	94	95
11a	99	99	96

[a] Determined by GC using a β-DEX capillary column. [b] See ref 7a.

As seen in the table, the first optimization step gave **1b** (containing a hexamethyleneimino group) as the second best ligand, together with the reference ligand **1a**. As for the second step, the most promising results were provided by the introduction of a *meta*-chloro substituent (**2a**), which guided the third and last step toward **2b**, containing both the *meta*-chloro and hexamethyleneimino moieties. Thus, a reduced set of optimal ligands (**1a**, **1b**, and **2b**) arose from the optimization process (with **2a** as the fourth place candidate). However, the high catalytic profile of all these ligands posed some problems for the identification of the absolute best hit.

Although enantioselectivity is generally used as the most important criteria for the selection of optimal ligands, differences in catalytic activity between ligands with similar enantioselectivity profiles have much deeper consequences on the practical value and economical interest of the processes where they participate. According to this idea, we decided to compare **1a**, **1b**, and **2a** from the points of view of catalytic activity and of enantioselectivity. Consequently, in order to gain a better insight of the catalytic activity of the three best ligands, the diethylzinc addition to benzaldehyde mediated by **1a**, **1b** and **2b** was monitored by in situ FTIR analysis. This technique uses an FTIR probe based on attenuated total reflection (ATR) directly immersed in the reaction media and records spectra of the solution in contact with the probe at defined time intervals. It has the advantages of being very simple to use and non invasive, and allows following the process in real time. In the present case, the addition reaction could be easily monitored following the absorbance at 1710 cm^{-1}, due to the characteristic stretching vibration of the carbonyl group in benzaldehyde. Thus, the decrease of the absorbance at this wavenumber is directly related to the conversion of the starting aldehyde in the reaction media.

The plots of the normalized absorption of the C═O group of benzaldehyde versus time are shown in Figure 5. Clear differences in catalytic activity are found for the three ligands

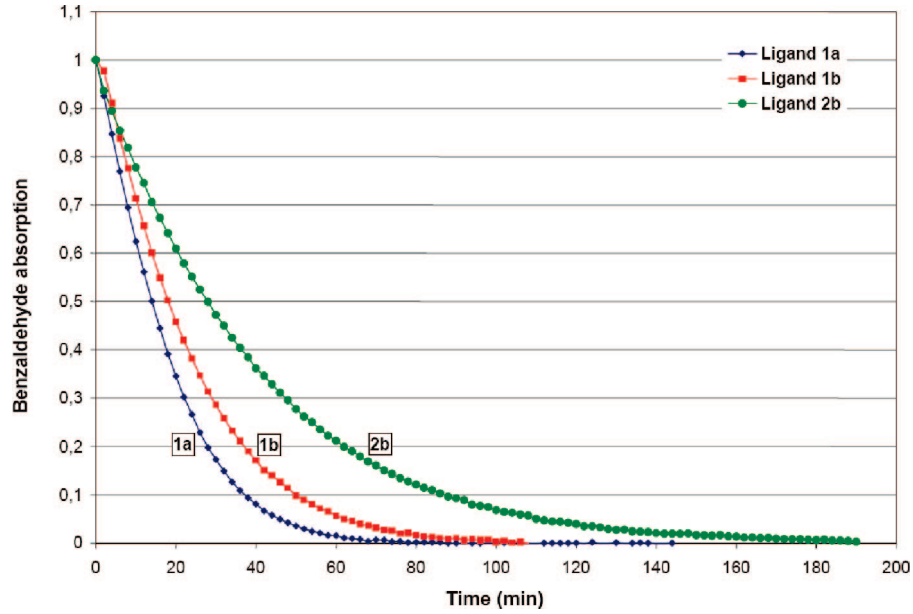
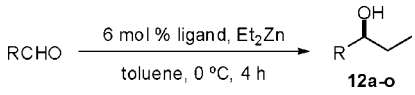


FIGURE 5. Comparison of the catalytic activity of ligands **1a**, **1b**, and **2b** in the addition of diethylzinc to benzaldehyde.

TABLE 4. Addition of Diethylzinc to Aldehydes Catalyzed by 1b and 2b



		ligand **1b**		ligand **2b**	
entry	aldehyde (product)	conv (%)[a]	ee (%)[a]	conv (%)[a]	ee (%)[a]
1	benzaldehyde (**12a**)	>99	98	>99	98
2	*o*-fluorobenzaldehyde (**12b**)	nd	nd	>99	95
3	*o*-tolualdehyde (**12c**)	>99	97	99	96
4	*o*-methoxybenzaldehyde (**12d**)	99	97	98	99
5	*m*-fluorobenzaldehyde (**12e**)	>99	97	>99	97
6	*m*-tolualdehyde (**12f**)	99	98	97	97
7	*m*-methoxybenzaldehyde (**12g**)	>99	98	>99	97
8	*p*-fluorobenzaldehyde (**12h**)	>99	98	>99	98
9	*p*-tolualdehyde (**12i**)	>99	98	>99	97
10	*p*-methoxybenzaldehyde (**12j**)	96	98	96	96
11	cinnamaldehyde (**12k**)	nd	nd	99	85
12	heptanal (**12 l**)	99	92	>99	84
13	3-phenylpropanal (**12m**)	99	93	99	86
14	2-ethylbutiraldehyde (**12n**)	99	97	91	96
15	(*E*)-α-methylcinnamaldehyde (**12o**)	96	97	62	94

[a] Determined by GC using a β-DEX capillary column.

studied. Amino alcohol **1a** exhibits the highest catalytic activity; thus, when the addition reaction is catalyzed by ligand **1a,** benzaldehyde is completely consumed within 1 h. On the other side, amino alcohol **2b** is the less active ligand in the group; it takes up to 3 h for total consumption of benzaldehyde when **2b** is used in the reaction. Ligand **1b**, in turn, possesses an intermediate activity, requiring 2 h for total benzaldehyde consumption.

For comparison of the enantioselectivity induced by the three ligands, **1b** and **2b** were tested in the ethylation of a representative family of aldehydes (the corresponding results for **1a** have been previously reported[7a]).

We have collected in Table 4 the conversions and enantioselectivities recorded for the diethylzinc addition to the selected family of aldehydes using ligands **1b** and **2b**. Remarkably, in entries 1 and 6−10 for **1b** and 1, 4, and 8 for **2b** the results obtained are comparable or superior to the ones displayed by ligand **1a**.[7a]

At first sight differences between both ligands are minimal, but as illustrated in Table 4, they behave in a slightly different manner depending on the substrate. Therefore, **1b** gives consistently high levels of stereoinduction (98% ee) in *meta*- and *para*-substituted aromatic aldehydes (entries 6−10), whereas **2b** is extremely enantioselective (99% ee, entry 4) in the diethylzinc addition to *o*-methoxybenzaldehyde. For example, enantiopure 1-aryl-1-propanols and, in particular, 1-(*o*-methoxyphenyl)-1-propanol, are basic building blocks of a recently discovered family of calcium receptor agonists.[20]

From a global perspective, the catalytic behavior of **1b** and **2b** in the enantioselective ethylation of aldehydes is very similar to that of **1a**, so that the results obtained using *standard* amounts of ligand do not allow drawing definitive conclusions on the existence of an optimal ligand within the considered set. Therefore, we decided to push the catalytic profile of these molecules to the limit by decreasing the catalyst loading to 0.5 mol %. Noteworthy, this is 1 order of magnitude below the usual amount of chiral ligand normally employed in this type of reaction. Under these conditions, a selection of aldehydes was reacted with Et_2Zn, and the results are summarized in Table 5.

In general, ligand **1a** proved superior in terms of conversion, while the differences observed in enantioselectivity were not significant in most of the cases studied. It is interesting to realize that the more reactive, electron-poor substrates like *p*-trifluoromethylbenzaldehyde (entry 2) are completely converted despite the very low amount of catalytic ligand used. As a general trend, the differences between ligands are accentuated when poorly reactive, electron-rich aldehydes are used as substrates (entries 1 and 4−7). Thus, although these reactions were not optimized for complete conversion, it is clear that

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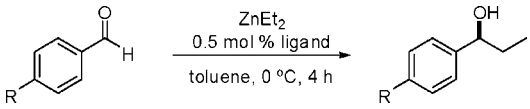
TABLE 5. Addition of Diethylzinc to Aldehydes Catalyzed by 1a, 1b, and 2b in the Presence of 0.5 mol % Ligand



		ligand **1a**		ligand **1b**		ligand **2b**	
entry	R	conv (%)[a]	ee (%)[a]	conv (%)[a]	ee (%)[a]	conv (%)[a]	ee (%)[a]
1	CH_3	63.9	94.9	56.3	94.2	44.4	93.0
2	CF_3	99.1	95.8	99.0	94.5	97.8	93.9
3	F	69.1	94.6	60.1	93.8	53.0	93.6
4	CH_3O	44.5	94.6	23.0	94.3	23.1	92.6
5	H	85.7	95.4	81.6	95.1	60.0	93.7
6	*t*-Bu	49.7	94.9	50.1	94.7	39.1	93.7
7	Ph	77.0	94.7	71.7	93.7	61.0	92.9

[a] Determined by GC using a β-DEX capillary column.

electron-rich substrates represent the most stringent test for the discrimination between highly active ligands.

Catalytic Enantioselective Additions of $ZnMe_2$. Although chiral 1-aryl ethanols are more important building blocks than 1-aryl propanols, they are usually prepared by asymmetric ketone reduction rather than by enantioselective methyl addition. This is basically due to the low reactivity of $ZnMe_2$ as compared to $ZnEt_2$, and thus improving the performance of such a reaction is of great practical interest.[21] In a recent paper, we established that the presence of cyclic amino groups in triarylethylene derived amino alcohol ligands was crucial for the achievement of high conversions and enantioselectivities in this reaction. In particular, we found that ligand **1a** was very useful for this transformation, although methylations induced by this ligand were still slow if compared with the corresponding $ZnEt_2$ addition.[7b] According to this characteristic, the amino alcohol promoted methylation of aldehydes appeared as an appropriate benchmark for the systematic evaluation of the optimal ligands **1a**, **1b**, and **2b.** In addition, the identification of new ligands able to efficiently mediate the enantioselective methylation of aldehydes is a matter of considerable interest. Thus, **1a**, **1b**, and **2b** were evaluated in the methylation of a representative group of aldehydes, results being summarized in Table 6. These reactions were carried out with a 10 mol % of catalyst loading at room temperature to drive the reaction at a reasonable rate. Still, 24 h were required to attain good conversions.

As it is readily seen, the behavior exhibited by **1a**, **1b**, and **2b** in the methylation of aldehydes almost exactly reproduces what is observed with the same ligands in the corresponding ethylation reactions. Thus, the use of ligand **1a** consistently leads to higher conversions and enantioselectivities, and only ligand **1b** shows comparable activity and enantioselectivity for the most reactive *p*-trifluoromethylbenzaldehyde (entry 7). On the other hand, ligand **2b** turned out to be clearly inferior for the asymmetric addition of $ZnMe_2$ to aldehydes. This shows that this particular addition reaction, characterized by higher activation energies, is more sensitive to structural variations in the ligand than the corresponding $ZnEt_2$ additions.

The trends of catalytic activity for the optimal ligands shown in Table 6 were made evident when the dimethylzinc addition to benzaldehyde was monitored by in situ FTIR for the three ligands (Figure 6). Since the catalytic addition of dimethylzinc is much slower than the addition of other alkyl or aryl zinc reagents and the background, noncatalytic reaction does not take place at a measurable rate, the reaction represents an optimal test to compare the catalytic performance of similar ligands. The addition reaction performed at 0 °C mediated by ligand **1a** proceeds with nearly total conversion after 24 h, whereas for ligands **1b** and **2b** full conversions are far from being achieved within the same reaction time (64% for **1b** and 39% for **2b** respectively). It is thus evident that ligand **1a** presents a much higher catalytic activity in comparison with ligands **1b** and **2b**.

Catalytic Enantioselective Arylation Reactions. Since the asymmetric reduction of diaryl ketones to afford enantiopure diarylmethanols is a difficult task due to the steric and electronic similarities between the *re* and *si* faces of the substrate,[22] the catalytic enantioselective addition of aryl fragments to aldehydes arises as the best method for the preparation of this class of compounds.[23] Although several new reagents, additives, and catalysts have been developed recently to substitute expensive diphenylzinc as a source of phenyl groups,[24–29] the formation and asymmetric addition of the mixed species EtPhZn (prepared from $ZnEt_2$ and $ZnPh_2$) introduced by Bolm is still a fast and simple way to perform this particular transformation.[27,9j] Key to the success of this methodology is the avoidance of highly reactive diphenylzinc in the reaction medium. In this way, the competitive, fast background addition of $ZnPh_2$ and its deletereous effects on enantioselectivity are efficiently suppressed. Therefore, it is still of great interest to develop and study new catalysts that can efficiently carry out this reaction for particular substrates.

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(22) Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659, and references therein.

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(25) Triarylboranes/$ZnEt_2$: (a) Dahmen, S.; Lormann, M. *Org. Lett.* **2005**, *7*, 4597. (b) Rudolph, J.; Lormann, M.; Bolm, C.; Dahmen, S. *Adv. Synth. Catal.* **2005**, *347*, 1361. (c) Bolm, C.; Schmidt, F.; Zani, L. *Tetrahedron: Asymmetry* **2005**, *16*, 1367. (d) Bolm, C.; Zani, L.; Rudolph, J.; Schiffers, I. *Synthesis* **2004**, 2173. (e) Rudolph, J.; Schmidt, F.; Bolm, C. *Adv. Synth. Catal.* **2004**, *346*, 867.

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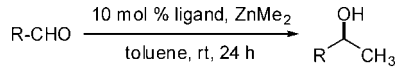
TABLE 6. Addition of Dimethylzinc to Aldehydes Catalyzed by 1a, 1b, and 2b



13a-h

		ligand **1a**		ligand **1b**		ligand **2b**	
entry	aldehyde (product)	conv (%)[a]	ee (%)[a]	conv (%)[a]	ee (%)[a]	conv (%)[a]	ee (%)[a]
1	heptanal (**13a**)	88	65	88	61	84	60
2	(*E*)-α-methylcinnamaldehyde (**13b**)	45	89	26	88	15	79
3	cyclohexylcarbaldehyde (**13c**)	93	84	80	86	56	81
4	*p*-methoxybenzaldehyde (**13d**)	80	84	53	83	32	79
5	benzaldehyde(**13e**)	96	90	79	90	57	89
6	*o*-tolualdehyde(**13f**)	63	88	39	84	32	79
7	*p*-trifluoromethylbenzaldehyde (**13g**)	>99	91	98	91	94	88
8	*m*-tolualdehyde (**13h**)	93	91	76	90	57	88

[a] Determined by GC using a β-DEX capillary column.

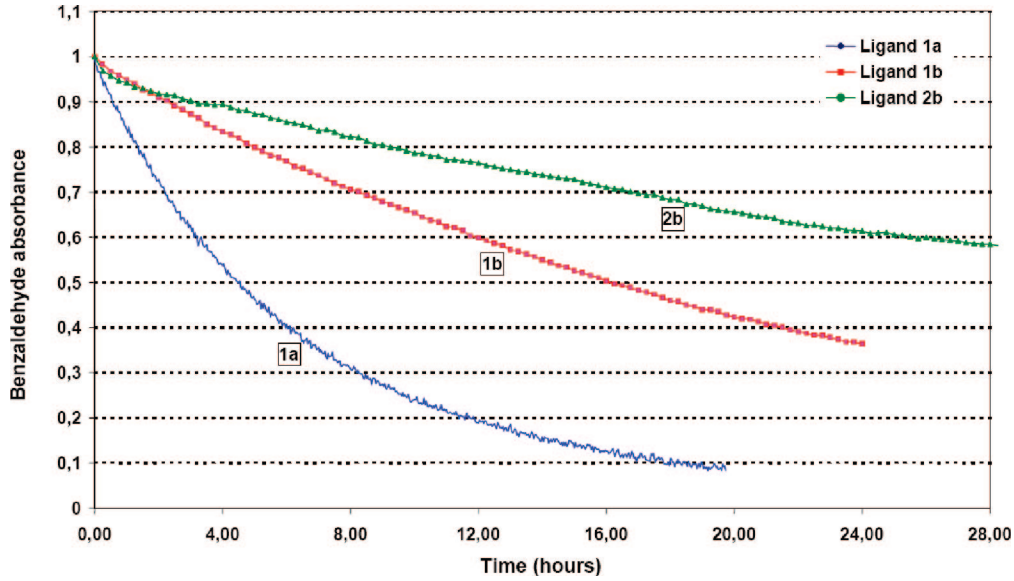


FIGURE 6. Comparison of the catalytic activity of ligands **1a**, **1b**, and **2b** in the addition of dimethylzinc to benzaldehyde at 0 °C.

We applied our catalysts set to this reaction under the conditions previously optimized for ligand **1a**.[9j] As anticipated, the reactions were fast at 10 °C and were complete within 1 h. High conversions and enantioselectivities were recorded for fully α-substituted aldehydes (aromatic and α,β-unsaturated), even though only 5 mol % of amino alcohol was used (see Table 7, entries 3−8). For aliphatic aldehydes, although conversions were essentially complete with the three studied ligands, ee's were below 70% (Table 7, entries 1 and 2).

It is worth mentioning that, for this particular reaction, the three considered ligands behave almost equally with all of the studied substrates. Accordingly, it is evident that a fast reaction such as the arylation of aldehydes, when performed at a fixed, nonoptimized reaction time, is not suitable for the discrimination between similar ligands.

Turning our attention to kinetic behavior, monitoring of the phenylation reaction of *p*-tolualdehyde by in situ FTIR shows that the three considered ligands present in this reaction the same catalytic activity trend already observed for the ethylation and the methylation of benzaldehyde (Figure 7). That is, **1a** is the most active ligand, followed by **1b**, while **2a** is substantially less active. The reactions used for kinetic analysis were performed at 0 °C, using only 2.5 mol % of ligand with the aim of slowing down the process in order to be able to detect differences in activity. Even under these demanding experimental conditions, the reaction is completed for all three ligands in a 60−70 min reaction time. Thus, if reaction progress was only inspected after such a period, the three ligands would appear as practically equivalent.

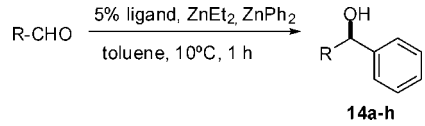
On the other hand, if the reactions were quenched after only 3 min, conversions would be 75% with **1a**, 50% with **1b**, and 22% with **2b**. From the perspective of a potential practical application, where TON was important for economic reasons (energy cost, reactor occupation, etc.), the three ligands would appear as markedly different, **1a** being clearly preferred.

Conclusions

In summary, we have shown that amino alcohol ligands belonging to a common structural type (2-aryl-2-cyclialkylamino-1,1-diphenylethanols) exhibit marked differences in their catalytic behavior when used as ligands for the enantioselective C−C bond formation by addition to aldehydes. We have also shown that a benchmark-guided, structural fine-tuning of the considered ligands can be easily performed through a short, iterative process when the ligands (as it is the case here) have a modular design.

Very interestingly, the best hit ligand in the benchmark-guided process (**1a**) has been shown to be also optimal for mechanisti-

TABLE 7. Addition of a Mixed Phenylzinc Species to Aldehydes Catalyzed by 1a, 1b, and 2b



14a-h

		ligand **1a**		ligand **1b**		ligand **2b**	
entry	aldehyde (product)	conv (%)[a]	ee (%)[b]	conv (%)[a]	ee (%)[b]	conv (%)[a]	ee (%)[b]
1	heptanal (**14a**)	96	67	96	63	96	62
2	cyclohexylcarbaldehyde (**14b**)	97	66	97	63	>99	62
3	(*E*)-α-methylcinnamaldehyde (**14c**)	96	94	95	93	95	92
4	*p*-methoxybenzaldehyde (**14d**)	99	96	97	96	98	94
5	*p*-phenylbenzaldehyde (**14e**)	97	96	98	96	97	95
6	*o*-tolualdehyde (**14f**)	99	97	97	95	97	94
7	*p*-trifluoromethylbenzaldehyde (**14g**)	99	94	98	94	98	93
8	*p*-tolualdehyde (**14h**)	96	97	97	97	99	96

[a] Determined by ^{1}H NMR. [b] Determined by HPLC using a chiral stationary phase.

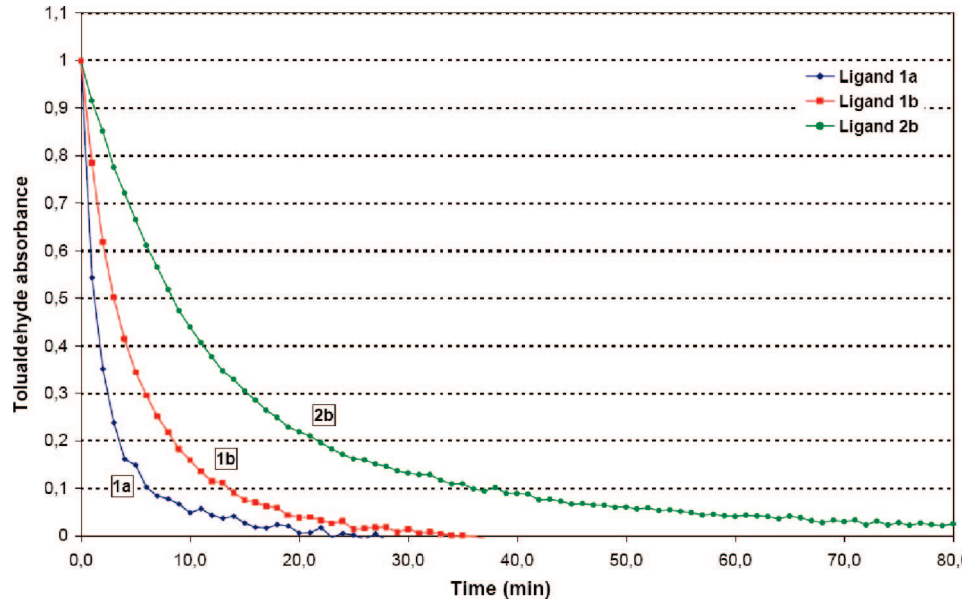


FIGURE 7. Comparison of the catalytic activity of ligands **1a**, **1b**, and **2b** in the addition of PhZnEt to *p*-tolualdehyde at 10 °C.

cally related chemistries not explicitly included in the benchmarking process. This behavior, that underlies the existence of *privileged ligands*, allows keeping the toolkit of catalytic ligands for a given type of process within a reasonable size.

From a methodological point of view, an important consequence of this study concerns the possible ways to discriminate between highly efficient, apparently equivalent ligands (**1a**, **1b**, and **2b**, in the present case). Thus, we have shown that important differences in catalytic activity exist even between ligands depicting very similar enantioselectivity profiles. We have also shown that these differences, which can have a deep impact on the economy of catalytic processes, are only detected when the considered ligands are submitted to stringent tests, i.e., poorly reactive substrates, low ligand loading, and/or short reaction times.

As an additional bonus, the preparation by Jacobsen epoxidation of a family of 2-aryl-1,1-diphenylethene oxides has led to the identification of a linear free-energy relationship between the electronic character of the aryl substituent in the starting olefin and the enantiomeric ratio of the corresponding epoxide.

Experimental Section

General Procedure for the Enantioselective Epoxidation of Olefins 1−11 (GP1). A solution of olefin (5 mmol) in CH_2Cl_2 (10 mL), (*S,S*)-Jacobsen catalyst (0.25 mmol) and 4-phenylpyridine *N*-oxide (0.3 mmol) was cooled to 0 °C. Buffered bleach (7.5 mL, pH = 11.3) precooled to 0 °C was added dropwise in such a way that the internal temperature of the reaction mixture was maintained at 0−5 °C, and the reaction was stirred at 0 °C. When the complete disappearance (ca. 3−6 h) of starting material was ascertained by TLC, the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic phases were washed with water and dried over anhydrous Na_2SO_4 before concentration in vacuo to furnish the crude reaction mixture. Purification was effected by flash column chromatography on silica gel (pretreated with Et_3N 2.5% v/v) and *n*-hexanes/EtOAc mixtures as eluent to afford analytically pure products.

(3*S*)-2,2,3-Triphenyloxirane (1).[11] Following the general procedure GP1, compound **1**, a white crystalline solid, was isolated in 97% yield (264 g) and 92% ee. The enantiomeric purity was enhanced to >99% ee by a single recrystallization from hexanes. The ee was determined by HPLC (Chiralcel-ODR column; eluent,

MeOH; flow rate, 0.5 mL/min; $\lambda = 254$nm). Peaks appeared at $t_S = 10.6$ min for the *S* isomer (major), and $t_R = 16.2$ min for the *R* isomer.

(3*S*)-2,2-Diphenyl-3-*m*-chlorophenyl-oxirane (2). Following the general procedure GP1 a white crystalline solid (2.5 g, 77% yield) was obtained with 88% ee, which upon recrystallization from hexanes afforded enantiomerically pure (>99% ee) **2**. The ee was determined by HPLC (Chiralcel-OD column); eluent, *n*-hexane/2-propanol (19:1); flow rate 0.5 mL/ min, *S* isomer, $t_S = 10.1$ min (major), and *R* isomer, $t_R = 11.5$ min; mp 100 °C. $[\alpha]^{23}_D$: +46.7 (*c* 1.79, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−6.87 (series of m, 14H); 4.29 (s, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 140.5, 137.6, 135.3, 133.8, 129.0, 128.9, 128.4, 127.9,127.8, 126.9, 126.3, 125.8, 124.8, 68.8, 67.1. IR (KBr) 3075, 3035, 2985, 1597, 1479, 1449, 897, 877, 785, 767, 758, 715, 698, 684, 629, 590 cm^{-1}. MS (CI, NH_3) *m*/*z* 307 ($C_{20}H_{15}ClO$, 7), 324 (100). Anal. Calcd for $C_{20}H_{15}ClO$: C, 78.30; H, 4.93. Found: C, 78.34; H, 4.94.

(3*S*)-2,2-Diphenyl-3-*o*-chlorophenyloxirane (3). Following the general procedure GP1, compound **3** (1.46 g, 95% yield, 83% ee) was obtained as a white crystalline solid. Upon one recrystallization from hexanes the enantiomeric purity was increased to >99% ee. The ee was determined by HPLC (Chiralcel-ODR); eluent, MeOH/$NaClO_4$ (0.5 M) 9:1; flow rate 0.5 mL/min, *R* isomer, $t_R = 38.1$ min, and *S* isomer, $t_S = 43.7$ min (major); mp 76 °C. $[\alpha]^{23}_D$: +97.2 (*c* 1.83, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24−6.66 (series of m, 14H); 4.36 (s, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 140.5, 136.2, 133.6, 132.6, 128.6, 128.5, 128.4, 128.1, 128.0, 127.7, 127.4, 126.9, 68.7, 64.9. IR (KBr) 3082, 3053, 3018, 2989, 1493, 1476, 1449, 1263, 1053, 1028, 901, 754, 706, 644, 615, 588 cm^{-1}. MS (CI, NH_3) *m*/*z* 307 ($C_{20}H_{15}ClO$, 11), 324 (100); Anal. Calcd for $C_{20}H_{15}ClO$: C, 78.30; H, 4.93; Cl, 11.56. Found: C, 78.53; H, 4.92; Cl, 11.76.

(3*S*)-2,2-Diphenyl-3-*p*-nitrophenyloxirane (4). Following the general procedure GP1 compound **4** (1.59 g, >99% yield) was obtained with 96% ee as a white crystalline solid, which upon one recrystallization from hexane gave enantiomerically pure (>99% ee) **4**. The ee was determined by HPLC (Chiralcel-ODR); eluent MeOH; flow rate 0.5 mL/ min, *R* isomer, $t_R = 13.8$ min, and *S* isomer, $t_S = 19.3$ min (major); mp 84 °C. $[\alpha]^{23}_D$: +66.3 (*c* 1.23, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03−8.00 (m, 2H), 7.36−7.19 (m, 12H), 4.42 (s, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 47.2, 142.8, 139.8, 134.7, 128.9, 128.4, 128.2, 127.4, 126.2, 69.3, 66.8. MS (EI,70 eV) *m*/*z* 317 (M^+, 23), 165 ($M - C_7H_5NO_3^+$, 100). Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.71; H, 4.88; N, 4.42. Found: C,75.79; H, 4.77; N, 4.42.

(3*S*)-2,2-Diphenyl-3-*p*-fluorophenyloxirane (5). Following the general procedure GP1, compound **5** (1.35 g, 93% yield, 93% ee) was obtained as a white crystalline solid. Upon one recrystallization from hexanes the enantiomeric purity was increased to >99% ee. The ee was determined by HPLC (Chiralcel-ODR column); eluent MeOH/NaClO4 (0.5M) in 9:1 ratio; flow rate 0.5 mL/min, *R* isomer, $t_R = 21.1$ min, and *S* isomer, $t_S = 23.6$ min (major); mp 125 °C. $[\alpha]^{23}_D$: + 66.8 (*c* = 1.07 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37−7.19 (m,10H), 7.03−6.90 (m, 2H), 6.88−6.79 (m, 2H), 4.30 (s,1H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 163.8, 160.6, 140.6, 135.5, 131.2, 129.1, 128.4, 128.3, 127.9, 127.8, 127.6, 126.2, 114.8, 114.5, 68.6, 67.3. IR (KBr) 3085, 3062, 3000, 2989, 1599, 1508, 1447, 1221, 1155, 835, 752, 702, 582, 565 cm^{-1}. MS (EI, 70 eV) *m*/*z* 290 (M^+, 11), 165 ($M - C_7H_5FO^+$, 100); Anal. Calcd for $C_{20}H_{16}FO$: C, 82.74; H, 5.21. Found: C, 82.81; H, 5.21.

(3*S*)-2,2-Diphenyl-3-*p*-methoxyphenyloxirane (6). Following the general procedure GP1, compound **6** (1.39 g, 92% yield, 90% ee) was obtained as a white crystalline solid. Upon one recrystallization from hexanes the enantiomeric purity was increased to >99% ee. The ee was determined by HPLC (Chiralcel-ODR column); eluent MeOH; flow rate 0.5 mL/ min, *S* isomer, $t_S = 14.9$ min (major), and *R* isomer, $t_R = 17.9$ min; mp 96 °C. $[\alpha]^{23}_D$: +69.8 (*c* 1.04, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35−7.22 (m, 10H), 6.93 (d, $J = 8.8$ Hz, 2H), 6.68 (d, $J = 8.8$ Hz, 2H), 4.26 (s, 1H), 3.73 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 159.5, 141.5, 136.3, 133.0, 130.5, 129.7, 128.8, 128.5, 128.3, 128.1, 128.0, 126.7, 113.6, 69.0, 68.5, 55.5. IR (KBr) 3028, 3020, 2980, 2860, 1611, 1516, 1447, 1248, 1173, 1030, 835, 760, 746, 696 cm^{-1}. MS (EI, 70 eV) *m*/*z* 302 (M^+, 22). 165 ($M - C_8H_8O_2^+$, 100). Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42, H, 5.99. Found: C, 83.32, H, 5.99.

(3*S*)-2,2-Diphenyl-3-naphthalen-2-yl-oxirane (7). Following the general procedure GP1, compound **7** (1.55 g, 96% yield, 94% ee) was obtained as a white crystalline solid. Upon one recrystallization from hexanes the enantiomeric purity was increased to >99% ee. The ee was determined by HPLC (Chiralcel-ODR column); eluent MeOH; flow rate 0.5 mL/ min, *R* isomer, $t_R = 16.5$ min, and *S* isomer, $t_S = 18.8$ min (major); mp 115 °C. $[\alpha]^{23}_D$: +49 (*c* 0.76, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76−7.66 (m, 2H), 7.62−7.57 (m, 2H), 7.45−7.30 (m, 7H), 7.27−7.05 (m, 6H), 4.48 (s, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 140.9, 135.6, 133.1, 132.9, 132.7, 129.2, 128.4, 127.9, 127.8, 127.6, 127.3, 126.3, 126.0, 125.9, 124.3, 68.9, 68.3. IR (KBr) 3023, 3000, 2941, 1493, 1447, 825, 756, 696, 663, 623, 584, cm^{-1}. MS (CI, NH_3) *m*/*z* 306.5 ($C_{24}H_{18}^+$, 6), 340 (100). Anal. Calcd for $C_{24}H_{18}O$: C, 89.41; H, 5.63. Found: C, 89.47; H, 5.62.

(3*S*)-3-Methyl-2,2-diphenyloxirane (8).[30] Following the general procedure GP1, compound **8** (0.284 g, 27% yield, 95% ee) was obtained as a white crystalline compound. Upon one recrystallization from hexanes the enantiomeric purity was increased to >99% ee.

(3*S*)-2,2-Diphenyl-3-*p*-tolyloxirane (9). Following the general procedure GP1, compound **9** (1.07 g, 75% yield, 91% ee) was obtained as a white crystalline solid. Upon one recrystallization from hexanes the enantiomeric purity was increased to >99% ee. The ee was determined by HPLC (Chiralcel-ODR column); eluent MeOH/$NaClO_4$ (0.5 M) in a 9:1 ratio; flow rate 0.5 mL/min; *R* isomer, $t_R = 24.9$ min, and *S* isomer, $t_R = 27.6$ min (major); mp 80 °C. $[\alpha]^{23}_D$: +66.3 (*c* 1.23, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36−7.21 (m, 10H), 6.93−6.92 (m, 4H), 4.28 (s,1H), 2.24 (s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 137.2, 135.9, 132.3, 129.1, 128.3, 128.2, 128.0, 127.8, 127.6, 127.4, 126.0, 126.2, 68.5, 68.1, 21.1. IR (KBr) 3035, 3015, 2902, 1518, 1493, 14449, 816, 760, 744, 698 cm^{-1}. MS (EI, 70 eV) *m*/*z* 286 (M^+, 27), 165 ($M - C_8H_80^+$, 100). Anal. Calcd for $C_{21}H_{18}O$: C, 88.08; H, 6.39. Found: C, 88.15; H, 6.35.

(3*S*)-2,2-Diphenyl-3-*m*-tolyloxirane (10). Following the general procedure GP1, compound **10** (2.17 g, 76% yield, 84% ee) was obtained as a white crystalline solid. Upon one recrystallization from hexanes the enantiomeric purity was increased to >99% ee. The ee was determined by HPLC analysis (Chiralcel-OD column); eluent, *n*-hexanes/2-propanol (19:1); flow rate 0.5 mL/min, *S* isomer, $t_S = 8.5$ min (major), and *R* isomer, $t_R = 17.6$ min; mp 111 °C. $[\alpha]^{23}_D$: +56.7 (*c* 1.86, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41−6.79 (series of m, 14H), 4.29 (s, 1H), 2.19 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 141.1, 137.2, 135.9, 135.3, 129.2, 128.4, 128.3, 127.7, 127.5, 127.4, 126.3, 123.8, 68.6, 68.0, 21.2. IR (KBr) 3027, 3000, 2950, 2802, 1601, 1491, 1449, 1333, 914, 879, 837, 764, 750, 704, 652, 632, 588 cm^{-1}. MS (CI, NH_3) *m*/*z* 286 ($C_{21}H_{18}O$, 0), 304 (100). Anal. Calcd for $C_{21}H_{18}$ O: C, 88.07; H, 6.35. Found: C, 88.30; H, 6.40.

(3*S*)-2,2-Diphenyl-3-*o*-tolyloxirane (11). Following the general procedure GP1, compound **11** (0.750 g, 53% yield, 77% ee) was obtained as a white crystalline solid. Upon one recrystallization from hexanes the enantiomeric purity was increased to >99% ee. The ee was determined by HPLC (Chiralcel-OD column); eluent, *n*-hexanes/2-propanol (19:1); flow rate 0.5 mL/min, *S* isomer, $t_S = 8.9$ min (major), and *R* isomer, $t_R = 9.8$ min; mp 95 °C. $[\alpha]^{23}_D$: +76 (*c* 1.38, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.49−6.90 (series of m, 14H); 4.47 (s, 1H), 2.42 (s, 3H). ^{13}C NMR (50.3 MHz,

(30) (a) Chini, M.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 5939. (b) Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Giovanni, E.; Macchia, F.; Pinesci, M. *J. Org. Chem.* **1993**, *58*, 1221.

$CDCl_3$) δ 141.0, 136.7,135.1, 133.7, 129.3, 128.4, 128.3, 127.9, 127.6, 127.4, 127.3, 126.8, 126.2, 125.3, 68.3, 65.8, 19.2. IR (KBr) 3060, 2956, 1491, 1460, 1447, 901, 764, 748, 721,702, 648, 623, 586 cm^{-1}. MS (CI, NH_3) *m/z* 286 ($C_{21}H_{18}O$, 0), 304 (100). Anal. Calcd for $C_{21}H_{18}O$: C, 88.07; H, 6.35. Found: C, 88.16; H, 6.34.

Epoxide Ring-Opening Reactions.[30] General Procedure 2 (GP2). A mixture of the oxirane (1.0 mmol), $LiClO_4$ (214 mg, 2.0 mmol), and amine (10.0 mmol) was heated at 100 °C under N_2. After the complete disappearance of the oxirane, the excess of amine was distilled under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), washed with water (2 × 100 mL), dried (Na_2SO4), and concentrated under reduced pressure to give the crude product, which was purified by chromatography on silica gel pretreated with Et_3N (2.5% v/v) using hexanes/EtOAc as eluent. **General Procedure 3 (GP3).** A solution of the oxirane (1.0 mmol) in anhydrous acetonitrile (2 mL) was treated with $LiClO_4$ (1.07 g, 10.0 mmol) and the cyclic amine (10.0 mmol), and the reaction mixture was stirred at 80 °C under nitrogen atmosphere until the complete disappearance of the starting oxirane (ca. 24−96 h). The reaction mixture was diluted with water (25 mL) and extracted with dichloromethane (3 × 25 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude product. Purification by column chromatography on silicagel pretreated with Et_3N (2.5% v/v) and hexane/EtOAc as eluent afforded analytically pure compounds.

(*R*)-2-Piperidino-1,1,2-triphenylethanol (1a).[7a] Following the general procedure GP2 for oxirane **1** (1.0 mmol, 272 mg), and piperidine (1.0 mL, 10.0 mmol) for 24 h, compound **1a** was isolated (351 mg, 98%) as white crystals. All spectroscopic data matched those reported in the literature.

(2*R*)-2-Azepan-1-yl-1,1,2-triphenylethanol (1b). Following the general procedure GP3 for oxirane **1** (1.0 mmol, 272 mg), and hexamethyleneimine (1.13 mL, 10.0 mmol) for 24 h, compound **1b** was isolated (334 mg, 90%) as a white solid; mp 160 °C. $[\alpha]^{23}_D$: −8.1 (*c* 1.99, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 7.75−7.57 (2H, m), 7.39−6.90 (13H, m), 5.51 (1H, br s), 4.78 (1H, s), 2.76−2.59 (2H, m), 2.48−2.31 (2H, m), 1.45−1.26 (8H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.1, 145.8, 138.2, 131.0, 127.8, 127.5, 127.2, 127.0, 126.8, 126.7, 126.2, 125.9, 125.7, 79.3, 78.0, 55.4, 29.2, 26.2. IR (KBr): 3402, 3084, 3059, 3023, 2918, 2843, 1493, 1449, 1317, 1148, 1055, 760, 748, 700 cm^{-1}. MS (CI, NH_3) *m/z* 371 ($C_{26}H_{29}NO.H^+$, 100). Anal. Calcd for $C_{26}H_{29}NO$: C, 84.06; H, 7.87; N, 3.77. Found: C, 84.05; H, 7.96; N, 3.71.

(*R*)-2-Azocan-1-yl-1,1,2-triphenylethanol (1c). Following the general procedure GP3 for oxirane **1** (1.0 mmol, 272 mg), and heptamethyleneimine (1.26 mL, 10.0 mmol) for 48 h, compound **1c** was isolated (72 mg, 18%) as a white solid; mp 149 °C. $[\alpha]^{23}_D$: −78.1 (*c* 1.21, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 7.73−7.69 (2H, m), 7.35−6.90 (13H, series of m), 5.38 (1H, br s), 4.80 (1H, s), 2.74−2.59 (2H, m), 2.43−2.30 (2H, m), 1.50−1.21 (10H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 149.1, 146.1, 138.1, 131.2, 127.9, 127.4, 127.2, 126.8, 126.5, 126.2, 125.8, 125.6, 79.6, 78.9, 54.8, 28.0, 27.3, 25.2. IR (KBr): 3416, 3075, 3046, 3021, 2927, 2855, 1493, 1449, 1319, 1175, 1121, 993, 972, 762, 746, 702 cm^{-1}. MS (CI, NH_3) *m/z* 385 ($C_{27}H_{31}NO.H^+$, 100). Anal. Calcd for $C_{27}H_{31}NO$: C, 84.11; H, 8.11; N, 3.63. Found: C, 84.16; H, 8.11; N, 3.63.

(*R*)-2-(3,3-Dimethylpiperidine-yl)-1,1,2-triphenylethanol (1d). Following the general procedure GP3 for oxirane **1** (1.0 mmol, 272 mg), and 3,3-dimethylpiperidine (1.41 mL, 10.0 mmol) for 48 h, compound **1d** was isolated (380 mg, 99%) as a white solid; mp 147 °C. $[\alpha]^{23}_D$: −131.5 (*c* 1.11, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 7.69−7.65 (2H, m), 7.33−6.90 (13H, m), 5.56 (1H, s), 4.55 (1H, s), 2.47−2.36 (1H, m), 2.13 (1H, d, J = 11.1 Hz), 1.93−1.78 (2H, m), 1.43−1.34 (2H, m), 1.07−0.98 (2H, m), 0.83 (3H, s), 0.69 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.2, 145.7, 137.1, 131.3, 127.9, 127.3, 127.2, 126.8, 126.6, 126.1, 125.6, 79.4, 77.1, 65.9, 54.2, 37.0, 31.5, 27.2, 26.8, 23.0. IR (KBr): 3417, 3064, 3025, 2938, 2817, 1495, 1449, 976, 750, 700, 654, 636 cm^{-1}. MS (CI, NH_3) *m/z* 385 ($C_{27}H_{31}NO.H^+$, 100). Anal. Calcd for $C_{27}H_{31}NO$: C, 84.11; H, 8.10; N, 3.63. Found: C, 84.32; H, 8.16; N, 3.64.

(*R*)-1,1,2-Triphenyl-2-pyrrolidine-yl-ethanol (1e). Following the general procedure GP3 for oxirane **1** (1.0 mmol, 272 mg), and pyrrolidine (0.82 mL, 10.0 mmol) for 48 h, compound **1e** was isolated (312 mg, 91%) as a white solid; mp 155 °C. $[\alpha]^{23}_D$: +7.3 (*c* 0.96, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 7.86−7.83 (2H, m), 7.33−6.77 (13H, m), 4.52 (1H, s), 2.28−2.16 (4H, m), 1.57−1.51 (4H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 149.8, 146.1, 139.9, 130.1, 128.0, 127.3, 127.1, 126.8, 126.2, 125.9, 125.3, 125.2, 78.2, 76.4, 54.3, 23.3. IR (KBr): 3388, 3025, 2967, 2811, 1491, 1449, 1034, 746, 698, 636 cm^{-1}. MS (CI, NH_3) *m/z* 343 ($C_{24}H_{25}NO.H^+$, 100). Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 84.11; H, 7.36; N, 3.93.

(*R*)-2-(3-Clorophenyl)-1,1-diphenyl-2-piperidine-1-yl-ethanol (2a). Following the general procedure GP3 for oxirane **2** (1.0 mmol, 307 mg), and piperidine (1.0 mL, 10.0 mmol) for 48 h, compound **2a** was isolated (284 mg, 72%) as a white solid; mp 167 °C. $[\alpha]^{23}_D$: −106.0 (*c* 1.12, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 7.67−7.63 (2H, m), 7.36−6.92 (12H, m), 5.59 (1H, br s), 4.49 (1H, s), 2.46−2.34 (2H, m), 2.06−1.96 (2H, m), 1.45−1.26 (6H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 148.9, 145.4, 139.7, 133.3, 131.1, 129.4, 128.7, 128.0, 127.4, 127.0, 126.6, 126.4, 125.9, 125.6, 78.9, 77.0, 54.6, 26.8, 24.1. IR (KBr): 3290, 3060, 2934, 2851, 1597, 1493, 1476, 1449, 1084, 1055, 1034, 793, 146, 696, 665 cm^{-1}. MS (CI, NH_3) *m/z* 392 ($C_{25}H_{26}ClNO.H^+$, 100). Anal. Calcd for $C_{25}H_{26}ClNO$: C, 76.61; H, 6.69; N, 3.57; Cl, 9.05. Found: C, 76.89; H, 6.70; N, 3.61; Cl, 9.30.

(2*R*)-2-Azepan-1-yl-2-(3-chlorophenyl)-1,1-diphenyl-ethanol (2b). Following the general procedure GP3 for oxirane **2** (1.0 mmol, 307 mg), and hexamethyleneimine (1.13 mL, 10.0 mmol) for 48 h, compound **2b** was isolated (290 mg, 72%) as a white solid; mp 161 °C. $[\alpha]^{23}_D$: −55.3 (*c* 1.13, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 7.66−7.63 (2H, m), 7.33−6.97 (12H, series of m), 5.08 (1H, br s), 4.76 (1H, s), 2.75−2.67 (2H, m), 2.42−2.36 (2H, m), 1.48−1.33 (8H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 148.5, 145.3, 140.3, 133.3, 130.8, 129.1, 128.6, 127.9, 127.4, 126.9, 126.4, 126.3, 125.9, 125.8, 79.5, 77.2, 55.4, 29.2, 26.5). IR (KBr): 3573−3274 (br), 3060, 3027, 2927, 2853, 1659, 1449, 1279, 762, 702, 638 cm^{-1}. MS (CI, NH_3) *m/z* 406 ($C_{26}H_{28}ClNO.H^+$, 100). Anal. Calcd for $C_{26}H_{28}ClNO$: C, 76.93; H, 6.95; N, 3.45; Cl, 8.73. Found: C, 76.98; H, 6.91; N, 3.34 Cl, 8.51.

(*R*)-2-(2-Chlorophenyl)-1,1-diphenyl-2-piperidine-1-yl-ethanol (3a). Following the general procedure GP3 for oxirane **3** (1.0 mmol, 307 mg), and piperidine (1.0 mL, 10.0 mmol) for 72 h, compound **3a** was isolated (36 mg, 9%) as a white solid; mp 169 °C. $[\alpha]^{23}_D$: −216.2 (*c* 1.39, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 7.74−7.70 (2H, m), 7.60−6.55 (1H, series of m), 7.34−6.33 (11H, m), 5.81 (1H, br s), 5.33 (1H, s), 2.50−2.42 (2H, m), 2.06−2.0 (2H, m), 1.42−1.26 (6H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 149.3, 145.8, 136.1, 135.4, 133.2, 128.8, 128.1, 127.4, 126.2, 125.8, 125.6, 125.4, 78.9, 71.5, 54.0, 27.0, 24.2. IR (KBr): 3395, 3060, 3025, 2923, 2844, 2833, 2819, 1449, 1173, 1057, 1034, 748, 708, 665 cm^{-1}. MS (CI, NH_3) *m/z* 392 ($C_{25}H_{26}ClNO.H^+$, 100).

(*R*)-2-(4-Fluorophenyl)-1,1-diphenyl-2-piperidine-1-yl-ethanol (5a). Following the general procedure GP3 for oxirane **5** (1.0 mmol, 290 mg), and piperidine (1.0 mL, 10.0 mmol) for 24 h, compound **5a** was isolated (350 mg, 93%) as a white solid; mp 151 °C. $[\alpha]^{23}_D$: −123.0 (*c* 0.67, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.67−7.64 (2H, m), 7.32−6.94 (10H, m), 6.83−6.78 (2H, m), 5.69 (1H, br s), 4.53 (1H, s), 2.39−2.35 (2H, m), 2.00−1.97 (2H, m), 1.42−1.37 (4H, m), 1.29−1.27 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 159.9, 149.0, 145.5, 132.6, 132.5, 127.9, 127.3, 126.7, 126.2, 125.7, 125.5, 114.4, 114.1, 78.7, 76.7, 54.5, 26.7, 24.1. IR (KBr): 3455, 3030, 3000, 2944, 2841, 1607, 1508, 1449, 1227, 1165, 1055, 748, 696, 550 cm^{-1}. MS (CI, NH_3) *m/z* 371 ($C_{25}H_{26}FNO.H^+$, 100). Anal. Calcd for $C_{25}H_{26}FNO$: C, 79.97; H, 6.98; N, 3.73. Found: C, 79.83; H, 6.94; N, 3.74.

(*R*)-2-(4-Methoxyphenyl)-1,1-diphenyl-2-piperidine-1-yl-ethanol (6a). Following the general procedure GP3 for oxirane **6** (1.0 mmol, 302 mg), and piperidine (1.0 mL, 10.0 mmol) for 24 h, compound **6a** was isolated (392 mg, 75% yield) as a white solid; mp 119 °C. $[\alpha]^{23}_D$: −98.1 (*c* 0.38, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74−7.60 (2H, m), 7.38−6.92 (10H, m), 6.68−6.63 (2H, m), 6.05 (1H, s), 4.46 (1H, s), 3.72 (3H, s), 2.43−2.32 (2H, m), 2.05−1.92 (2H, m), 1.50−1.20 (6H, m).^{13}C NMR (50.3 MHz, $CDCl_3$): δ 158.5, 149.5, 147.8, 132.3, 129.6, 127.8, 127.2, 126.9, 126.1, 125.7, 112.7, 78.5, 77.1, 55.0, 54.3, 26.8, 24.1. IR (KBr): 3492, 3024, 2930, 2801, 1609, 1512, 1449, 1250, 1180, 1034, 754, 704 cm^{-1}. HRMS (ESI+): *m*/*z* Calcd for $C_{26}H_{30}NO_2$ $[M+H]^+$: 388.2271, found: 388.2280.

(*R*)-2-Naphthlen-2-yl-1,1-diphenyl-2-piperidine-1-yl-ethanol (7a). Following the general procedure GP3 for oxirane **7** (1.0 mmol, 322 mg), and piperidine (1.0 mL, 10.0 mmol) for 48 h, compound **7a** was isolated (258 mg, 63%) as a white solid; mp 174 °C. $[\alpha]^{23}_D$: −161.8 (*c* 0.61, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74−6.86 (17H, series of m), 6.04 (1H, br s), 4.70 (1H, s), 2.57- 2.40 (2H, m), 2.16−1.99 (2H, m), 1.44−1.40 (4H, m), 1.26−1.20 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.3, 145.5, 135.1, 132.7, 132.3, 130.3, 129.2, 127.9, 127.4, 127.2, 126.9, 126.8, 126.2, 125.7, 78.6, 77.8, 54.5, 26.8, 24.1. IR (KBr): 3465, 3040, 2925, 2915, 2780, 1493, 1447, 1314, 1059, 746, 694, 663, 478 cm^{-1}. MS (CI, NH_3) *m*/*z* 407 ($C_{29}H_{29}NO.H^+$, 100). Anal. Calcd for $C_{29}H_{29}NO$: C, 85.47; H, 7.17; N, 3.44. Found: C, 85.35; H, 7.17; N, 3.18.

(*R*)-1,1-Diphenyl-2-piperidine-1-yl-propan-1-ol (8a). Following the general procedure GP3 for oxirane **8** (1.0 mmol, 286 mg), and piperidine (1.0 mL, 10.0 mmol) for 48 h, compound **8a** was isolated (287 mg, 97%) as an oil. $[\alpha]^{23}_D$: −56.9 (*c* 1.40, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43−7.17 (10H, series of m), 3.47 (1H, q, J = 7.7 Hz), 2.38−2.24 (4H, m), 1.68−137 (6H, m), 1.41 (3H, d, J = 7.7 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 146.4, 144.8, 128.0, 127.9, 127.4, 127.1, 126.9, 126.4, 77.3, 67.0, 52.3, 26.6, 24.4, 10.7. IR (KBr): 3652−3058 (br), 2934, 2853, 2809, 1493, 1447, 1165, 1034, 769, 698, 611 cm^{-1}. MS (CI, NH_3) *m*/*z* 296 ($C_{20}H_{25}NO.H^+$, 100). Anal. Calcd for: $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.08; H, 8.31; N, 4.70.

(*R*)-1,1-Diphenyl-2-piperidine-1-yl-2-*p*-tolylethanol (9a). Following the general procedure GP3 for oxirane **9** (1.0 mmol, 286 mg), and piperidine (1.0 mL, 10.0 mmol) for 24 h, compound **9a** was isolated (346 mg, 93% yield) as a white solid; mp 175 °C. $[\alpha]^{23}_D$: −34.1 (*c* 1.03, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.66−7.62 (2H, m), 7.34−7.23 (4H, m), 7.17−6.91 (8H, m), 4.48 (1H, s), 2.44−2.36 (2H, m), 2.23 (3H, s), 2.00−1.96 (2H, m), 1.43−1.38 (4H, m), 1.30−1.26 (4H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 149.4, 145.8, 136.4, 134.0, 131.2, 128.1, 127.8, 127.2, 126.9, 126.1, 125.7, 125.6, 78.5, 77.5, 54.3, 26.8, 24.1, 21.0. IR (KBr): 3495, 2936, 1514, 1493, 1447, 1315, 1171, 1055, 970, 744, 696, 617 cm^{-1}. MS (CI, NH_3) *m*/*z* 357 ($C_{26}H_{29}NO.H^+$, 1), 372 (100). Anal. Calcd for $C_{26}H_{29}NO$: C, 84.06; H, 7.87; N, 3.77. Found: C, 84.21; H, 7.80; N, 3.66.

(*R*)-1,1-Diphenyl-2-piperidine-1-yl-2-*m*-tolyl-ethanol (10a). Following the general procedure GP3 for oxirane **10** (1.0 mmol, 286 mg), and piperidine (1.0 mL, 10.0 mmol) for 72 h, compound **10a** was isolated (244 mg, 66%) as a white solid; mp 157 °C. $[\alpha]^{23}_D$: −67.2 (*c* 1.07, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.66−7.63 (2H, m), 7.33−6.91 (12H, m), 4.46 (1H, s), 2.46−2.31 (2H, m), 2.19 (3H, s), 2.05−1.94 (2H, m), 1.46−1.26 (6H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 149.4, 145.9, 137.1, 136.7, 132.1, 128.4, 127.8, 127.5, 127.2, 127.1, 126.9, 126.1, 125.7, 125.8, 125.7, 125.6, 78.5, 77.8, 54.3, 26.8, 24.1, 21.4. IR (KBr): 3400, 3058, 2934, 2853, 1605, 1493, 1449, 1153, 1055, 1034, 796, 740, 704 cm^{-1}. MS (CI, NH_3) *m*/*z* 371 ($C_{26}H_{29}NO.H^+$, 100). Anal. Calcd for $C_{26}H_{29}NO$: C, 84.06; H, 7.87; N, 3.77. Found: C, 84.04; H, 7.83; N, 3.66.

(*R*)-1,1-Diphenyl-2-piperidine-1-yl-2-*o*-tolylethanol (11a). Following the general procedure GP3 for oxirane **11** (1.0 mmol, 286 mg), and piperidine (1.0 mL, 10.0 mmol) for 72 h, compound **11a** was isolated (160 mg, 42% yield) as a white solid; mp 154 °C. $[\alpha]^{23}_D$: −171.4 (*c* 1.95, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.83−6.77 (14H, series of m), 4.92 (1H, s), 2.54−2.39 (2H, m), 2.46 (3H, s), 2.0−1.92 (2H, m), 1.38.1.26 (6H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 149.8, 146.1, 136.7, 136.5, 132.3, 131.7, 130.0, 129.8, 128.2, 128.0, 127.2, 126.6, 126.2, 126.1, 125.4, 125.1, 78.7, 71.7, 54.1, 27.0, 24.3, 21.4. IR (KBr): 3366, 3082, 3065, 3058, 3033, 3018, 2923, 2820, 1491, 1449, 1315, 1055, 742, 696, 669, 638 cm^{-1}. MS (CI, NH_3) *m*/*z* 371 ($C_{26}H_{29}NO.H^+$, 100). Anal. Calcd for $C_{26}H_{29}NO$: C, 84.06; H, 7.87; N, 3.77. Found: C, 84.01; H, 7.74; N, 3.74.

General Procedure for the Enantioselective Amino Alcohol-Catalyzed Addition of Diethylzinc to Aldehydes (GP4). (a) With 6 mol % of the ligand. To a solution of the amino alcohol ligand (0.03 mmol, 6 mol %) in toluene (1 mL) under argon was added diethylzinc (1.1 mL of a 1 M in hexanes solution, 1.1 mmol) at room temperature. The mixture was stirred for 20 min and then cooled to 0 °C. The aldehyde (0.50 mmol) was added dropwise. The mixture was stirred for the corresponding reaction time. The reaction was quenched by addition of a saturated NH_4Cl solution (5 mL). The mixture was then extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried and concentrated in vacuo. The enantiomeric purity of the resulting alcohols was determined from the crude mixture by GC analysis. When necessary, in the case that the peaks corresponding to the enantiomeric alcohols were not properly resolved by GC, another aliquot was taken and the alcohols transformed into their acetyl derivatives. Therefore, to 0.5 mL of the organic layer diluted with 0.5 mL of CH_2Cl_2 were added Ac_2O (0.1 mL, 1.06 mmol), Et_3N (0.1 mL, 0.7 mmol), and DMAP (catalytic amount) successively. After 5 h at room temperature, the mixture was extracted with Et_2O, and the organic layers were washed with 1 M NaCl saturated solution. Enantiomeric purity of the resulting derivatives was determined from the organic extract by GC analysis. **(b) With 0.5 mol % of the ligand.** To a solution of the amino alcohol ligand (0.005 mmol, 0.5 mol %) in toluene (2 mL) under argon was added diethylzinc (2.2 mL of a 1 M in hexanes solution, 2.2 mmol) at room temperature. The mixture was stirred for 20 min and then cooled to 0 °C. The aldehyde (1.0 mmol) was added dropwise. The mixture was stirred for 4 h under Ar. The reaction was quenched by the addition of a saturated NH_4Cl solution (3 mL). The mixture was then extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried and concentrated in vacuo. Conversion and ee were determined as above.

(*S*)-1-Phenylpropanol[31] (12a). Following the general procedure GP4 for benzaldehyde (51 μL, 0.50 mmol) the title compound was obtained. The ee and the conversion were determined by GC. The enantiomers were not separable by gas chromatography but as their corresponding acetates. GC (acetate deriv): β-DEX 120 column, 115 °C, t_S = 13.8 min, t_R = 14.5 min.

(*S*)-1-(2-Fluorophenyl)-propanol[32] (12b). Following the general procedure GP4 for *o*-fluorobenzaldehyde (52 μL, 0.50 mmol), the title compound was obtained. The ee and the conversion were determined by GC: β-DEX 120 column, 110 °C, t_R = 17.1 min, t_S = 18.4 min.

(*S*)-1-(2-Tolyl)-propanol[33] (12c). Following the general procedure GP4 for *o*-methylbenzaldehyde (58 μL, 0.50 mmol), the title compound was obtained. The ee and the conversion were determined by GC: β-DEX 120 column, 120 °C, t_R = 17.5 min, t_S = 18.9 min.

(*S*)-1-(2-Methoxyphenyl)-propanol[34] (12d). Following the general procedure GP4 for *o*-methoxybenzaldehyde (60 μL, 0.50 mmol), the title compound was obtained. The ee and the conversion

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were determined by GC: β-DEX 120 column, 125 °C, t_R = 28.7 min, t_S = 29.6 min.

(*S*)-1-(3-Fluoro-phenyl)-propanol[35] (12e). Following the general procedure GP4 for *m*-fluorobenzaldehyde (53 μL, 0.50 mmol), the title compound was obtained. The ee and the conversion were determined by GC: β-DEX 120 column, 110 °C, t_R = 18.0 min, t_S = 19.2 min.

(*S*)-1-(3-Tolyl)-propanol[36] (12f). Following the general procedure GP4 for *m*-methylbenzaldehyde (59 μL, 0.50 mmol), the title compound was obtained. The ee and the conversion were determined by GC: β-DEX 120 column, 120 °C, t_R = 16.6 min, t_S = 18.0 min.

(*S*)-1-(3-Methoxyphenyl)-propanol[37] (12g). Following the general procedure GP4 for *m*-methoxybenzaldehyde (61 μL, 0.50 mmol), the title compound was obtained. The ee and the conversion were determined by GC: β-DEX 120 column, 125 °C, t_R = 29.5 min, t_S = 30.6 min.

(*S*)-1-(4-Fluorophenyl)-propanol[38] (12h). Following the general procedure GP4 for *p*-fluorobenzaldehyde (53 μL, 0.50 mmol) the title compound was obtained. The ee and the conversion were determined by GC: β-DEX 120 column, 110 °C, t_R = 19.3 min, t_S = 21.2 min.

(*S*)-1-(4-Tolyl)-propanol[39] (12i). Following the general procedure GP4 for *p*-methylbenzaldehyde (59 μL, 0.50 mmol) the title compound was obtained. The ee and the conversion were determined by GC: β-DEX 120 column, 120 °C, t_R = 14.8 min, t_S = 16.1 min.

(*S*)-1-(3-Methoxyphenyl)-propanol[39](12j). Following the general procedure GP4 for *p*-methoxybenzaldehyde (61 μL, 0.50 mmol), the title compound was obtained. The ee and the conversion were determined by GC. The enantiomers were not completely separable by gas chromatography but as their corresponding acetates. GC (acetate deriv): β-DEX 120 column, 125 °C, t_S = 31.0 min, t_R = 32.9 min.

(*S*)-(*E*)-1-Phenyl-1-penten-3-ol[40] (12k). Following the general procedure GP4 for *trans*-cinnamaldehyde (63 μL, 0.50 mmol), the title compound was obtained. The ee and the conversion were determined by GC. The enantiomers were not completely separable by gas chromatography but as their corresponding acetates. GC (acetate deriv): β-DEX 120 column, 140 °C, t_S = 16.7 min, t_R = 17.4 min.

(*S*)-3-Nonanol[41] (12l). Following the general procedure GP4 for heptanal (70 μL, 0.50 mmol), the title compound was obtained. The ee and the conversion were determined by GC. The enantiomers were not separable by gas chromatography but as their corresponding acetates. GC (acetate deriv): β-DEX 120 column, 100 °C, t_S = 9.3 min, t_R = 10.6 min.

(*S*)-1-Phenyl-3-pentanol[42] (12m). Following the general procedure GP4 for 3-phenylpropanal (66 μL, 0.50 mmol), the title compound was obtained. The ee and the conversion were determined by GC. The enantiomers were not separable by gas chromatography but as their corresponding acetates. GC (acetate deriv): Column β-DEX 120 Isoterm 140 °C: t_S = 16.3 min, t_R = 17.4 min.

(*S*)-4-Ethyl-3-hexanol[43] (12n). Following the general procedure GP4 for 2-ethylbutyraldehyde (62 μL, 0.50 mmol), the title compound was obtained. The ee and the conversion were determined by GC. The enantiomers were not separable by gas chromatography but as their corresponding acetates. GC (acetate deriv): Column β-DEX 120 Isoterm 65 °C, t_S = 8.3 min, t_R = 8.7 min.

(*S*)-(*E*)-2-Methyl-1-phenyl-1-penten-3-ol[44] (12o). Following the general procedure GP4 for (*E*)-α-methylcinnamaldehyde (70 μL, 0.50 mmol), the title compound was obtained. The ee and the conversion were determined by GC. The enantiomers were not separable by gas chromatography but as their corresponding acetates. GC (acetate deriv): Column β-DEX 120 Isoterm 140 °C: t_S = 17.0 min, t_R = 17.7 min.

General Procedure for the Enantioselective Amino Alcohol-Catalyzed Addition of Dimethylzinc to Aldehydes (GP5). To a solution of the chiral ligand (0.05 mmol, 10 mol %) in toluene (2 mL) under argon was added 2 M dimethylzinc (0.5 mL, 1.0 mmol) in toluene via syringe, and the reaction mixture was stirred at room temperature for 30 min. The reaction was then cooled to 0 °C, and the aldehyde (0.5 mmol) was added dropwise. After 24 h at the same temperature, the reaction was quenched by careful addition of HCl (1 M, 3 mL). An aliquot was taken from the organic layer and analyzed by gas chromatography.

When necessary, in the case that the peaks corresponding to the enantiomeric alcohols were not properly resolved by GC, another aliquot was taken and the alcohols were transformed in their acetyl derivatives. Therefore, to 0.5 mL of the organic layer diluted with 0.5 mL of CH_2Cl_2 were added Ac_2O (0.1 mL, 1.06 mmol), Et_3N (0.1 mL, 0.7 mmol), and DMAP (catalytic amount) successively. After 5 h at room temperature, the mixture was extracted with Et_2O, and the organic layers were washed with 1 M NaCl saturated solution. Enantiomeric purity of the resulting derivatives was determined from the organic extract by GC analysis.

(*S*)-2-Octanol[45] (13a). Following the general procedure *GP5* for heptanal (70 μL, 0.50 mmol), the desired product was obtained. The ee and the conversion were determined by GC. The enantiomers were not separable by gas chromatography but as their corresponding acetates. GC (acetate deriv): β-DEX 120 column, 100 °C, t_S = 8.5 min, t_R = 9.5 min.

(*S*)-(*E*)-3-Methyl-4-phenyl-3-buten-2-ol[35] (13b). Following the general procedure GP5 for (*E*)-α-methylcinnamaldehyde (70 μL, 0.50 mmol), the desired product was obtained. The ee and the conversion were determined by GC. The enantiomers were not completely separable by gas chromatography but as their corresponding acetates. GC (acetate deriv): β-DEX 120 Isoterm 140 °C: t_S = 16.9 min, t_R = 17.5 min.

(*S*)-1-Cyclohexyl-ethanol[46] (13c). Following the general procedure GP5 for cyclohexanecarbaldehyde (61 μL, 0.50 mmol), the desired product was obtained. The ee and the conversion were determined by GC: β-DEX 120 Isoterm 100 °C: t_R = 16.6 min, t_S = 17.9 min.

(*S*)-1-(4-Methoxyphenyl)-ethanol[21](13d). Following the general procedure GP5 for *p*-methoxybenzaldehyde (61 μL, 0.50 mmol), the desired product was obtained. The ee and the conversion were determined by GC: β-DEX 120 Isoterm 125 °C: t_R = 30.1 min, t_S = 31.5 min.

(*S*)-1-Phenyl-ethanol[47] (13e). Following the general procedure GP5 for benzaldehyde (51 μL, 0.50 mmol), the desired product was obtained. The ee and the conversion were determined by GC. The enantiomers were not completely separable by gas chromatography but as their corresponding acetates. GC (acetate deriv): β-DEX 120 Isoterm 115 °C, t_S = 13.2 min, t_R = 13.9 min.

(*S*)-1-*o*-Tolyl-ethanol[48] (13f). Following the general procedure GP5 for *o*-tolualdehyde (58 μL, 0.50 mmol), the desired product

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was obtained. The ee and the conversion were determined by GC: β-DEX 120 Isoterm 115 °C: t_R = 22.5 min, t_S = 26.6 min.

(*S*)-1-(4-Trifluoromethylphenyl)-ethanol[48] (13g). Following the general procedure GP5 for *p*-methoxybenzaldehyde (68 μL, 0.50 mmol), the desired product was obtained. The ee and the conversion were determined by GC: β-DEX 120 Isoterm 115 °C: t_R = 14.2 min, t_S = 16.6 min.

(*S*)-1-*m*-Tolyl-ethanol[48](13h). Following the general procedure GP5 for *m*-tolualdehyde (59 μL, 0.50 mmol), the desired product was obtained. The ee and the conversion were determined by GC: β-DEX 120 Isoterm 115 °C: t_R = 17.3 min, t_S = 18.7 min.

General Procedure for the Enantioselective Amino Alcohol-Catalyzed Addition of a Mixed Phenylzinc Species to Aldehydes (GP6). A 6.4 mL aliquot of a mother solution containing Ph_2Zn (234 mg, 1.07 mmol) and Et_2Zn (266 mg, 2.16 mmol) in anhydrous toluene (20 mL) was added to the amino alcohol ligand (0.025 mmol, 5 mol %), under argon. After stirring for 20 min at room temperature, the reaction mixture was cooled to 10 °C before the corresponding aldehyde (0.50 mmol) was added dropwise. After 1 h at that temperature, the reaction was quenched by careful addition of 5 mL of 1 M HCl. It was extracted with Et_2O (3 × 10 mL) and dried over $MgSO_4$, and the solvent was removed under vacuum. The conversion of the reaction was determined by ^{1}H NMR and the ee by HPLC using the chiral column indicated.

(*R*)-1-Phenyl-1-heptanol[27c] (14a). Following the general procedure GP6 for heptanal (70 μL, 0.50 mmol), the title compound was obtained. HPLC: Daicel CHIRALCEL-ODH. Hexane/2-propanol 95:5, 0.5 mL/min, λ= 254 nm, t_R= 13.3 min, t_S= 14.3 min.

(*R*)-Cyclohexyl-phenyl-methanol[49] (14b). Following the general procedure GP6 for cyclohexanecarbaldehyde (61 μL, 0.50 mmol), the title compound was obtained. HPLC: Daicel CHIRALCEL-ADH. Hexane/2-propanol 90:10, 0.5 mL/min, λ= 254 nm, t_S = 23.9 min, t_R = 25.6 min.

(*R*)-(*E*)-2-Methyl-1,3-diphenyl-2-propen-1-ol[50] (14c). Following the general procedure GP6 for (*E*)-α-methyl-cinnamaldehyde (70 μL, 0.50 mmol), the title compound was obtained. HPLC (*p*-nitrobenzoate derivative): Daicel CHIRALCEL-ADH. Hexane/2-propanol 99:1, 0.5 mL/min, λ= 254 nm, t_S = 87.7 min, t_R = 92.8 min.

(*S*)-(4-Methoxy-phenyl)-phenyl-methanol[27f] (14d). Following the general procedure GP6 for *p*-methoxybenzaldehyde (61 μL, 0.50 mmol), the title compound was obtained. HPLC: Daicel CHIRALCEL-ADH. Hexane/2-propanol 95:5, 0.5 mL/min, λ = 254 nm, t_R = 40.0 min, t_S = 43.5 min.

(*S*)-4-Biphenylphenylmethanol[27f] (14e). Following the general procedure GP6 for 4-biphenylcarbaldehyde (130 mg, 0.50 mmol), the title compound was obtained. HPLC: Daicel CHIRALCEL-ODH. Hexane/2-propanol 95:5, 0.5 mL/min, λ = 254 nm, t_R = 56.3 min, t_S = 59.4 min.

(*S*)-Phenyl-o-tolyl-methanol[51] (14f). Following the general procedure GP6 for *o*-tolualdehyde (58 μL, 0.50 mmol), the title compound was obtained. HPLC: Daicel CHIRALPACK-ODH. Hexane/2-propanol 95:5, 1.0 mL/min, λ = 254 nm, t_S = 21.4 min, t_R = 23.4 min.

(*S*)-Phenyl-(4-trifluoromethyl-phenyl)-methanol[52] (14g). Following the general procedure GP6 for *p*-trifluoromethyl-benzaldehyde (68 μL, 0.50 mmol), the title compound was obtained. HPLC: Daicel CHIRALPACK-ODH. Hexane/2-propanol 95:5, 0.5 mL/min, λ = 254 nm, t_R = 31.1 min, t_S = 34.0 min.

(*S*)-Phenyl-*p*-tolyl-methanol[27f] (14h). Following the general procedure GP6 for *p*-tolualdehyde (59 μL, 0.50 mmol), the title compound was obtained. HPLC: Daicel CHIRALCEL-ODH. Hexane/2-propanol 95:5, 0.5 mL/min, λ = 254 nm, t_S = 28.0 min, t_R = 31.2 min.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **2**−**11**, **1b**−**1e**, **2a**−**2b**, and **3a**−**11a**. Experimental procedures and spectroscopic data of the starting olefins. This material is available free of charge via the Internet at http://pubs.acs.org.

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