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Rational design of chiral 1,1′-binaphthylazepine-based ligands for the enantioselective addition of $ZnEt_2$ to aromatic aldehydes

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Abstract—By rational design, novel atropisomeric 1,1-binaphthylazepine-based 1,2-amino alcohols **1f** and **1g** have been prepared in enantiopure form and tested as catalytic precursors in the enantioselective addition of diethylzinc to aromatic aldehydes: the corresponding (*S*)-1-arylpropanols have been obtained in quantitative yields and e.e.s up to 95%. A rationale explaining the stereochemical outcome of the reaction, as well as the influence of structural features of the ligands on the enantioselectivity of the addition, is also provided.

1. Introduction

In recent years enantiopure 1,1′-binaphthylazepines have been successfully employed as catalytic chiral ligands in several asymmetric processes.[1] However, an interpretation of their efficiency in these processes has never been provided and the rational design of chiral auxiliaries of this type for a specific reaction has never been approached. Therefore, in order to determine the structural features which affect the efficiency of such ligands and to improve their performance we recently decided to start an investigation aimed at evaluating the behavior, as chiral catalysts, of some binapthylazepine-based 1,2-amino alcohols (Fig. 1).[2,3] The enantioselective addition of $ZnEt_2$ to arylaldehydes was taken as a benchmark reaction.[4] As a matter of fact, only a single previous study was reported by Noyori and co-workers who, using the simplest amino alcohol of this series, (*S*)-**1a**, in the addition of $ZnEt_2$ to benzaldehyde, obtained a moderate 49% e.e. of (*S*)-1-phenylpropanol.[1d] Furthermore, on the basis of computational studies, Goldfuss and Houk[5] suggested that the low enantioselectivity of **1a** was due to the lack of a substituent at the oxygen bearing carbon atom C(2). With the aim of determining if the introduction of substituents of increasing size on C(2) really would afford better results, we prepared[2] some new enantiopure binaphthylazepine 1,2-amino alcohols and tested[3] them as catalytic precursors in the enantioselective ethylation of arylaldehydes. We observed that, in all cases, (*S*)-binaphthyl moieties induced the formation of the (*S*)-alcohol and that, by simply increasing the size of the R groups, with no changes to the chiral backbone of such molecules, it was possible to dramatically increase the enantioselectivity.

In fact, with ligand **1b** the enantioselectivity in the ethylation of benzaldehyde increased to 64% e.e. from the 49% e.e. of Noyori's ligand **1a**. Increasing the size of the R group in **1c**, substituted with a spirocyclohexyl moiety, and in **1d** led to even higher e.e.s of 81 and 87%, respectively. Interestingly, a further increase in the

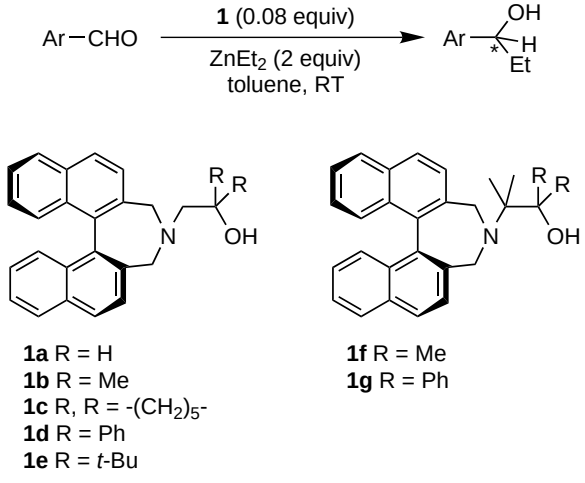

Figure 1.

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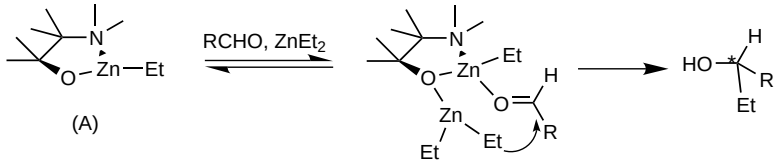
steric hindrance at C(2) in **1e**, with introduction of two *tert*-butyl moieties, led, on the contrary, to a drop in the enantioselectivity to 64% e.e. An analogous decrease occurred with the introduction of a stereogenic center at C(2).[3] Ligand **1d**, having a diphenylhydroxymethyl moiety[6] (the so called 'magic group'), was also tested in the addition of $ZnEt_2$ to a number of arylaldehydes, affording the corresponding 1-arylpropanols quickly and rapidly in e.e.s ranging from 70 to 87%.

It is generally accepted that the active catalytic species in the asymmetric ethylation of aldehydes with $ZnEt_2$ in the presence of an amino alcohol ligand is the chelated ethylzinc alkoxide (A), formed by reaction between the amino alcohol and a molecule of diethylzinc (Scheme 1).[4a] This species, coordinating both the aldehyde and a second molecule of $ZnEt_2$, then promotes the stereoselective ethylation of the carbonyl. Taking this mechanistic rationale into account we can suppose that in the amino alcohols **1b–e** the chirality of the binaphthyl moiety affects the reaction center in some way, thus leading to asymmetric induction. Chirality transmission from the binaphthyl moiety to the N–Zn–O fragment must therefore occur and, reasonably, this transmission is mediated by the groups linked to the C(2) carbon bearing the oxygen atom.

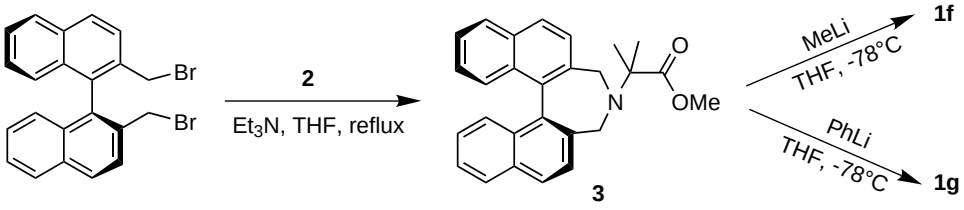
We thought that possible improvement in the enantioselectivity could also be achieved by introduction of substituents on the C(N) of the amino ethanol moiety. These groups could in fact give rise to steric interactions with both the chiral binaphthyl moiety and the phenyl groups at C(2), thus affording better chirality transfer. Herein, we therefore describe the preparation of the two new binaphthylazepine-based ligands **1f** and **1g** and the results achieved in their use as catalytic precursors in the enantioselective ethylation of arylaldehydes.

2. Results and discussion

Both amino alcohols **1f** and **1g** were easily prepared (Scheme 2) by addition of excess of MeLi or PhLi, respectively, to the binaphthylazepine amino ester (*S*)-**3**. The latter was, in turn, obtained in 83% yield by reaction of (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthalene[2,7] with the *p*-toluenesulfonate salt of methyl-2-amino-2-methylpropanoate **2**, in the presence of triethylamine in THF. Reaction of (*S*)-**3** with MeLi in THF at −78°C then afforded (*S*)-**1f** in 44% yield while reaction of (*S*)-**3** with PhLi in THF at −78°C provided (*S*)-**1g** in 74% yield.



Scheme 1.



Scheme 2.

Table 1. Enantioselective addition of $ZnEt_2$ to benzaldehyde mediated by ligands (*S*)-**1b**, **d**, **f** and **g**

Run	Ligand[a]	Time (min)	Temp. (°C)	Yield (%)[b]	E.e. (%)[c] (ac)[d]
1[e]	(*S*)-**1b**	840	20	97[f]	64 (*S*)
2[e]	(*S*)-**1d**	30	20	99	87 (*S*)
3	(*S*)-**1d**[g]	40	20	99	84 (*S*)
4	(*S*)-**1f**	120	20	98	62 (*S*)
5	(*S*)-**1g**	60	20	99	95 (*S*)
6	(*S*)-**1g**[g]	70	20	99	94 (*S*)

[a] 8 mol% of ligand was used.
[b] Chromatographic (GLC) yield. No traces of benzyl alcohol were detected.
[c] Determined by HPLC on a Chiralcel OD column.
[d] Determined by elution order on a Chiralcel OD column.[4d]
[e] See Ref. 3.
[f] About 1 mol% of benzyl alcohol was detected.
[g] 3 mol% of ligand was used.

The 1,2-amino alcohols **1f** and **1g** were tested (Table 1) in the enantioselective addition of diethylzinc to benzaldehyde and the results compared with those of the parent disubstituted amino alcohols **1b** and **1d** (Table 1).[3] The reactions were carried out in dry toluene at 20°C in the presence of 8 mol% of chiral ligand and monitored by TLC and GC–MS analysis. When complete conversion of the aldehyde was detected, the mixture was quenched by addition of 10% aqueous HCl. After extraction with Et_2O, drying, and evaporation of solvent, the product ratio was directly determined on the crude mixture by GC–MS and the e.e. of the product 1-phenyl-1-propanol was measured by HPLC on a chiral stationary phase.

The results in Table 1 show that in the presence of catalytic amounts of compounds **1f** and **1g**, diethylzinc adds smoothly and cleanly to benzaldehyde providing (*S*)-1-phenyl-1-propanol with complete conversion and no traces of benzyl alcohol. It is worth noting that while the tetramethyl derivative **1f** (run 4) affords a moderate 62% e.e., i.e. with almost the same enantioselectivity as that induced by the dimethyl compound **1b** (run 1), the dimethyldiphenyl azepine **1g** induces the formation of the alcohol (run 5) with 95% e.e., a value significantly higher than that observed using the corresponding diphenyl precursor **1d** (run 2). This result confirms the positive effect of the diphenylhydroxymethyl portion in inducing higher enantioselectivity and points out the significant effect of the *gem*-dimethyl moiety in allowing better transfer of chirality to the C(2) carbon. In order to further test the efficiency of **1d** and **1g**, two trials using only 3 mol% of these ligands were performed (runs 3 and 6), obtaining in both cases enantioselectivities comparable with those obtained with 8 mol% of ligand, even though slightly longer reaction times were required. This result is a further indication of the efficiency and suitability of this type of binaphthylazepine-based ligands for asymmetric catalysis.

The most efficient ligand of the tetrasubstituted family, **1g**, was compared with the best disubstituted one, **1d**[3] in the ethylation of a number of different aromatic aldehydes (Table 2). Both ligands afforded high e.e. values, almost irrespective of the steric and electronic nature of the substrates (a moderate detrimental effect on both the reaction rate and enantioselectivity was observed when the aldehyde contained an electron-donating methoxy group in the *para*-phenyl position) (runs 3 and 4). With all aldehydes the tetrasubstituted ligand **1g** afforded higher e.e.s than the parent **1d**, confirming the result obtained in the case of benzaldehyde, and also confirming our expectations about the best efficiency of chirality transfer in this type of ligand. In particular, with ligand **1g** e.e.s in the range 87–95% were obtained, which is, with any substrate, about 7–10% higher[8] than those afforded using **1d**.

A great number of experimental[4,9] and theoretical[5,10] studies on the mechanism of the asymmetric addition of diethylzinc to aldehydes have been reported, defining the intermediates of the reaction and providing some proposals about the possible transition states. Much of the evidence points out that the complexation of the ethylzinc aminoalkoxide (A) (Scheme 1)[4a] with both the aldehyde and a second molecule of diethylzinc, promotes the migration of an ethyl moiety to the carbonyl group through a tricyclic transition state like those depicted in Fig. 2.[10a] The energy differences between the transition states which lead to opposite enantiomers, calculated at ab initio or semiempirical levels, have been employed to explain the stereochemical outcome and the enantioselectivity displayed by different catalysts.[5,10] By means of semiempirical PM3 calculations Goldfuss and Houk[5] reported that in the addition of diethylzinc to benzaldehyde catalyzed by **1a**, the four possible transition states (Fig. 2),[11] exhibit an *anti*-(*S*)< *anti*-(*R*)<*syn*-(*R*)<*syn*-(*S*) order of relative energies. A small energy difference is present between the *anti* and *syn* structures, with the *anti*-(*S*) transition state being of slightly lower energy than the *anti*-(*R*). On the basis of

Table 2. Addition of $ZnEt_2$ to arylaldehydes mediated by ligands (*S*)-**1d** and (*S*)-**1g**[a]

Run	Ligand	Ar	Time (min)	Yield (%)[b]	E.e. (%)[c] (ac)[d]
1[e]	**1d**	C_6H_5	30	99	87 (*S*)
2	**1g**	C_6H_5	45	99	95 (*S*)
3[e]	**1d**	4-$CH_3OC_6H_4$	90	99	80 (*S*)
4	**1g**	4-$CH_3OC_6H_4$	90	99	87 (*S*)
5[e]	**1d**	4-CNC_6H_4	10	99	84[f] (*S*)[g]
6	**1g**	4-CNC_6H_4	10	99	95[f] (*S*)[g]
7[e,h]	**1d**	4-$CF_3C_6H_4$	20	99	85[i] (*S*)[g]
8	**1g**	4-$CF_3C_6H_4$	20	99	94[i] (*S*)[g]

[a] 8 mol% of amino alcohol was used.
[b] Chromatographic (GLC) yield. No traces of benzyl alcohol were detected.
[c] Determined by HPLC on a Chiralcel OD column.
[d] Determined by elution order on a Chiralcel OD column.[4d]
[e] See Ref. 3.
[f] Determined by HPLC on a Chiralcel OJ column.
[g] Determined by comparison of $[\alpha]_D$ with literature values.[16]
[h] Experiment reported in Ref. 3 was repeated and a more accurate e.e. value was determined by HPLC analysis of alcohol acetate.
[i] Determined by HPLC of its acetate derivative on a Chiralcel OJ column.

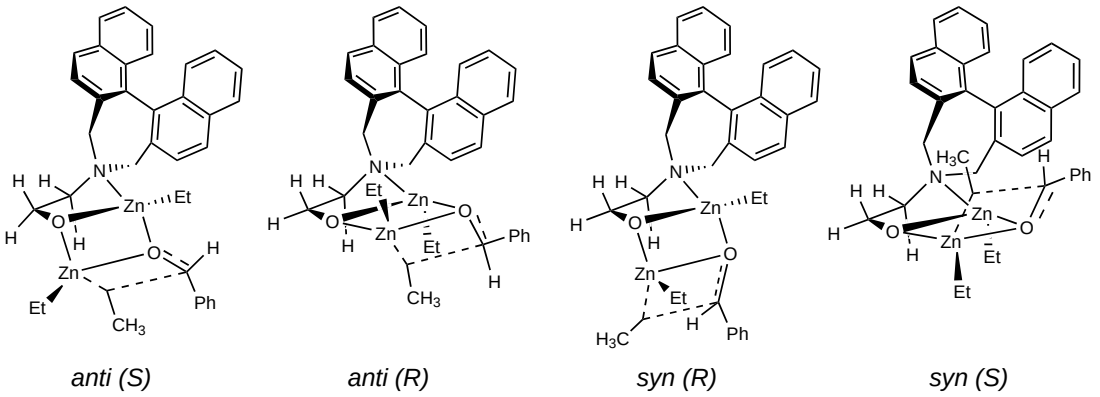


Figure 2.

this observation the preferential formation of the (*S*)-1-phenylpropanol and the low enantioselectivity achieved with **1a** could be explained. Taking these studies into account we can attempt to provide a *qualitative* rationale for the stereochemical outcome of the reaction with **1d** and **1g**, as well as of the influence of the substituents present on the amino alcoholic moiety. We can in fact reasonably suppose that also in **1d** and **1g** the two most stable transition states are *anti*-(*S*) and *anti*-(*R*) (Fig. 3) and therefore that the enantioselectivity of the reaction is primarily determined by the energy difference of the transition states.[12] In the *anti*-(*S*) and *anti*-(*R*)-transition states of **1d** and **1g** the steric influence of the benzylic CH_2 forces the groups on the carbon bearing the nitrogen (hydrogens in **1d** and methyl groups in **1g**) to adopt a pseudo-equatorial and pseudo-axial position, in turn forcing one of the phenyl groups (Ph*) on C(2) to be in an axial position and over the plane of the five-membered Zn aminoalkoxide ring. From Fig. 3 we can see that in *anti*-(*R*) the axial phenyl Ph* and the ethyl group on zinc (Et*) are on the same side of the ring, while in *anti*-(*S*) the Ph* and Et* moieties are on opposite sides. Therefore, greater destabilization of the *anti*-(*R*) with respect to the *anti*-(*S*) transition state results, giving rise to a greater energy difference between the two transition states, and leading to the higher enantioselectivity observed experimentally for **1d** and **1g** with respect to **1a**. The introduction of two more methyl groups on the nitrogen bearing carbon in **1g** gives rise to stronger steric interaction with both the benzylic CH_2 on one side and the C(2) phenyl groups on the other, forcing the Ph* group even closer to the Et* group. Enhancement of the energy difference between the *anti*-(*S*) and *anti*-(*R*) transition states results, leading to a higher enantioselectivity. In summary, in ligand **1d**, and even more in **1g**, by simple steric interactions, efficient chirality transfer from the atropisomeric chiral binaphthyl backbone to the achiral amino alcohol moiety can occur, generating a chiral environment around the zinc atom in the zinc aminoalkoxide complex.[13,14] Chirality transfer from these compounds is so efficient that even if no stereogenic center is present close to the complexing zinc atom, high enantiodiscrimination in the ethylation step is achieved. These results show, once more, how simple and rational modifications of the amino alcohol chain of these atropisomeric ligands without introducing stereogenic carbons can allow significant improvement of the efficiency and asymmetric induction properties of such ligands in the asymmetric ethylation of arylaldehydes.

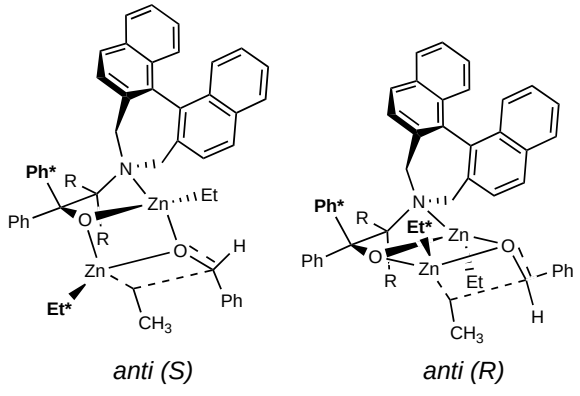


Figure 3.

3. Conclusions

By means of a rational analysis of the structural features affecting the efficiency of the 1,1′-binaphthylazepine-based amino alcohols and making therefore suitable modifications to their structure it was possible to markedly improve the enantioselectivity of such ligands in the addition of $ZnEt_2$ to aryl aldehydes. The results obtained in this reaction with ligand **1g** are among the highest displayed by a catalytic precursor having only axial chirality.[15] This fact may stimulate further theoretical investigations to quantitatively and more rigorously clarify the correlation between structure and catalytic activity of these ligands. As shown here and in our previous work[2] 1,1-binaphthylazepine amino alcohols can be easily prepared in both enantiomeric forms starting from commercially available enantiopure 1,1′-binaphthol. The marked improvement in the performance of the ligands obtained here as a result of simple structural modifications makes this type of compound promising precursors for preparing tailor-made ligands for asymmetric catalysis. Work is now in

progress on the use of these compounds as catalytic precursors for other enantioselective transformations.

4. Experimental

4.1. General procedures

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on a Bruker Aspect 300 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. THF was freshly distilled prior its use on sodium benzophenone ketyl and stored under nitrogen atmosphere. Enantiopure (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthalene was prepared as previously described.[2] 2-Methyl-2-aminopropanoic acid (α-amino isobutyrric acid) (Aldrich) was used as purchased. Triethylamine was distilled over CaH_2 and stored under nitrogen on KOH. Methyllithium (Aldrich) was used as a 1.6 M solution in diethylether, phenyllithium (Aldrich) was used as a 1.8 M solution in cyclohexane/diethylether (7:3). Addition of organometallics were performed using syringe–septum cap technique under nitrogen atmosphere. Toluene was freshly distilled prior its use on sodium benzophenone ketyl under nitrogen atmosphere. Diethylzinc was used as a 1.0 M solution in hexane (Aldrich) and was used as purchased. Commercially available (Aldrich) benzaldehyde, 4-anisaldehyde, and 4-trifluoromethylbenzaldehyde were distilled prior their use and stored under nitrogen atmosphere. Commercially available (Aldrich) 4-cyanobenzaldehyde was used as purchased. All the 1-aryl-1-propanols obtained by addition of diethylzinc to arylaldehydes showed NMR spectra in full agreement with literature data. Enantiomeric excesses of the optically active 1-aryl-1-propanols were determined by HPLC analysis performed on a JASCO PU-1580 pump with a Varian 2550 UV detector and Daicel Chiralcel OD or OJ columns. Analytical TLC was performed on 0.2 mm silica gel plate Merck 60 F-254. Mixture composition was determined by GLC–MS on a Hewlett–Packard 6890 chromatograph equipped with a HP-5973 mass detector.

4.2. Methyl 2-methyl-2-aminopropanoate *p*-toluenesulfonate, 2

A solution of 2-methyl-2-aminopropanoic acid (5.17 g, 50 mmol) and *p*-toluenesulfonic acid monohydrate (19.0 g, 100 mmol) in methanol (250 mL) was stirred under reflux for 40 h. After evaporation of the solvent under reduced pressure, the oily residue was submitted to lyophilization for 2 h. The residue was triturated with Et_2O (500 mL) and then filtered. The recovered solid was recrystallized from acetone to afford **2** as a white solid (7.36 g, 51%). Evaporation of the mother liquor afforded a further 2.6 g of slightly impure **2**. Mp 147–148°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (s, 6H), 2.35 (s, 3H), 3.71 (s, 3H), 7.16 (d, 2H, $J=8.05$ Hz), 7.76 (d, 2H, $J=8.05$ Hz), 8.32 (br s, 3H).

4.3. (*S*)-(+)-2,2′-[2-(Methoxycarbonyl-(1,1-dimethyl)-ethyl)2-azapropane-1,3-diyl]-1,1′-binaphthalen, 3

To a solution of (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthalene (660 mg, 1.5 mmol) in anhydrous THF (45 mL), under nitrogen, was added **2** (694 mg, 2.4 mmol) followed by triethylamine (1.6 mL, 11.4 mmol). The mixture was stirred under reflux for 6 days, then cooled to rt. The resulting suspension was filtered, the solid washed with THF and the collected organic phases were evaporated to dryness. The recovered solid residue was dissolved in $CHCl_3$ and washed with saturated NH_4Cl, water and brine, then dried over anhydrous Na_2SO_4. After evaporation of solvent the crude was purified by column chromatography (SiO_2; $CHCl_3$/ethyl-acetate 95:5) recovering (*S*)-**3** (495 mg, 83%) as a slightly yellow glass. $[\alpha]_D^{20}=+301.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 3H), 1.46 (s, 3H), 3.49 (d, 2H, $J=12.5$ Hz), 3.52 (s, 3H), 3.93 (d, 2H, $J=12.5$ Hz), 7.20–7.26 (m, 2H), 7.39–7.46 (m, 4H), 7.54 (d, 2H, $J=8.3$ Hz), 7.92 (d, 4H, $J=8.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1, 135.1, 134.2, 133.0, 131.3, 128.4, 128.3, 128.2, 127.5, 125.6, 125.3, 62.9, 51.5, 49.8, 24.9. Anal. calcd for $C_{27}H_{25}NO_2$:C, 82.00; H, 6.37; N, 3.54; O, 8.09. Found: C, 82.05; H, 6.30; N, 3.46; O, 8.19%.

4.4. (*S*)-(+)-2,2′-[2-(1,1,2,2-Tetramethyl-2-hydroxy-ethyl)-2-azapropane-1,3-diyl]-1,1′-binaphthalene, 1f

To a solution of (*S*)-**3** (158 mg, 0.4 mmol) in anhydrous THF (3 mL), under nitrogen at −78°C, was added dropwise a solution of MeLi in diethyl ether (1.6 M, 1.5 mL, 2.4 mmol). The mixture was stirred at −78°C for 90 min, then quenched with water and the solvent evaporated under reduced pressure. The recovered residue was dissolved in $CHCl_3$ and washed sequentially with saturated NH_4Cl, water, and brine. The organic phase was then dried over anhydrous Na_2SO_4 and concentrated to dryness. The recovered residue was purified by column chromatography (SiO_2; $CHCl_3$/ethyl-acetate 1:1) yielding (*S*)-**1f** as a glassy colorless solid (70 mg, 44%) and the corresponding ketone (60 mg) formed from single addition of MeLi to (*S*)-**3**. $[\alpha]_D^{20}=+245$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 3H), 1.23 (s, 3H), 1.26 (s, 3H), 1.41 (s, 3H), 3.42 (d, 2H, $J=12.4$ Hz), 4.13 (d, 2H, $J=12.4$ Hz), 5.4–5.8 (br s, 1H), 7.2–7.3 (m, 2H), 7.4–7.5 (m, 4H), 7.58 (d, 2H, $J=8.3$ Hz), 7.94 (dd, 4H, $J=5.2$, 7.9 Hz). Anal. calcd for $C_{28}H_{29}NO$: C, 85.02; H, 7.39; N, 3.54; O, 4.04. Found: C, 84.96; H, 7.44; N, 3.49; O, 4.11%.

4.5. (*S*)-(+)-2,2′-[2-(1,1-Dimethyl-2,2-diphenyl-2-hydroxy-ethyl)-2-azapropane-1,3-diyl]-1,1′-binaphthalene, 1g

To a solution of (*S*)-**3** (198 mg, 0.5 mmol) in anhydrous THF (4 mL), under nitrogen at −78°C, was added dropwise a solution of PhLi (1.8 M in cyclohexane/diethylether 7:3, 1.7 mL, 3.0 mmol). The resulting mixture was stirred at −78°C for 12 h, then quenched with water and the solvent evaporated to dryness. The recovered residue was dissolved in Et_2O (40 mL) and

washed sequentially with saturated NH_4Cl, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The recovered residue was purified by column chromatography (SiO_2; petroleum ether/Et_2O 95/5) affording pure (*S*)-**1g** as a glassy white solid (193 mg, 74%). $[\alpha]_D^{20} = +154$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.63 (s, 3H), 3.14 (d, 2H, $J = 12.6$ Hz), 3.54 (d, 2H, $J = 12.6$ Hz), 6.3–6.7 (br s, 1H), 7.1–7.5 (m, 14H), 7.8–8.0 (m, 8H). Anal. calcd for $C_{38}H_{33}NO$: C, 87.83; H, 6.40; N, 2.70; O, 3.08. Found: C, 87.68; H, 6.49; N, 2.66; O, 3.17%.

4.6. Typical procedure for the addition of diethylzinc to arylaldehydes

To a solution of the ligand (0.05 mmol) in dry toluene (3 mL) under a nitrogen atmosphere at rt, was added a solution of $ZnEt_2$ in hexane (1.0 M, 1.25 mL, 1.25 mmol). The mixture was stirred for 30 min, then a solution of the arylaldehyde (0.62 mmol) in dry toluene (1.3 mL) was added. The mixture was monitored by GC–MS analysis and when no more traces of the aldehyde were detected the reaction was quenched by addition of 10% aqueous HCl. The mixture was extracted with Et_2O and the organic phase was washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent the recovered solid residue was directly analyzed by GC–MS and HPLC.

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8. An e.e. increase of about 10% could appear, at a first glance, as a limited success. However, it has to be noted that an e.e. enhancement from 85 to 95% requires (see, for instance: Izumi, Y.; Tai, A. *Stereodifferentiating Reactions*; Academic Press: New York, 1977; Chapter 7, p. 178.) a $\Delta\Delta G^*$ gain of about 1 kcal/mol, i.e. a large energy difference. The e.e.s experimentally observed in the ethylation of benzaldehyde in fact correspond to a $\Delta\Delta G^*$ of 0.62 kcal/mol for **1a**, 1.55 kcal/mol for **1d**, and 2.13 kcal/mol for **1g**, respectively. This means that **1g** gives rise to TSs having larger differences, in energy and structure, with respect to those given by **1d** and **1a**.
9. See, for example: Paleo, M. R.; Cabeza, I.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 2108.
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11. The sketches in Figs. 2 and 3, although based upon the transition states calculated in Ref. 5, are just pictorial representations. For nomenclature of TS's, see Ref. 5.
12. Inspection of Fig. 2 shows a high steric crowding in the *syn*-(*R*) and *syn*-(*S*) transition states, thereby suggesting a high energy level for these structures. Therefore, their influence on the reaction path can be considered negligible and they can be reasonably ruled out from our discussion.
13. For a recent study on substituent effects, see: Ohga, T.; Umeda, S.; Kawanami, Y. *Tetrahedron* **2001**, *57*, 4825.
14. Indirect evidence for such a chiral environment can be also obtained from the ^1H NMR spectra of **1f** and **1g**. In fact, in both of these amino alcohols, the diastereotopic methyl groups on the nitrogen-bearing carbon display in the ^1H NMR spectrum a very large signal separation, of

68 Hz in **1f** and of 111 Hz in **1g**. The diastereotopicity of the phenyl groups on C(2) in **1d** and **1g** is not clearly revealed by the ^{1}H and ^{13}C NMR spectra as in the case of the methyl groups, due to the large number of aromatic signals present in their spectra. However, the signals for the methyl groups, which in **1b** and **1f** are on C(2), display a significant signal separation of 6.5 Hz, suggesting that also more remote groups on C(2) are subject to the influence of the chiral binaphthyl moiety.

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