Tetrahedron: *Asymmetry* 19 (2008) 1784–1789

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

1,1′-Binaphthylazepine-based ligands for the enantioselective dialkylzinc addition to aromatic aldehydes

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ARTICLE INFO

Article history:
Received 13 May 2008
Accepted 25 July 2008
Available online 9 August 2008

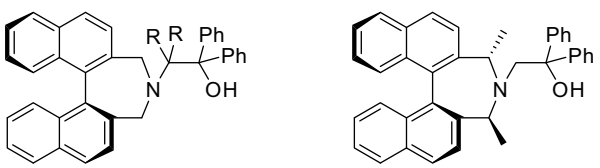
ABSTRACT

The new 1,1′-binaphthylazepine ligand **1c** has been prepared and tested in the enantioselective addition of Et_2Zn to arylaldehydes, allowing us to reach ee's up to 97% and giving extremely rapid reactions (10–20 min). Aminoalcohol **1c** and the analogous compounds **1a** and **1b** were then tested in the enantioselective addition of Bu_2Zn and Me_2Zn to arylaldehydes. All of the ligands efficiently catalyze the Bu_2Zn addition to benzaldehyde, providing good yields in short reaction times (2–4 h) and high ee (up to 96%). In the enantioselective methylation of arylaldehydes ligands **1b** and **1c** gave high yields (88–97%) and good to high (80–90%) ee's.

1. Introduction

The enantioselective addition of dialkylzinc reagents to aldehydes is one of the most studied and effective reactions for asymmetric C–C bond formation.[1] Hundreds of chiral ligands have been employed as successful catalytic precursors in this reaction, and detailed mechanistic studies have been undertaken, providing a deep understanding of the asymmetric induction mechanism.[2] For these reasons this reaction 'has become a classical test to design new chiral ligands for catalytic enantioselective syntheses', as stated by Pu and Yu in their comprehensive review.[1c] However, the large majority of the studies on the asymmetric dialkylzinc addition to aldehydes concern the use of Et_2Zn, while the analogous Me_2Zn[3,4] and Bu_2Zn[3b,g,t,4a,i,5] have been employed only sporadically, and systematic investigations of their behavior in this reaction are still lacking. Only some recent studies[3r–u,4f,h,j] have addressed the issue of investigating the reactivity of Me_2Zn with different aromatic aldehydes, reaching good to high enantioselectivity in the methylation reaction. The scarce popularity of Me_2Zn and Bu_2Zn in this reaction is mainly due to their reduced reactivity, clearly established by Noyori et al.,[2a,d] who reported that the relative reactivity of Me_2Zn, Bu_2Zn, and Et_2Zn in the alkylation of benzaldehyde catalyzed by DAIB is a 1:8:21 ratio.[6] The lower reactivity of the former two reagents requires higher reaction temperatures and longer reaction times and often determines either lower chemical yields and enantioselectivity with respect to Et_2Zn. On the other hand, the enantioselective alkylation with Me_2Zn and Bu_2Zn provides a much more synthetically attractive outcome than the Et_2Zn counterpart, given that a great number of bioactive compound bear a chiral methyl carbinol moiety[7] or can derive from butyl substituted alcohols.[8] In fact, despite the enormous number of studies concerning the enantioselective addition of Et_2Zn to aldehydes, no synthetic application of this reaction has been reported so far while few, but significant, examples concern the employment of the methylation and butylation reactions in the synthesis of bioactive compounds.[9]

We also recently employed the enantioselective addition of Et_2Zn to aldehydes to test the efficiency of new chiral ligands for asymmetric synthesis. On the basis of mechanistic considerations we rationally designed new 1,1′-binaphthylazepine aminoalcohols of general formula **1** (Fig. 1) demonstrating that, by simply tuning the size of the substituents on the C(O), with no changes on the chiral atropisomeric binaphthyl backbone, a very high increase of the enantioselectivity could be achieved.[10,11] The further insertion of substituents on the C(N), giving rise to steric interactions with both the chiral binaphthyl moiety and the substituents on the C(O), provided an even better chirality transfer between these two moieties, allowing us to obtain ee's of up to 95% in the ethylation of several arylaldehydes with ligand **1b**.[12,13] By means of these



1a R = H
1b R = Me

1c

Figure 1.

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doi:10.1016/j.tetasy.2008.07.026

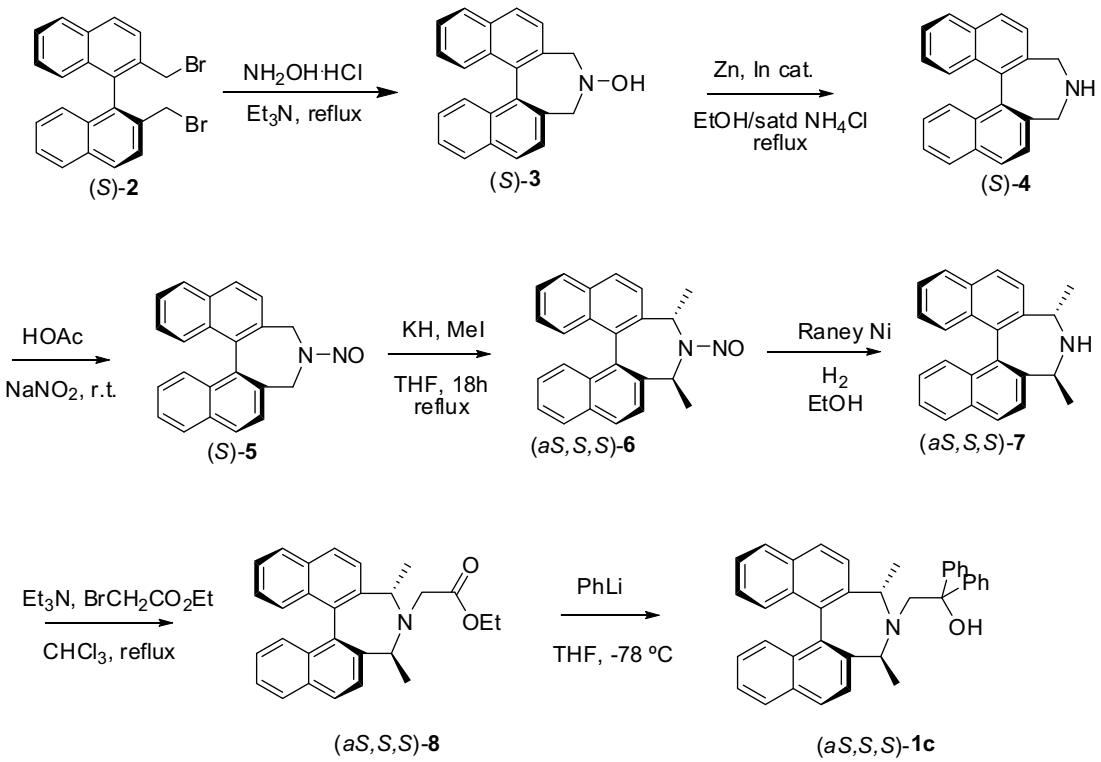
studies we also provided a qualitative rationale of the stereochemical outcome of the reaction with these ligands defining the influence of the substituents carried by the aminoalcoholic moiety. The chiral ligands **1a**,**b**, which were the most efficient ones in the ethylation reaction, were then also tested in the enantioselective addition of zinc acetylides and diphenylzinc to arylaldehydes, providing moderate to good ee's.[14]

Our previously developed ligands **1a** and **1b** present the peculiar feature of displaying only axial chirality and a *pseudo*-C_2 symmetry.[15] The enantioselectivity improvement was achieved by ensuring an efficient chirality transfer from the chiral binaphthyl moiety to the achiral aminoalcoholic fragment. The latter being the moiety which provides the zinc amino alkoxide involved in the enantioselective catalytic cycle.[1a] In searching for even more efficient aminoalcoholic ligands of this family, we herein explore a new approach to ensure such chirality transfer. We reasoned that this effect could be similarly achieved by introducing two methyls on the benzylic positions of the 1,1′-binaphthylazepine moiety. These groups could sterically connect the chiral binaphthyl moiety and the phenyls on the C(O) providing a chiral environment on the aminoalcoholic fragment. The new ligand **1c**, designed on the basis of this concept, although having two additional chiral centers, still retain the peculiar *pseudo*-C_2 symmetry. Herein we report the preparation of the new binaphthylazepine-based ligand **1c** and a comparative study of this ligand in the enantioselective ethylation of arylaldehydes. The use of aminoalcohols **1a**, **1b**, and **1c** in the Me_2Zn and Bu_2Zn enantioselective addition to arylaldehydes is also described with the aim of investigating the behavior of our ligands in these synthetically very important transformations.

2. Results and discussion

2.1. Synthesis of chiral ligands

Aminoalcohols **1a**,**b** were prepared as already described,[10,12] starting from dibromide (*S*)-**2**, in turn obtained from (*S*)-BINOL.[10,16] The new 1,1′-binaphthylazepine aminoalcohol (*aS,S,S*)-**1c** was also prepared starting from dibromide (*S*)-**2** according to the procedure described in Scheme 1. Dibromide (*S*)-**2** was treated with $NH_2OH{\cdot}HCl$ in refluxing Et_3N for 15 h obtaining hydroxylamine (*S*)-**3** in 65% yield. The latter was then reduced with zinc and a catalytic amount of indium[17] heating at reflux in a 1:2 solution of ethanol and saturated aqueous NH_4Cl to afford, after chromatographic purification, binaphthylazepine (*S*)-**4** in 97% yield. Starting from (*S*)-**4** the *N*-nitroso dimethylazepine (*aS,S,S*)-**6** was obtained following a procedure described by Rychnovsky et al.[18] Azepine (*S*)-**4** was dissolved in acetic acid, and was treated at room temperature with an aqueous solution of $NaNO_2$. After neutralization with 10 M aqueous NaOH and workup *N*-nitroso-azepine (*S*)-**5** was isolated in 87% yield. The latter was dimethylated by treatment with KH in THF at room temperature and quenching the resulting dianion with excess of methyl iodide at reflux. After workup the dimethylated *N*-nitroso-azepine (*aS,S,S*)-**6** was obtained in 83% yield. The deprotection of the *N*-nitroso derivative (*aS,S,S*)-**6**, originally described by Rychnovsky et al.[18] by using gaseous HCl, was instead more smoothly achieved by treatment with H_2 in EtOH in the presence of Raney-Ni.[19] After one night at room temperature the mixture was filtered through Celite to remove the metal catalyst, smoothly affording (*aS,S,S*)-**7** in 80% yield. The absolute configuration of the two newly formed benzylic stereocenters was confirmed by ^1H NMR analysis. The ^1H NMR of **7** showed in fact a high symmetry of the molecule, allied with a C_2 symmetric molecular structure, and then with a *anti* disposition of the two methyls. The comparison of the ^1H NMR spectrum with the literature data[18,20] clearly confirmed that, among the two possible diastereoisomers, only the desired (*aS,S,S*)-**7** was obtained. The dimethylazepine (*aS,S,S*)-**7** was then N-alkylated with ethyl bromoacetate, heating at reflux in chloroform in the presence of Et_3N. After workup and column chromatography, the aminoester (*aS,S,S*)-**8** was obtained in 41% yield. Finally, compound (*aS,S,S*)-**8** was treated with PhLi in THF at −70 °C affording, after workup and chromatographic purification, aminoalcohol (*aS,S,S*)-**1c** in 51% yield.



Scheme 1.

2.2. Enantioselective alkylations

The 1,2-aminoalcohol **1c** was tested in the enantioselective addition of diethylzinc to arylaldehydes, and the results were compared with those of the parent disubstituted aminoalcohols **1a**,**b** (Table 1). The reaction was carried out in dry toluene at 20 °C in the presence of 8 mol % of chiral ligand and monitored by TLC and GC–MS. When complete conversion of the aldehyde was detected, the mixture was quenched by the addition of 10% aqueous HCl. After extraction with Et_2O, drying, and evaporation of the solvent, the product ratio was directly determined on the crude mixture by GC–MS while the ee of the product 1-aryl-1-propanol was measured by HPLC or GC on chiral stationary phases (Fig. 2).

Table 1
Enantioselective addition of Et_2Zn to arylaldehydes mediated by ligands **1a–c**[a]

Run	Ligand	Ar	Time (min)	Yield[b] (%)	ee[c] (ac)[d] (%)
1[e]	**1a**	C_6H_5	30	99	87 (*S*)
2[e]	**1b**	C_6H_5	45	99	95 (*S*)
3	**1c**	C_6H_5	15	99	97 (*S*)
4[e]	**1a**	4-$CH_3OC_6H_4$	90	99	80 (*S*)
5[e]	**1b**	4-$CH_3OC_6H_4$	90	99	87 (*S*)
6	**1c**	4-$CH_3OC_6H_4$	15	99	93 (*S*)
7[e]	**1a**	4-CNC_6H_4	10	99	84[f] (*S*)[g]
8[e]	**1b**	4-CNC_6H_4	10	99	95[f] (*S*)[g]
9	**1c**	4-CNC_6H_4	10	99	96[f] (*S*)[g]
10[e]	**1a**	4-$CF_3C_6H_4$	20	99	85[h] (*S*)[g]
11[e]	**1b**	4-$CF_3C_6H_4$	20	99	94[h] (*S*)[g]
12	**1c**	4-$CF_3C_6H_4$	20	99	96[i] (*S*)

[a] Reaction conditions: aldehyde/ligand/Et_2Zn = 1.0:0.08:2.0, in toluene at rt.
[b] Chromatographic (GLC) yield. Isolated yields 2–3% lower than the chromatographic ones were obtained after purification on a silica gel column. No traces of benzylalcohols were detected.
[c] Determined by HPLC on Chiralcel OD-H.
[d] Determined by elution order on Chiralcel OD-H.[21]
[e] See Refs. 11 and 12.
[f] Determined by HPLC on Chiralcel OJ.
[g] Determined by comparison of $[\alpha]_D$ with literature values.[22]
[h] Determined by HPLC on Chiralcel OJ of its acetate.
[i] Determined by GC on Hydrodex-β-3P chiral column.

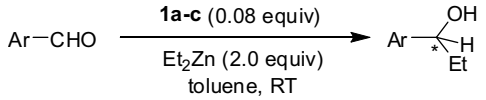


Figure 2.

The results listed in Table 1 show that the addition of Et_2Zn to benzaldehyde catalyzed by ligand **1c** provides, with complete conversion, the corresponding (*S*)-carbinol in 97% ee (run 3), a value slightly higher than the one achieved with ligand **1b** and much better than the result given by **1a**. Also, in the ethylation of differently substituted aromatic aldehydes, ligand **1c** provided ee's that were always higher than the previous ligands **1a** and **1b**, confirming the result obtained in the case of benzaldehyde. By using **1c**, an improvement in enantioselectivity of up to 6% with respect to **1b** was observed (run 6), and the ee values obtained, in the 93–97% range, were almost independent of both the steric and electronic nature of the carbonyl substrates. Notably, **1c** also provided much faster reactions (10–20 min) than the other aminoalcohols with all the aldehydes studied, including the usually less reactive *para*-methoxy substituted benzaldehyde. This result then looked encouraging toward the use of this aminoalcohol in catalyzing the addition to aldehydes of the less reactive alkylzinc reagents Me_2Zn and Bu_2Zn. This study also points out that in **1c**, the presence of the two benzylic methyls on the binaphthylazepine fragment ensures an efficient chirality transfer from the latter chiral moiety to the achiral aminoalcoholic counterpart. The higher levels of enantioselectivity and the higher reaction speed achieved suggest that within this ligand a chirality transmission even better than in the case of **1b** is achieved. With all the ligands studied **1a–c**, having (*S*) configured binaphthyl moiety, alcohols of (*S*)-absolute configuration were obtained, revealing the same sense of enantioinduction. Also in **1c**, which has two additional stereogenic centers, the sense and value of the enantioselectivity appeared to be determined mainly by the atropisomeric binaphthyl system, and therefore the mechanism of enantioinduction with ligand **1c** should be the same as suggested with the other 1,1′-binaphthylazepine aminoalcohols.[12]

1,1′-Binaphthylazepine aminoalcohols **1a–c** were then tested as catalytic precursors in the enantioselective addition of Bu_2Zn to benzaldehyde and in the addition of Me_2Zn to differently substituted arylaldehydes (Table 2). The reaction was carried out in dry toluene, at 0 °C in the case of Bu_2Zn and at room temperature with Me_2Zn. In both cases 3.0 equiv of the dialkylzinc and 10 mol % of the chiral ligand were employed. The reactions were monitored by TLC and GC–MS and when complete conversion of the aldehyde was detected, the mixture was quenched by the 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 ee of the obtained 1-aryl-carbinol was measured by HPLC or GC on chiral stationary phases (Fig. 3).

Table 2
Enantioselective addition of R_2Zn to arylaldehydes mediated by ligands **1a–c**[a]

Run	Ligand	R	Ar	Time (h)	Yield[b] (%)	ee[c] (ac) (%)
1	**1a**	*n*-Bu	C_6H_5	4	85	88 (S)[d]
2	**1b**	*n*-Bu	C_6H_5	3	84	96 (S)[d]
3	**1c**	*n*-Bu	C_6H_5	2	90	96 (S)[d]
4	**1a**	Me	C_6H_5	29	42	36 (S)[e]
5	**1b**	Me	C_6H_5	23	92	80 (S)[e]
6	**1c**	Me	C_6H_5	14	96	80 (S)[e]
7	**1a**	Me	4-$CH_3OC_6H_4$	39	38	38 (S)[f]
8	**1b**	Me	4-$CH_3OC_6H_4$	30	88	64 (S)[f]
9	**1c**	Me	4-$CH_3OC_6H_4$	15	90	90 (S)[f]
10	**1a**	Me	4-$CF_3C_6H_4$	8	91	36[g] (S)[h]
11	**1b**	Me	4-$CF_3C_6H_4$	4.5	97	80[g] (S)[h]
12	**1c**	Me	4-$CF_3C_6H_4$	1	94	80[g] (S)[h]

[a] Reaction conditions: aldehyde/ligand/R_2Zn = 1.0:0.1:3.0, in toluene at 0 °C with Bu_2Zn and at rt with Me_2Zn.
[b] Chromatographic (GLC) yield. Isolated yields 2–3% lower than the chromatographic ones were obtained after purification on a silica gel column. No traces of benzylalcohols were detected.
[c] Determined by HPLC on Chiralcel OD-H.
[d] Determined by comparison of $[\alpha]_D$ with literature values.[23]
[e] Determined by comparison of $[\alpha]_D$ with literature values.[24]
[f] Determined by comparison of $[\alpha]_D$ with literature values.[2d]
[g] Determined by GC on Hydrodex-β-3P chiral column.
[h] Determined by comparison of $[\alpha]_D$ with literature values.[3v]

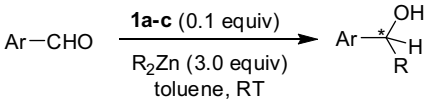


Figure 3.

As inferred from Table 2, ligands **1a–c** efficiently catalyze the addition of Bu_2Zn to benzaldehyde, providing good to high (84–90%) conversion of the substrate in 2–4 h, that is, in a reaction time significantly shorter than those reported in the literature with other catalysts (usually from 15 h to some days).[5] Compound **1a** afforded a high 88% ee, while both aminoalcohols **1b** and **1c** provided an excellent 96% ee, which is, to the best of our knowledge, among the highest values ever obtained in this reaction.[5]

Also, in the addition of Me_2Zn to benzaldehyde ligands **1b** and **1c** led to the 1-phenylethanol with high conversion (92–96%) and good 80% ee, while the parent ligand **1a** afforded a modest 36% ee and a low 42% yield. The same results were obtained in the Me_2Zn addition to 4-CF_3 benzaldehyde, where **1b** and **1c** gave almost complete

conversion and 80% ee, while **1a** provided again a moderate 36% ee. Interestingly, in the Me_2Zn addition to 4-OMe benzaldehyde larger differences among the three ligands tested were instead observed. In fact, **1a** was again the worse one, providing modest yield and ee, while **1b**, albeit giving good 88% yield, allowed us to reach a moderate 64% ee. Conversely, ligand **1c** afforded a similar 90% yield, but an excellent 90% ee, among the highest ever reached in this reaction. We can then conclude that in the methylation reaction, ligand **1c** always provided the fastest reactions, the highest yields and ee's, reaching 90% ee in the addition to *p*-anisaldehyde. Ligand **1b** gave rise to slower reactions, but provided yields and ee's comparable with **1c**, except for *p*-anisaldehyde. Finally, ligand **1a** was, as observed in the ethylation reaction, the worst of three, always providing low yields and ee's and much slower reactions.

In both butylation and methylation, carbinols of (*S*)-absolute configuration were obtained, such as in the corresponding ethylation reaction, then allowing us to envisage that the same induction mechanism is operative in all these transformations.

3. Conclusions

In conclusion, we have described herein the synthesis of the new *pseudo*-C_2 symmetric 1,1′-binaphthylazepine aminoalcohol **1c**. This compound proved to be an efficient ligand for the enantioselective addition of Et_2Zn to arylaldehydes allowing us to obtain ee's up to 97% and giving extremely rapid reactions (10–20 min). Aminoalcohol **1c** and the analogous compounds **1a** and **1b**, previously described by us, were then tested in the enantioselective addition of Bu_2Zn and Me_2Zn to arylaldehydes. All ligands efficiently catalyze the Bu_2Zn addition to benzaldehyde, providing good yields in shorter reaction times (2–4 h) and higher ee (up to 96%) than in the examples reported in the literature.

In the enantioselective methylation of arylaldehydes, ligands **1b** and **1c** gave high yields (88–97%) and good to high (80–90%) ee's. Particularly interesting is the Me_2Zn addition to *p*-anisaldehyde, where ligand **1c** allowed us to reach a 90% ee, which is an excellent result for this reaction.

These results show that ligands **1b** and **1c** can be then considered efficient chiral catalytic precursors for the enantioselective addition of both Bu_2Zn and Me_2Zn, which is a reaction endowed with interesting synthetic applications. Some synthetic applications of the enantioselective alkylation of aldehydes catalyzed by these 1,1′-binaphthylazepine ligands is currently under investigation in our laboratory.

4. Experimental

4.1. General procedures

^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian INOVA 500 MHz spectrometer using TMS as internal standard. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Melting points were taken using a Kofler Reichert-Jung Thermovar apparatus, and are uncorrected. GC–MS analyses were performed on a Hewlett Packard 6890 chromatograph equipped with a HP-5973 mass detector. Column chromatography was carried out using Macherey-Nagel Silica Gel 60 (70–230 mesh). Analytical thin-layer chromatography (TLC) was performed on Macherey-Nagel aluminum sheets precoated with silica gel (0.25 mm). Toluene and THF were freshly distilled prior to their use on sodium benzophenone ketyl and were stored under a nitrogen atmosphere. $CHCl_3$ was freshly distilled over CaH_2 prior to its use. Triethylamine was distilled over CaH_2 and stored under nitrogen on KOH. The addition of organometallics was performed using a syringe-septum cap technique under a nitrogen atmosphere. Phenyllithium (1.8 M solution in dibutylether), diethylzinc (1.0 M in hexane), dibutylzinc (1.0 M in heptane), and dimethylzinc (2.0 M in toluene) were used as purchased (Aldrich). Commercially available (Aldrich) benzaldehyde, 4-anisaldehyde, and 4-trifluoromethylbenzaldehyde were distilled prior to their use, and were stored under a nitrogen atmosphere. Unless otherwise specified, the reagents were used without any purification. Enantiopure (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthalene **2** was prepared as previously described.[10] All the 1-aryl-1-alkanols obtained by dialkylzinc addition to arylaldehydes showed NMR spectra in full agreement with the literature data. Enantiomeric excesses of the optically active 1-aryl-1-alkanols were determined by HPLC analysis performed on a JASCO PU-1580 pump with a Varian 2550 UV detector and Daicel Chiralcel OD-H or OJ columns. Enantiomeric excesses of 1-(4-trifluoromethylphenyl)-1-alkanols were determined by GC analyses on a Hewlett Packard 6890 chromatograph equipped with a flame ionization detector (FID) using a hydrodex-β-3P column (25 m × 0.25 mm, [heptakis(2,6-di-*O*-methyl-3-*O*-pentyl)]-β-cyclodextrin) and nitrogen as carrier gas.

4.2. (*S*)-(+)-3,5-Dihydro-4*H*-dinaphth[2,1-*c*:1′2′-*e*]azepine-*N*-hydroxide 3

A solution of (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthalene (**2**) (2.0 g, 4.54 mmol) and hydroxylamine hydrochloride (0.96 g, 13.8 mmol) in triethylamine (35 mL), under nitrogen, was stirred at reflux for 15 h. The resulting suspension was filtered, the solid residue washed with diethyl ether, and the collected organic phases were evaporated to dryness. The recovered solid residue was washed with petroleum ether, affording hydroxylamine **3** (1.27 g, 90%), which was used without further purification. Mp 180.0–182.7 °C; $[\alpha]_D^{20} = +354.7$ (*c* 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 2.80 (br s, 1H); 3.38 (d, *J* = 8.8 Hz, 1H); 3.88 (d, *J* = 14.3 Hz, 1H); 4.08 (d, *J* = 14.3 Hz, 1H); 4.19 (d, *J* = 8.8 Hz, 1H); 7.3 (d, *J* = 7.5 Hz, 2H); 7.48 (dd, J_1 = 8.0 Hz; J_2 = 7.5 Hz, 4H); 7.63 (d, *J* = 8.0 Hz, 2H); 7.96 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 105.0; 126.2; 126.6; 127.7; 127.8; 128.6; 128.8; 133.6; 133.8; 143.4; 159.9. Anal. Calcd for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50. Found: C, 84.81; H, 5.48; N, 4.56.

4.3. (*S*)-(+)-3,5-Dihydro-4*H*-dinaphth[2,1-*c*:1′2′-*e*]azepine 4

N-Hydroxy-azepine **3** (1.27 g, 4.1 mmol) was added to a 2:1 solution of EtOH and saturated aqueous NH_4Cl. Indium powder (23.5 mg, 0.2 mmol) and zinc (533 mg, 8.2 mmol) were than added, and the mixture was stirred under reflux for 20 h. After cooling, the mixture was filtered through Celite and concentrated. A saturated Na_2CO_3 solution was added, and the solution was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated in vacuo. The crude was purified by column chromatography (SiO_2; diethyl ether/methanol 9:1) affording binaphthylazepine **4** as a white solid (1.19 g, 98%). Mp 147–149 °C (lit.[25] mp 147–149 °C); $[\alpha]_D^{20} = +543.7$ (*c* 0.54, $CHCl_3$) {lit.[25,26] $[\alpha]_D^{20} = +574.8$ (*c* 0.8, $CHCl_3$)}; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 2.12 (br s, 1H); 3.53 (d, *J* = 11.7 Hz, 2H), 3.85 (d, *J* = 11.7 Hz, 2H); 7.23–7.31 (m, 2H); 7.43–7.50 (m, 4H); 7.58 (d, *J* = 8.3 Hz, 2H); 7.94–8.02 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 48.4; 125.2; 125.6; 126.8; 127.1; 128.1; 128.7; 131.2; 132.8; 134.6; 134.8. Anal. Calcd for $C_{22}H_{17}N$: C, 89.46; H, 5.80; N, 4.74. Found: C, 89.52; H, 5.86; N, 4.69.

4.4. (*S*)-(−)-*N*-Nitroso-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine 5

To a solution of **4** (0.79 g; 2.68 mmol) in acetic acid (28 mL) was added dropwise a solution of $NaNO_2$ (533 mg; 7.73 mmol)

in H_2O (8 mL). The mixture was stirred at rt for 2 h, and then was poured into an ice bath cooled flask. The mixture was basified by the addition of 10 M aqueous NaOH, then extracted with toluene. The collected organic phases were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, product **5** was obtained as a yellow solid (760 mg, 87%), and was used without further purification. Mp 57.5–57.7 °C; $[\alpha]_D^{25} = -212.3$ (*c* 0.68; $CHCl_3$) {lit.[18] $[\alpha]_D^{25} = -195.1$ (*c* 0.99; $CHCl_3$)}; ^1H NMR (500 MHz; $CDCl_3$): δ (ppm) 3.65 (d, *J* = 15.0 Hz, 1H); 4.74 (d, *J* = 13.5 Hz, 1H); 5.67 (d, *J* = 15.0 Hz, 1H), 5.72 (d, *J* = 13.5 Hz, 1H); 7.28–7.34 (m, 2H); 7.40–7.45 (m, 2H); 7.54–7.57 (m, 3H); 7.70 (d, *J* = 8.5 Hz, 1H); 7.99–8.05 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 47.4, 54.2, 126.3, 126.4, 126.5, 127.1, 127.5, 127.8, 128.2, 129.1, 129.6, 130.4, 131.1, 131.7, 133.4, 133.9. Anal. Calcd for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97; N, 8.64. Found: C, 81.52; H, 5.05; N, 8.62.

4.5. (*aS,S,S*)-(−)-*N*-Nitroso-3,5-dihydro-3,5-dimethyl-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine 6

To a solution of **5** (610 mg; 1.88 mmol) in anhydrous THF (69 mL) under nitrogen was added KH (30% dispersion in mineral oil, 1.04 g, 26.00 mmol) previously washed with anhydrous hexane. The mixture was stirred at rt for 30 min, then CH_3I (1.9 mL; 30.00 mmol) was added, causing the formation of a white precipitate. The mixture was heated at reflux for 18 h and then, after cooling in an ice bath, H_2O was added to dissolve the precipitate. The aqueous phase was separated and extracted with Et_2O. The collected organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, compound **6** was recovered as a yellow solid (560 mg, 84%). Mp 225.8 °C; $[\alpha]_D^{25} = -175.1$ (*c* 0.94; $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.176 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 7.5 Hz, 3H), 6.09 (q, *J* = 7.0 Hz, 1H), 6.17 (q, *J* = 7.5 Hz, 1H), 7.38–7.27 (m, 4H), 7.54–7.49 (m, 3H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.97 (t, *J* = 7.0 Hz, 3H), 8.02 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 17.7, 21.4, 55.6, 64.9, 126.6, 126.7, 127.4, 127.5, 127.8, 128.4, 128.5, 129.7, 129.9, 132.8, 133.5. Anal. Calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.83; H, 5.68; N, 7.91.

4.6. (*aS,S,S*)-(+)-3,5-Dihydro-3,5-dimethyl-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine 7

To a solution of **6** (550 mg, 1.56 mmol) in anhydrous ethanol was added activated Raney-Ni under nitrogen atmosphere, and a stream of hydrogen was bubbled overnight in the mixture. The turbid white suspension was filtered over a short path of Celite, and the solid residue was washed with ethanol. The collected solution was evaporated to dryness affording amine **7** as a yellow solid (300 mg, 59%). Mp 137.4–137.7 °C (lit.[18] mp 137–138 °C); $[\alpha]_D^{20} = +369.8$ (*c* 0.86, $CHCl_3$) (lit.[20] $[\alpha]_D^{23} = +365$ (*c* 1.0, CH_2Cl_2)); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.79 (d, *J* = 7.5 Hz, 6H), 2.4 (br s, 1H); 4.37 (q, *J* = 7.2 Hz, 2H), 7.21 (ddd, *J* = 7.5, 7.2, 1.0 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 140.3, 134.4, 133.3, 133.1, 129.2, 128.5, 128.4, 128.3, 126.1, 125.8, 57.2, 22.4. Anal. Calcd for $C_{24}H_{21}N$: C, 89.12; H, 6.54; N, 4.33. Found: C, 89.16; H, 6.50; N, 4.37.

4.7. (*aS,S,S*)-(+)-*N*-Ethoxycarbonylethyl-3,5-dihydro-3,5-dimethyl-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine 8

To a solution of amine **7** (300 mg; 0.90 mmol) in anhydrous $CHCl_3$ (28.5 mL), under nitrogen, were added anhydrous Et_3N (3.51 mL, 25.32 mmol) and ethyl bromoacetate (390 μL, 3.54 mmol). The mixture was heated at reflux for 24 h, then cooled at rt, diluted with $CHCl_3$, and extracted with 10% aqueous HCl. The aqueous phase was neutralized with 10% aqueous NaOH, and was extracted with $CHCl_3$. The organic phase was dried over anhydrous Na_2SO_4 and evaporated, providing a solid residue. After chromatographic purification (SiO_2, $CHCl_3$/ethyl acetate 97:3), compound **8** was recovered as a white solid (153 mg, 41%). ^1H NMR (500 MHz; $CDCl_3$): δ (ppm) 0.68 (d, *J* = 7.5 Hz, 6H); 1.31 (t, *J* = 7.0 Hz, 3H); 3.64 (d, *J* = 17 Hz, 1H); 3.68 (d, *J* = 17 Hz, 1H); 4.18–4.25 (m, 4H); 7.26 (t, *J* = 7.5 Hz, 2H); 7.39 (d, *J* = 9.0 Hz, 2H); 7.45 (t, *J* = 7.5 Hz, 2H); 7.52 (d, *J* = 8.5 Hz, 2H); 7.92–7.95 (m, 4H). Anal. Calcd for $C_{28}H_{27}NO_2$: C, 82.12; H, 6.65; N, 3.42. Found: C, 82.15; H, 6.67; N, 3.48.

4.8. (*aS,S,S*)-(+)-*N*-(2,2-Diphenyl-2-hydroxyethyl)-3,5-dihydro-3,5-dimethyl-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine 1c

To a solution of **8** (140 mg; 0.34 mmol) in anhydrous THF (40 mL) was added at −78 °C, under nitrogen, PhLi (1.8 M, 1.32 mL, 2.38 mmol). The mixture was stirred for 4 h at −78 °C, then quenched with 10% aqueous HCl. The aqueous phase was extracted with Et_2O, and the collected organic phases were dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude was purified by column chromatography (SiO_2; petroleum ether/Et_2O 95:5) to afford compound **1c** as a white solid (90 mg, 51%). Mp 77.0–80.0 °C; $[\alpha]_D^{25} = +3.2$ (*c* 0.57, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ (ppm) 0.47 (d, *J* = 7.0 Hz, 6H); 3.62 (d, *J* = 13.5 Hz, 1H); 3.81 (q, *J* = 7.0 Hz, 2H); 3.89 (d, *J* = 13.5 Hz, 1H); 7.22–7.25 (m, 4H); 7.28–7.31 (m, 3H); 7.33–7.38 (m, 5H); 7.45 (t, *J* = 7.2 Hz, 2H); 7.61 (d, *J* = 8.0 Hz, 2H); 7.72 (d, *J* = 8.0 Hz, 2H); 7.91–7.93 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 18.5, 63.6, 65.6, 73.8, 125.3, 125.5, 125.8, 125.9, 126.6, 127.1, 128.0, 128.1, 128.2, 128.9, 132.6, 132.8, 134.1, 139.8, 146.9, 147.6. Anal. Calcd for $C_{38}H_{33}NO$: C, 87.83; H, 6.40; N, 2.70. Found: C, 87.78; H, 6.44; N, 2.75.

4.9. Typical procedure for the diethylzinc addition 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 Et_2Zn in hexane (1.0 M, 1.25 mL, 1.25 mmol). The mixture was stirred for 30 min, then a solution of arylaldehyde (0.62 mmol) in dry toluene (1.3 mL) was added. The mixture was monitored by GC–MS, 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 solvent, the crude was directly analyzed by GC–MS to determine the yield and by either HPLC or GC to establish the ee.

4.10. Typical procedure for the dibutyl and dimethyl addition to arylaldehydes

To a solution of the ligand (0.06 mmol) in dry toluene (3 mL) under a nitrogen atmosphere at rt was added a solution of the dialkylzinc (1.80 mmol). The mixture was stirred for 30 min at rt or at 0 °C, then a solution of arylaldehyde (0.60 mmol) in dry toluene (1.3 mL) was added. The mixture was monitored by GC–MS, and when no more traces of the aldehyde were detected the reaction was quenched by the 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 crude was directly analyzed by GC–MS to determine the yield and by either HPLC or GC to establish the ee.

Acknowledgments

Financial support from MIUR and Università della Basilicata (Potenza) is gratefully acknowledged. We thank Dr. M. G. Pizzuti for preliminary studies on the synthesis of ligand **1c**.

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