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1,1′-Binaphthylazepine-based ligands for asymmetric catalysis. Part 1: Preparation and characterization of some new aminoalcohols and diamines

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Abstract—Starting from (*S*)-1,1′-binaphthol, a series of ten novel enantiopure 1,1′-binaphthylazepine-based aminoalcohols and diamines **1a**–**1j** were efficiently prepared and fully characterized. These derivatives, having either only an atropisomeric bridged-binaphthyl backbone or an additional stereogenic carbon center, can be interesting ligands for asymmetric catalysis.

1. Introduction

Optically active 2,2′-disubstituted-1,1′-binaphthyls constitute the chiral backbone of a large number of auxiliaries and ligands for asymmetric synthesis.[1] However, among them, chiral 1,1′-binaphthylazepine ligands (Fig. 1) have received only limited attention, despite the fact that in some cases they showed promising levels of enantiodiscrimination.

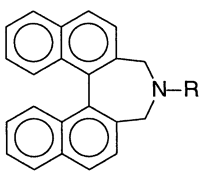

Figure 1.

The diamine with $R=CH_2CH_2N(CH_3)_2$, reported by Cram et al.[2] in 1981 for the stoichiometric enantioselective addition of RLi to aldehydes, has been more recently employed in the enantioselective dihydroxylation of olefins.[3] The simple amine with R = H was employed in the asymmetric Michael addition to crotonates,[4] while the alkyl-substituted amine having R = (*S*)-$CH(Ph)CH_3$ was used[5] as a ligand in the asymmetric reduction of ketones with borane. Oxaziridinium[6] and *N*-oxoammonium[7] salts of such binaphthylazepines were used, respectively, in the enantioselective epoxidation of alkenes and in the oxidation of secondary alcohols. Aminophosphines having such chiral scaffolds gave high enantioselectivities in allylic alkylation[8] and amination reactions,[8c] but gave only moderate results in cross-coupling reactions[8b] and hydrogenations.[8b] Finally, the aminoalcohol with R = CH_2CH_2OH was used by Noyori[9] in the catalytic enantioselective addition of $ZnEt_2$ to benzaldehyde, the secondary alcohol being obtained with moderate e.e. Very recently, higher e.e.s have been obtained in the same reaction employing binaphthylazepine-based *N*-benzyl and *N*-methylferrocenyl aminoalcohols possessing both axial and planar chirality.[10]

From this literature résumé it is evident that, although 1,1′-binaphthylazepine-based ligands have been known since the early 1980s, and have been tested in several asymmetric processes, they have been employed quite randomly and their use has never been approached in a systematic way. Moreover, a detailed study aimed at defining the structural features which are responsible for their efficiency as chiral inducers is still lacking. These considerations prompted us to carry out a systematic study on a larger group of chiral ligands belonging to this class, with the aim of improving their performance and widening their use as ligands in asymmetric catalysis. Taking into account the high efficiency displayed by aminoalcohols and diamines in asymmetric synthesis,[11] we decided to undertake an investigation aimed at evaluating the scope and limitations of the

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aminoalcohols and diamines **1a**–**1j** possessing the binaphthylazepine skeleton (Fig. 2) as chiral catalysts. Thus, we herein report the preparation and characterization of the ligands **1a**–**1j**.

2. Results and discussion

Compounds **1a**–**1j** can be easily obtained (vide infra) from homochiral (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthalene (*S*)-**2**, which is readily synthesized from enantiopure (*S*)-1,1′-binaphthol.[12] Compounds (*S*)-**1a**–**1g** have the interesting feature that, by changing the substituents at C(O), ligands where the chirality is either due only to atropisomerism or also due to the presence of a stereogenic center can be prepared. The binaphthylazepines (*S*)-**1h** and (*S*)-**1j**, having an additional aromatic or heteroaromatic moiety, were also prepared taking into account the promising enantioselectivity afforded by chiral aminopyridine[13] and aminophenol[11,14] ligands.

The dibromide (*S*)-**2**, common precursor for **1a**–**1j**, was prepared in enantiopure form by modifying a recent literature method (Scheme 1).[12] The ditriflate (*S*)-**3** was prepared from (*S*)-1,1′-binaphthol according to the literature.[15] A cross-coupling reaction[16] of (*S*)-**3** with MeMgBr in THF, in the presence of a nickel catalyst (5 mol%), provided the 2,2′-dimethyl derivative (*S*)-**4**. Instead of $NiCl_2$(dppp), as reported in the literature,[16] we tested both $NiCl_2$(dppe) and $NiCl_2(PPh_3)_2$ as catalysts in this reaction. The former afforded the coupled

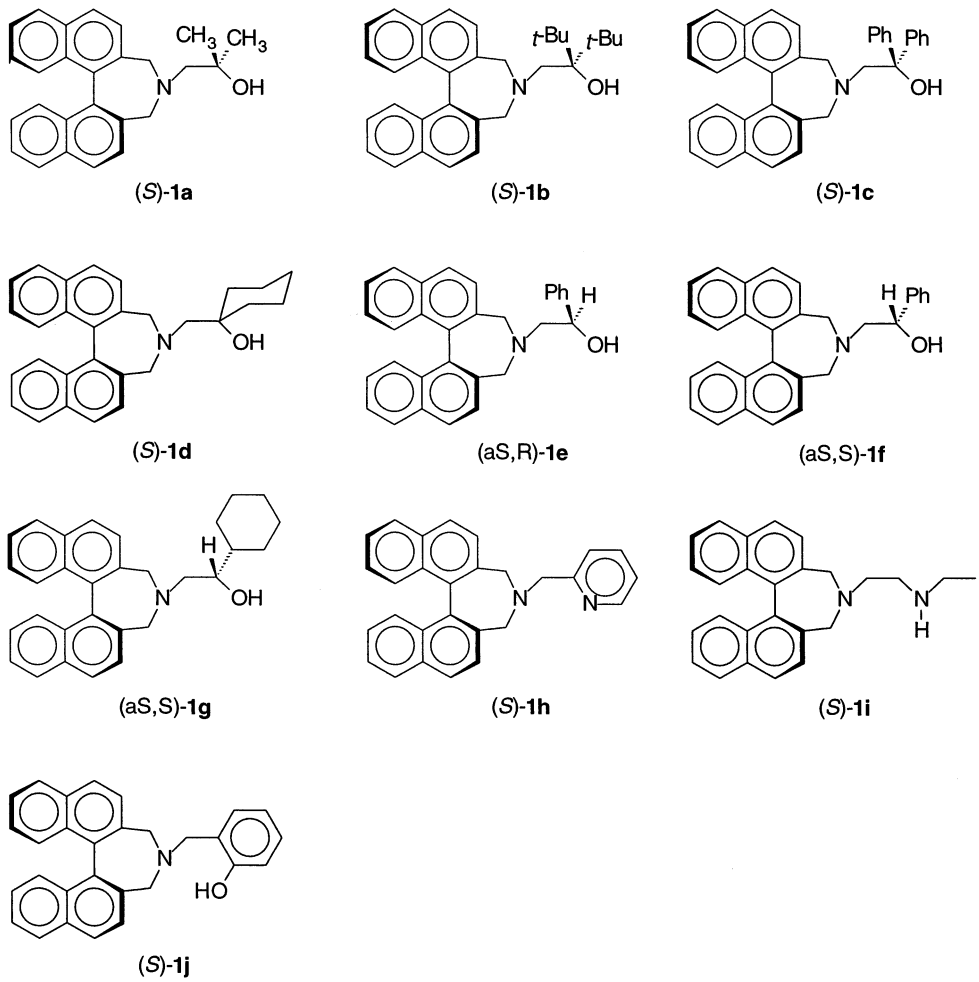
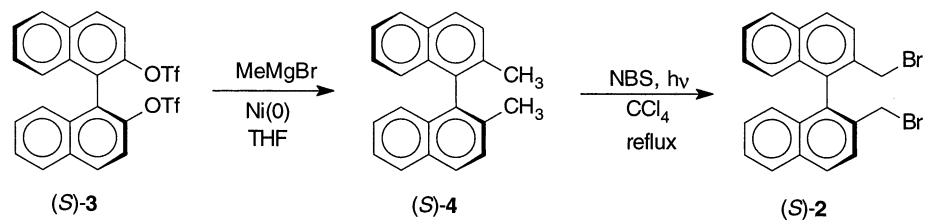
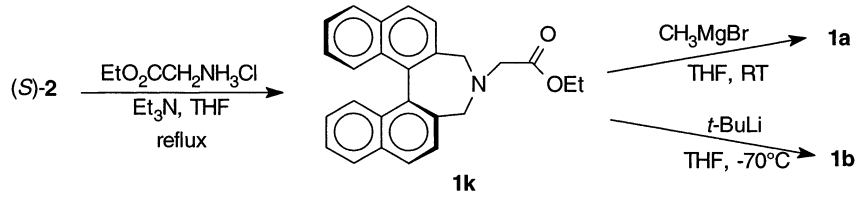


Figure 2.



Scheme 1.

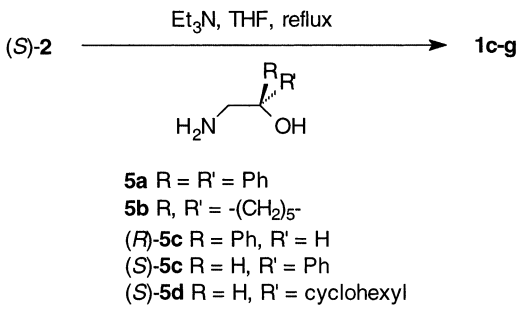


Scheme 2.

product (*S*)-**4** in 92% yield from a reaction of 48 h duration, while the latter gave rise, unexpectedly, to a rapid exothermic reaction (1 h) and afforded (*S*)-**4** in 90% yield. Subsequent benzylic bromination of (*S*)-**4** with NBS in refluxing CCl_4 (with light irradiation) afforded the desired (*S*)-**2** in 80% yield. HPLC analysis on a chiral column (Chiralcel OJ chiral stationary phase) showed that both (*S*)-**4** and (*S*)-**2** were enantiomerically pure. Therefore, the sequence from (*S*)-1,1′-binaphthol to (*S*)-**2** is completely stereospecific. Enantiopure (*S*)-**2** was then used to synthesize the binaphthylazepines **1a**–**1j**.

(*S*)-**2** was reacted with glycine ethyl ester hydrochloride, in the presence of excess of Et_3N in refluxing THF, affording (*S*)-**1k** in 50% yield (Scheme 2). The latter was then converted to the aminoalcohol (*S*)-**1a** (67% yield) by reaction with 2.2 equiv. of MeMgBr in THF and to compound (*S*)-**1b** (30% yield) by reaction with 2 equiv. of *tert*-BuLi in THF.

The synthesis of compounds **1c**–**1g** was performed following the same approach. The dibromide (*S*)-**2** was reacted with the aminoalcohol precursors **5a**–**5d** by heating under reflux in THF with excess Et_3N (Scheme 3). Thus, the diphenyl analog (*S*)-**1c** was prepared in 93% yield by reaction of (*S*)-**2** with 1,1-diphenyl-2-aminoethanol **5a** (previously obtained in 52% yield by reacting glycine ethyl ester hydrochloride with 6 equiv. of PhMgBr in THF).[17] Reaction of (*S*)-**2** with the commercially available 1-aminomethylcyclohexanol hydrochloride **5b** afforded the cyclohexyl analog (*S*)-**1d** in 91% yield. The monophenyl analog (*aS*,*R*)-**1e** was prepared in 55% yield by reaction between (*S*)-**2** and enantiomerically pure (*R*)-2-amino-1-phenylethanol[18] (*R*)-**5c** and, similarly, reaction of (*S*)-**2** with (*S*)-2-amino-1-phenylethanol (*S*)-**5c** and (*S*)-2-amino-1-cyclohexylethanol (*S*)-**5d** afforded the aminoalcohols (*aS*,*S*)-**1f** (84% yield) and (*aS*,*S*)-**1g** (92% yield), respectively.



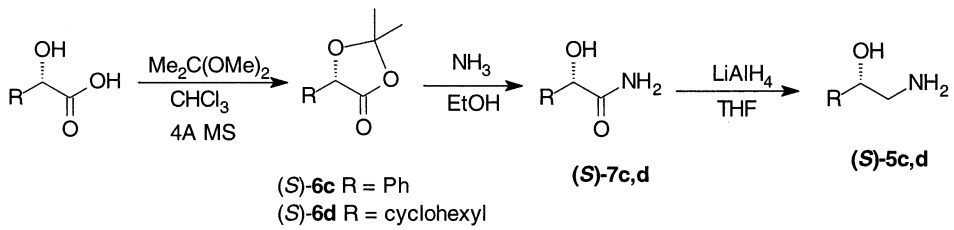
Scheme 3.

(*S*)-**5c** was prepared starting from (*S*)-mandelic acid according to the procedure reported in Scheme 4. (*S*)-Mandelic acid was treated with 2,2-dimethoxypropane in $CHCl_3$ in the presence of 4 Å molecular sieves to obtain the cyclic dioxolanone (*S*)-**6c** in 85% yield.[19] The latter was then reacted with NH_3 in EtOH to afford the (*S*)-mandelamide (*S*)-**7c** in 78% yield, which was subjected to $LiAlH_4$ reduction in THF to afford (*S*)-**5c** in 30% yield. Accordingly, (*S*)-**5d** was prepared from (*S*)-hexahydromandelic acid.

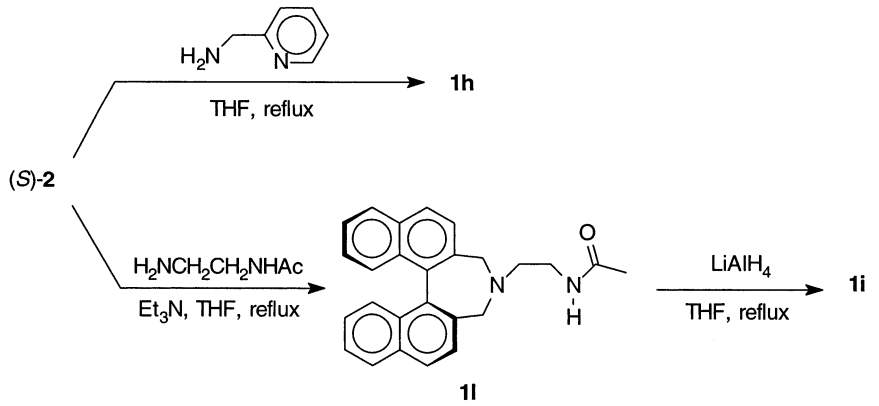
The aminopyridine (*S*)-**1h** was prepared in 90% yield by reacting (*S*)-**2** with 6.0 equiv. of 2-(aminomethyl)pyridine (Scheme 5). Reaction of (*S*)-**2** with 3 equiv. of *N*-acetylethylenediamine gave the compound (*S*)-**1l** in 97% yield, which was further reduced with $LiAlH_4$ in THF to obtain the diamine (*S*)-**1i** in 50% yield (Scheme 5). Finally, reaction of (*S*)-**2** with 2 equiv. of 2-methoxybenzylamine in THF containing 3 equiv. of Et_3N afforded (*S*)-**1m** in 69% yield. The latter was then demethylated with BBr_3 in CH_2Cl_2 at rt to provide the aminophenol (*S*)-**1j** in 96% yield (Scheme 6).

3. Conclusions

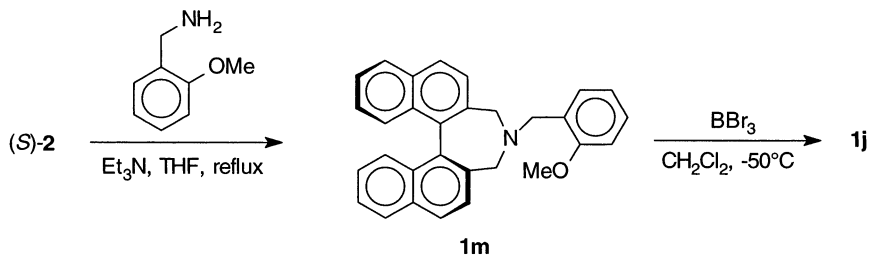
We have prepared and characterized a series of new 1,1′-binaphthylazepines **1a**–**1j** in enantiopure form. The synthetic methods developed for preparing **1a**–**1j** are very straightforward and efficient and **1a**–**1j**, dis-



Scheme 4.



Scheme 5.



Scheme 6.

playing either only atropisomeric chirality or additional stereogenic centers, constitute promising and interesting chiral ligands to be tested in the multitude of asymmetric tranformations catalyzed by aminoalcohols and diamines.[11] The availability of a large number of compounds with the same chiral backbone but with different structural features will allow the determination of the features which affect the performance of such compounds in asymmetric catalysis. This type of information will certainly be useful to both experimental and theoretical researchers in clarifying the correlation between structure and catalytic activity. The efficiency of compounds **1a**–**1g** as chiral ligands has been tested in the enantioselective addition of Et_2Zn to aromatic aldehydes, taken as a benchmark reaction.[20] Work is now in progress to study the efficiency of compounds **1a**–**1j** in other asymmetric transformations.

4. Experimental

4.1. General procedures

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. ^1H 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. Enantiomeric purities of compounds (*S*)-**2** and (*S*)-**4** were checked by HPLC analyses on a Daicel Chiralcel OJ chiral stationary phase using a 95:5 hexane/*iso*-propanol mixture as eluent. THF was freshly distilled prior to use from sodium benzophenone ketyl and stored under a nitrogen atmosphere. CCl_4 and CH_2Cl_2 were distilled, respectively, from CaH_2 and P_2O_5 and stored over activated 4 Å molecular sieves. Triethylamine was distilled over CaH_2 and stored under nitrogen on KOH. Methylmagnesium bromide (Aldrich) was used as a 3.0 M solution in diethyl ether, phenylmagnesium bromide (Aldrich) was used as a 1.0 M solution in THF, and *tert*-butyl lithium (Aldrich) was used as a 1.7 M solution in pentane. The additions of organometallic reagents were performed using the syringe-septum cap technique under a nitrogen atmosphere. Enantiopure (*R*)-2-amino-1-phenylethanol (*R*)-**5c**[18] and (*S*)-1,1′-binaphthol[21] were prepared according to literature procedures. (*S*)-1,1′-Bi-2-naphthol-bis(trifluoromethanesulfonate) (*S*)-**3** was prepared from (*S*)-1,1′-binaphthol according to literature procedures.[15] Glycine ethyl ester hydrochloride, 1-aminomethylcyclohexanol hydrochloride, 2-aminomethylpyridine, *N*-acetylethylendiamine, and 2-methoxybenzylamine were used as purchased (Aldrich). Analytical and preparative TLC were performed, respectively, on 0.2 and 2.0 mm silica gel plates Merck 60 F-254 and column chromatography was carried out with silica gel Merck 60 (80–230 mesh) or neutral aluminum oxide activity grade 1 Riedel deHaen (70–290 mesh).

4.2. (*S*)-(+)-2,2′-Dimethyl-1,1′-binaphthalene 4

To a solution of (*S*)-**3** (5.0 g, 9.1 mmol) and $NiCl_2(PPh_3)_2$ (417 mg, 0.64 mmol) in anhydrous Et_2O (35 mL) under nitrogen was slowly added MeMgBr (3.0 M, 12.2 mL, 36.4 mmol). During the addition the mixture spontaneously warmed and the solvent started to boil vigorously. The reaction was cooled with a

water-ice bath and monitored by TLC. After stirring for 1 h the solution was diluted with Et_2O, washed with 5% aqueous HCl, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (SiO_2; petroleum ether) affording (*S*)-**4** as a colorless glass (2.26 g, 88%). E.e. 99%; $[\alpha]_D^{21}=+37.7$ (*c* 1.0; $CHCl_3$) {lit.:[22] $[\alpha]_D^{20}=-35.6$ (*c* 1.0; $CHCl_3$) for (*R*)-**4** in 94% e.e.}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.0 (s, 6H), 7.0 (d, 2H, $J=8.4$ Hz), 7.2 (m, 2H), 7.4 (t, 2H, $J=7.4$ Hz), 7.5 (d, 2H, $J=8.4$ Hz), 7.9 (m, 4H).

4.3. (*S*)-(−)-2,2′-Dibromomethyl-1,1′-binaphthalene 2

To a solution of (*S*)-**4** (2.16 g, 7.66 mmol) in CCl_4 (20 mL) was added *N*-bromosuccinimide (2.72 g, 15.32 mmol). The solution was stirred under reflux under visible light for 4 h and cooled to rt. After evaporation of the solvent, the residue was dissolved in $CHCl_3$. The resultant organic solution was washed with H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The recovered product was dissolved in petroleum ether/CH_2Cl_2 (1:1) and filtered through a short pad of silica gel and the filtrate evaporated. The evaporation residue was purified by recrystallization from hexane to afford (*S*)-**2** as a white solid (2.73 g, 81%). Mp 183.0–183.7°C, lit.[23] mp 183.5–184°C; $[\alpha]_D^{21}=-160.0$ (*c* 1.0; benzene) {lit.:[23] $[\alpha]_D^{20}=-160.3$ (*c* 1.0; benzene) for (*S*)-**2** in 99% e.e.}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.2 (s, 4H), 7.1 (d, 2H, $J=8.4$ Hz), 7.2 (m, 2H), 7.3 (m, 2H), 7.5 (m, 2H), 7.7 (d, 2H, $J=8.5$ Hz), 8.0 (d, 2H, $J=8.5$ Hz).

4.4. (*S*)-(+)-2,2′-[2-(Ethoxycarbonylethyl)-2-azapropane-1,3-diyl]-1,1′-binaphthalene 1k

To a solution of (*S*)-**2** (200 mg, 0.45 mmol) in anhydrous THF (15 mL) under an inert atmosphere were added glycine ethyl ester hydrochloride (100 mg, 0.7 mmol) and triethylamine (251 μL, 1.8 mmol). The mixture was stirred under reflux for 48 h and then cooled to rt. The solution was filtered, the solid residue was washed with THF and the collected resulting solution was concentrated in vacuo. The recovered solid residue was dissolved in $CHCl_3$, washed sequentially with H_2O and brine, and the organic layer was dried over anhydrous Na_2SO_4. After evaporation of solvent, the recovered residue was purified by column chromatography (SiO_2; $CHCl_3$/MeOH, 6:1) affording **1k** (81 mg, 51%). $[\alpha]_D^{21}=+278$ (*c* 1.1; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.3 (t, 3H, $J=7.1$ Hz), 3.2 (d, 2H, $J=16.2$ Hz), 3.3 (d, 2H, $J=12.3$ Hz), 3.4 (d, 2H, $J=16.2$ Hz), 3.8 (d, 2H, $J=12.3$ Hz), 4.2 (q, 2H, $J=7.1$ Hz), 7.3 (m, 2H), 7.5 (m, 4H), 7.6 (d, 2H, $J=8.2$ Hz), 7.9 (d, 4H, $J=8.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 135.1, 133.3, 133.0, 131.4, 128.4, 128.3, 127.8, 127.5, 125.8, 125.5, 60.8, 57.8, 57.0, 55.7, 14.3. Anal. calcd for $C_{26}H_{23}NO_2$: C, 81.86; H, 6.08; N, 3.67. Found: C, 81.73; H, 5.96; N, 3.59%.

4.5. (*S*)-(+)-2,2′-[2-(2,2-Dimethyl-2-hydroxyethyl)-2-azapropane-1,3-diyl]-1,1′-binaphthalene 1a

To a solution of (*S*)-**1k** (172 mg, 0.45 mmol) in anhydrous THF (15 mL) under an inert atmosphere was added dropwise MeMgBr (3.0 M, 0.45 mL, 1.35 mmol). The mixture was stirred at rt for 16 h, then quenched with a few drops of H_2O and the solvent evaporated. The residue was dissolved in $CHCl_3$ and washed sequentially with H_2O and brine. The organic solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The recovered residue was purified by column chromatography (SiO_2; $CHCl_3$/Et_2O, 9:1) affording **1a** as a colorless glass (110 mg, 67%). $[\alpha]_D^{21}=+226.7$ (*c* 1.0; THF); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 3H), 1.26 (s, 3H), 2.21 (d, 1H, $J=13.8$ Hz), 2.85 (d, 1H, $J=13.8$ Hz), 3.1–3.6 (br s, 1H), 3.40 (d, 2H, $J=12.2$ Hz), 3.71 (d, 2H, $J=12.2$ Hz), 7.2–7.3 (m, 2H), 7.4–7.5 (m, 4H), 7.54 (d, 2H, $J=8.2$ Hz), 7.9–8.0 (m, 4H). Anal. calcd for $C_{26}H_{25}NO$: C, 84.98; H, 6.86; N, 3.81. Found: C, 84.91; H, 6.93; N, 3.77%.

4.6. (*S*)-(+)-2,2′-[2-(2,2-Di-*tert*-butyl-2-hydroxyethyl)-2-azapropane-1,3-diyl]-1,1′-binaphthalene 1b

To a solution of *tert*-BuLi (1.7 M, 1.1 mL, 1.8 mmol) in dry THF (2 mL) under nitrogen was added at −70°C a solution of (*S*)-**1k** (115 mg, 0.3 mmol) in dry THF (1 mL). The solution was stirred at −70°C for 90 min, then quenched with water, diluted with Et_2O and washed sequentially with saturated aqueous NH_4Cl and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The recovered residue was purified by column chromatography (SiO_2; petroleum ether/Et_2O, 7:3) affording **1b** as a slightly yellow glass (40 mg, 32%). $[\alpha]_D^{20}=+104.5$ (*c* 1.0; THF); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (s, 9H), 0.92 (s, 9H), 1.4–1.9 (br s, 1H), 2.21 (d, 1H, $J=14.0$ Hz), 2.88 (d, 1H, $J=14.0$ Hz), 3.41 (d, 2H, $J=12.1$ Hz), 3.69 (d, 2H, $J=12.1$ Hz), 7.2–7.3 (m, 2H), 7.4–7.5 (m, 4H), 7.54 (d, 2H, $J=8.2$ Hz), 7.9–8.0 (m, 4H). Anal. calcd for $C_{32}H_{37}NO$: C, 85.10; H, 8.26; N, 3.10. Found: C, 85.01; H, 8.39; N, 3.02%.

4.7. 2-Amino-1,1-diphenylethanol 5a

Glycine ethyl ester hydrochloride (1.4 g, 10 mmol) was slowly added (ca. 3 h) to a solution of PhMgBr (1.0 M, 60 mL, 60.0 mmol) in anhydrous THF (100 mL). The solution was stirred at 40°C for 3 h, then cooled at rt and quenched with H_2O (20 mL). The mixture was diluted with Et_2O (100 mL) and washed with brine. The aqueous layer was extracted twice with Et_2O/THF (3:2). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of solvent, the recovered residue was recrystallized three times from Et_2O and purified by column chromatography (SiO_2; $CHCl_3$/MeOH, 8:2) affording **5a** as a white solid (1.1 g, 52%). Mp 110°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.8–3.2 (br s, 3H), 3.38 (s, 2H), 7.2–7.5 (m, 10H).

4.8. (*S*)-(+)-2,2′-[2-(2,2-Diphenyl-2-hydroxyethyl)-2-azapropane-1,3-diyl]-1,1′-binaphthalene 1c

To a solution of (*S*)-**2** (440 mg, 0.1 mmol) in anhydrous THF (15 mL) under an inert atmosphere were added **5a** (341 mg, 1.6 mmol) and triethylamine (505 μL, 5.0 mmol). The resulting mixture was stirred under reflux

for 18 h then cooled to rt. The solution was filtered and the solid filtration residue was washed with THF and the collected resulting solution concentrated in vacuo. The solid evaporation residue was dissolved in CH_2Cl_2 and washed sequentially with H_2O and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (SiO_2; CH_2Cl_2/Et_2O, 96:4) affording **1c** as a glassy solid (455 mg, 93%). $[\alpha]_D^{21}=+85.0$ (*c* 1.0; THF); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.4–1.8 (br s, 1H), 3.20 (d, 3H, $J=12.5$ Hz), 3.28 (d, 2H, $J=12.4$ Hz), 3.73 (d, 1H, $J=12.9$ Hz), 7.1–7.5 (m, 14H), 7.53 (d, 2H, $J=8.2$ Hz), 7.61 (d, 2H, $J=8.1$ Hz), 7.93 (d, 4H, $J=8.2$ Hz). Anal. calcd for $C_{36}H_{29}NO$: C, 87.95; H, 5.95; N, 2.85. Found: C, 87.86; H, 6.03; N, 2.91%.

4.9. (*S*)-(+)-2,2′-[2-(1-Hydroxycyclohexylmethyl)-2-aza-propane-1,3-diyl]-1,1′-binaphthalene 1d

To a solution of (*S*)-**2** (440 mg, 1.0 mmol) in anhydrous THF (40 mL) under an inert atmosphere were added 1-aminomethylcyclohexanol hydrochloride (330 mg, 2.0 mmol) and triethylamine (665 μL, 5.0 mmol). The mixture was stirred at reflux for 24 h and then cooled to rt. The solution was filtered and the solid residue was washed with THF and the collected resulting solution was evaporated in vacuo. The resulting solid residue was dissolved in $CHCl_3$, washed sequentially with H_2O and brine, and the organic layer was dried over anhydrous Na_2SO_4. After evaporation of solvent, the residue was purified by column chromatography (neutral Al_2O_3; $CHCl_3$) affording **1d** as a colorless glass (370 mg, 91%). $[\alpha]_D^{21}=+223.8$ (*c* 1.0; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2–1.9 (m, 10H), 2.24 (d, 1H, $J=13.2$ Hz), 2.5–3.1 8 (br s, 1H), 2.89 (d, 1H, $J=13.2$ Hz), 3.42 (d, 2H, $J=12.2$ Hz), 3.73 (d, 2H, $J=12.2$ Hz), 7.2–7.3 (m, 2H), 7.4–7.5 (m, 4H), 7.55 (d, 2H, $J=8.2$ Hz), 7.9–8.0 (m, 4H). Anal. calcd for $C_{30}H_{33}NO$: C, 85.06; H, 7.85; N, 3.31. Found: C, 84.92; H, 7.77; N, 3.28%.

4.10. (*S*)-(+)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-one 6c

To a solution of (*S*)-mandelic acid (3.0 g, 19.7 mmol) and 2,2-dimethoxypropane (25 mL) in dry $CHCl_3$ (30 mL) were added activated 4 Å molecular sieves and the mixture was stirred for 2 days at room temperature. The mixture was filtered through a short pad of silica gel using $CHCl_3$ eluent. Evaporation of solvent from the eluate afforded pure **6c** as a white solid (3.05 g, 85%). Mp 72–73°C, lit.[19] mp 72–73°C; $[\alpha]_D^{20}=+91.0$ (*c* 1.0; THF), lit.:[19] $[\alpha]_D^{25}=+84.0$ (*c* 1.0; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (s, 3H), 1.74 (s, 3H), 5.40 (s, 1H), 7.3–7.5 (m, 5H).

4.11. (*S*)-(+)-Mandelamide 7c

(*S*)-**6c** (3 g, 16.66 mmol) was dissolved in a solution of NH_3 (2.0 M in anhydrous EtOH, 33 mL) and the mixture was stirred under a nitrogen atmosphere for 18 h at rt. The mixture was concentrated in vacuo and the residue triturated with hot Et_2O yielding, after evaporation of solvent, pure **7c** as a white solid (1.95 g, 77%). Mp 119–120°C; lit.[19] mp 118–120°C; $[\alpha]_D^{20}=+54.5$ (*c* 1.0; THF), lit.:[19] $[\alpha]_D^{25}=+94.7$ (*c* 2.4; water); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.7–2.1 (br s, 1H), 5.08 (s, 1H), 5.5–5.7 (br s, 1H), 5.9–6.1 (br s, 1H), 7.3–7.5 (m, 5H).

4.12. (*S*)-(+)-2-Amino-1-phenylethanol 5c

To a stirred solution of (*S*)-**7c** (1.74 g, 11.5 mmol) in dry THF (80 mL) under an inert atmosphere was added $LiAlH_4$ (4 g, 103.5 mmol). The mixture was heated under reflux for 3 days, cooled at rt and quenched with a minimum quantity of ice-water. The organic phase was diluted with EtOAc and the solid residue was washed with EtOAc. The collected organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The solid residue was dissolved in boiling hexane (400 mL), the insoluble remaining **7c** was filtered off, and the solution was left to cool yielding pure **5c** as a white solid (475 mg, 30%). $[\alpha]_D^{20}=+58.0$ (*c* 1.0; THF) {lit.:[18] $[\alpha]_D^{23}=+45.0$ (*c* 1.32; $CHCl_3$)}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.8–2.2 (br s, 3H), 2.79 (dd, 1H, $J=11.5$, 19.1 Hz), 2.98 (dd, 1H, $J=6.0$, 19.1 Hz), 4.62 (dd, 1H, $J=6.0$, 11.5 Hz), 7.2–7.4 (m, 5H).

4.13. (*aS,R*)-(+)-2,2′-[2-(2-Phenyl-2-hydroxyethyl)-2-aza-propane-1,3-diyl]-1,1′-binaphthalene 1e

To a solution of (*S*)-**2** (440 mg, 1 mmol) in anhydrous THF (30 mL) under a nitrogen atmosphere were added (*R*)-**5c** (165 mg, 1.2 mmol) and triethylamine (0.5 mL, 4 mmol). The solution was stirred under reflux for 16 h, then cooled to rt, diluted with Et_2O (60 mL), washed with saturated NH_4Cl and brine. The organic layer was dried on anhydrous Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography (neutral Al_2O_3; $CHCl_3$/ethyl acetate, 3:1) affording **1e** as a colorless glass (230 mg, 55%). $[\alpha]_D^{20}=+170$ (*c* 1.0; THF); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (dd, 1H, $J=10.6$, 13.0 Hz), 2.5–2.9 (br s, 1H), 2.88 (dd, 1H, $J=3.2$, 13.0 Hz), 3.31 (d, 2H, $J=12.3$ Hz), 3.76 (d, 2H, $J=12.3$ Hz), 4.95 (dd, 1H, $J=3.2$, 10.6 Hz), 7.2–7.3 (m, 4H), 7.3–7.4 (m, 2H), 7.4–7.5 (m, 5H), 7.57 (d, 2H, $J=8.3$ Hz), 7.9–8.0 (m, 4H). Anal. calcd for $C_{30}H_{25}NO$: C, 86.71; H, 6.06; N, 3.37. Found: C, 86.53; H, 5.98; N, 3.31%.

4.14. (*aS,S*)-(+)-2,2′-[2-(2-Phenyl-2-hydroxyethyl)-2-aza-propane-1,3-diyl]-1,1′-binaphthalene 1f

To a solution of (*S*)-**2** (220 mg, 0.5 mmol) in anhydrous THF (15 mL) under an inert atmosphere were added (*S*)-**5c** (82 mg, 0.6 mmol) and triethylamine (280 μL; 2 mmol). The resulting solution was stirred under reflux for 12 h, cooled to rt and diluted with Et_2O (40 mL). The solution was washed with saturated NH_4Cl and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography (neutral Al_2O_3; $CHCl_3$/ethyl acetate, 3:1) affording **1f** as a colorless glass (174 mg, 84%). $[\alpha]_D^{20}=+140.7$ (*c* 1.0; THF). ^{1}H NMR (300 MHz, $CDCl_3$): δ

1.4–2.0 (br s, 1H), 2.64 (dd, 1H, $J=3.3$, 12.1 Hz), 2.82 (dd, 1H, $J=12.1$, 10.5 Hz), 3.37 (d, 2H, $J=12.2$ Hz), 3.77 (d, 2H, $J=12.2$ Hz), 4.78 (dd, 1H, $J=3.3$, 10.5 Hz), 7.2–7.4 (m, 7H), 7.4–7.6 (m, 6H), 7.9–8.0 (m, 4H). Anal. calcd for $C_{30}H_{25}NO$: C, 86.71; H, 6.06; N, 3.37. Found: C, 86.59; H, 6.02; N, 3.28%.

4.15. (*S*)-(−)-2,2-Dimethyl-5-cyclohexyl-1,3-dioxolan-4-one 6d

To a solution of (*S*)-hexahydromandelic acid (1.0 g, 6.3 mmol) and 2,2-dimethoxypropane (8 mL, 63 mmol) in dry $CHCl_3$ (10 mL) were added activated 4 Å molecular sieves. The resultant mixture was stirred for 2 days at rt. The mixture was then filtered through a short pad of silica gel using $CHCl_3$ eluent. Evaporation of the solvent afforded pure **6d** as a white solid (1.25 g, 99%). Mp 35.5–36.0°C; $[\alpha]_D^{20}=-16.5$ (*c* 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.0–1.3 (m, 6H), 1.53 (s, 3H), 1.59 (s, 3H), 1.6–1.9 (m, 5H), 4.23 (d, 1H, $J=3.6$ Hz). Anal. calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.51; H, 9.07%.

4.16. (*S*)-(+)-Hexahydromandelamide 7d

(*S*)-**6d** (1.25 g, 6.3 mmol) was dissolved in a solution of NH_3 (2.0 M in anhydrous EtOH, 9.5 mL) and the mixture was stirred under an inert atmosphere for 18 h at rt. The mixture was then concentrated in vacuo and the residue was triturated with hot Et_2O yielding pure (*S*)-**7d** as a white solid (670 mg, 67%). Mp 157–158°C; $[\alpha]_D^{20}=+13.5$ (*c* 1.0; THF). ^1H NMR (300 MHz, $CDCl_3$): δ 1.0–1.4 (m, 6H), 1.5–1.9 (m, 5H), 2.55 (br s, 1H), 3.99 (br s, 1H), 5.5–5.7 (br s, 1H), 6.2–6.4 (br s, 1H). Anal. calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.20; H, 9.76; N, 8.79%.

4.17. (*S*)-(−)-2-Amino-1-cyclohexylethanol 5d

To a stirred solution of (*S*)-**7d** (660 mg, 4.2 mmol) in dry THF (30 mL) under an inert atmosphere was added $LiAlH_4$ (1.0 g, 25 mmol). The reaction mixture was heated under reflux for 2 days, then cooled to room temperature and quenched with ice-water. The mixture was diluted with EtOAc and the solid residue filtered off. The organic solution was then washed with brine, dried on anhydrous Na_2SO_4 and concentrated in vacuo. The recovered solid residue was dissolved in boiling hexane (300 mL), the resulting solution was filtered and left cooling, recovering unreacted (*S*)-**7d** as white crystals. The remaining mother liquor was concentrated in vacuo to afford **5d** as a white solid (395 mg, 66%). Mp 86.7–87°C; $[\alpha]_D^{20}=-44.0$ (*c* 1.0; THF). ^1H NMR (300 MHz, $CDCl_3$): δ 0.9–1.4 (m, 6H), 1.6–2.1 (m, 8H), 2.56 (dd, 1H, $J=8.9$, 12.5 Hz), 2.88 (dd, 1H, $J=3.1$, 12.5 Hz), 3.24 (ddd, 1H, $J=3.1$, 6.4, 12.5 Hz). Anal. calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.25; H, 12.17; N, 9.59%.

4.18. (*aS,S*)-(+)-2,2′-[2-(2-Cyclohexyl-2-hydroxyethyl)-2-azapropane-1,3-diyl]-1,1′-binaphthalene 1g

To a solution of (*S*)-**2** (220 mg, 0.5 mmol) in anhydrous THF (15 mL) under an inert atmosphere were added (*S*)-**5d** (86 mg, 0.6 mmol) and triethylamine (280 μL, 2 mmol) and the solution was stirred under reflux for 12 h. After cooling to rt, the solution was filtered and the solid residue was washed with THF. The resulting collected solution was then concentrated in vacuo, and the recovered residue was dissolved in Et_2O, washed with saturated NH_4Cl and brine. The organic layer was dried on anhydrous Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography (neutral Al_2O_3). Elution with petroleum ether/$CHCl_3$ (1:1) allowed recovery of unreacted (*S*)-**2**, then elution with $CHCl_3$/ethyl acetate (3:1) allowed recovery of **1g** as a colorless glass (194 mg, 92%). $[\alpha]_D^{20}=+220.5$ (*c* 1.0; THF). ^1H NMR (300 MHz, $CDCl_3$): δ 0.8–1.4 (m, 6H), 1.5–1.8 (m, 4H), 1.9–2.0 (m, 1H), 2.53 (dd, 1H, $J=3.0$, 11.7 Hz), 2.70 (dd, 1H, $J=11.7$, 10.8 Hz), 3.28 (d, 2H, $J=12.2$ Hz), 3.46 (ddd, 1H, $J=3.0$, 10.8, 6.4 Hz), 3.4–3.8 (br s, 1H), 3.71 (d, 2H, $J=12.2$ Hz), 7.2–7.3 (m, 2H), 7.4–7.5 (m, 4H), 7.54 (d, 2H, $J=8.3$ Hz), 7.9–8.0 (m, 4H). Anal. calcd for $C_{30}H_{31}NO$: C, 85.47; H, 7.41; N, 3.32. Found: C, 85.41; H, 7.52; N, 3.23%.

4.19. (*S*)-(+)-2,2′-[2-(Methyl-2-pyridyl)-2-azapropane-1,3-diyl]-1,1′-binaphthalene 1h

To a solution of (*S*)-**2** (440 mg, 1.0 mmol) in anhydrous THF (40 mL) under an inert atmosphere was added 2-aminomethylpyridine (620 μL, 6.0 mmol). The solution was stirred under reflux for 18 h then cooled to rt. The solution was filtered and the solid residue was washed with THF. The resulting collected solution was concentrated in vacuo. The recovered residue was dissolved in $CHCl_3$, washed sequentially with H_2O and brine, and the organic layer was dried over anhydrous Na_2SO_4. The solid residue recovered after evaporation of the solvent was then purified by column chromatography (neutral Al_2O_3; CH_2Cl_2/Et_2O, 85:15) affording **1h** as a slightly yellow glass (346 mg, 90%). $[\alpha]_D^{21}=+294.9$ (*c* 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 3.27 (d, 2H, $J=12.2$ Hz), 3.67 (d, 2H, $J=12.2$ Hz), 3.69 (d, 2H, $J=13.6$ Hz), 3.85 (d, 2H, $J=13.6$ Hz), 7.1–7.3 (m, 2H), 7.4–7.7 (m, 8H), 7.9–8.0 (m, 4H), 8.61 (m, 1H). Anal. calcd for $C_{28}H_{22}N_2$: C, 87.01; H, 5.74; N, 7.25. Found: C, 86.93; H, 5.73; N, 7.34%.

4.20. (*S*)-(+)-2,2′-[2-(*N*-Acetyl-2-aminoethyl)-2-azapropane-1,3-diyl]-1,1′-binaphthalene 1l

To a solution of (*S*)-**2** (440 mg, 1.0 mmol) in anhydrous THF (40 mL) under an inert atmosphere was added *N*-acetyl-ethylenediamine (290 μL, 3.0 mmol). The solution was stirred under reflux for 18 h then cooled to rt. The solution was filtered and the solid residue was washed with THF. The resulting solution was evaporated to dryness. The collected residue was dissolved in $CHCl_3$ and washed sequentially with H_2O and brine. The organic layer was dried on anhydrous Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography (SiO_2; $CHCl_3$/MeOH, 6:1) affording 372 mg of **1l** (98% yield) as a colorless glass. $[\alpha]_D^{21}=+231.7$ (*c* 1.0; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 2.03 (s, 3H), 2.5 (m, 1H), 2.8 (m, 1H), 3.20 (d, 2H, $J=12.2$ Hz), 3.4–3.5 (m, 2H), 3.66 (d, 2H,

$J=12.2$ Hz), 6.4 (br s, 1H), 7.2–7.3 (m, 2H), 7.4–7.6 (m, 6H), 7.9–8.0 (m, 4H). Anal. calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 82.25; H, 6.49; N, 7.26%.

4.21. (*S*)-(+)-2,2′-[2-(*N*-Ethyl-2-aminoethyl)-2-aza-propane-1,3-diyl]-1,1′-binaphthalene 1i

To a stirred solution of (*S*)-**1l** (180 mg, 0.47 mmol) in dry THF (6 mL) under an inert atmosphere was added $LiAlH_4$ (54 mg, 1.41 mmol). The reaction mixture was heated at reflux for 30 h then cooled at rt and quenched with ice-water. The mixture was diluted with $CHCl_3$, washed with brine, dried on anhydrous Na_2SO_4 and concentrated in vacuo. The recovered solid residue was purified by column chromatography (neutral Al_2O_3; $CHCl_3$/AcOEt/EtOH, 68:30:2) affording **1i** as a colorless glass (86 mg, 50%). $[\alpha]_D^{21}=+213.2$ (*c* 1.0; THF). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, 3H, $J=7.1$ Hz), 1.7–2.1 (br m, 1H), 2.5–2.6 (m, 1H), 2.73 (q, 2H, $J=7.1$ Hz), 2.7–2.9 (m, 3H), 3.20 (d, 2H, $J=12.2$ Hz), 3.68 (d, 2H, $J=12.2$ Hz), 7.2–7.3 (m, 2H), 7.4–7.5 (m, 4H), 7.54 (d, 2H, $J=8.2$ Hz), 7.9–8.0 (m, 4H). Anal. calcd for $C_{26}H_{26}N_2$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.29; H, 7.19; N, 7.52%.

4.22. (*S*)-(+)-2,2′-[2-(Methyl-2-methoxyphenyl)-2-aza-propane-1,3-diyl]-1,1′-binaphthalene 1m

To a solution of (*S*)-**2** (330 mg, 0.75 mmol) in anhydrous THF (22 mL) under an inert atmosphere were added 2-methoxybenzylamine (219 μL, 1.69 mmol) and triethylamine (420 μL, 3 mmol). The solution was then stirred under reflux for 12 h. After cooling to rt, the solution was filtered and the solid residue was washed with THF. The resulting solution was evaporated to dryness. The recovered residue was dissolved in Et_2O and washed with saturated NH_4Cl and brine. The organic layer was dried on anhydrous Na_2SO_4 and concentrated in vacuo. The recovered residue was purified by column chromatography (SiO_2; $CHCl_3$/ethyl acetate, 4:1) affording **1m** as a colorless glass (214 mg, 69%). $[\alpha]_D^{20}=+229$ (*c* 1.0; THF). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.28$ (d, 2H, $J=12.2$ Hz), 3.54 (d, 1H, $J=13.5$ Hz), 3.73 (d, 2H, $J=12.2$ Hz), 3.82 (d, 1H, $J=13.5$ Hz), 3.86 (s, 3H), 6.8–7.0 (m, 2H), 7.2–7.3 (m, 4H), 7.4–7.5 (m, 4H), 7.59 (d, 2H, $J=8.2$ Hz), 7.95 (d, 4H, $J=8.2$ Hz). Anal. calcd for $C_{30}H_{25}NO$: C, 86.71; H, 6.06; N, 3.37. Found: C, 86.56; H, 5.98.; N, 3.29%.

4.23. (*S*)-(+)-2,2′-[2-(Methyl-2-hydroxyphenyl)-2-aza-propane-1,3-diyl]-1,1′-binaphthalene 1j

To a solution of (*S*)-**1m** (155 mg, 0.37 mmol) in anhydrous CH_2Cl_2 (10 mL) under an inert atmosphere and cooled at −50°C was added a solution of BBr_3 in CH_2Cl_2 (1.0 M, 1.5 mL, 1.5 mmol). The solution was stirred at rt for 7 h, then quenched with saturated $NaHCO_3$ until a neutral pH was reached and washed with brine. The organic layer was dried on anhydrous Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography (SiO_2; $CHCl_3$/ethyl acetate, 4:1) obtaining pure **1j** as a colorless glass (144 mg, 96%). $[\alpha]_D^{20}=+213.8$ (*c* 1.0; THF); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.26 (br d, 2H, $J=12.5$ Hz), 3.76 (d, 2H, $J=12.5$ Hz), 3.79 (d, 1H, $J=13.2$ Hz), 3.84 (d, 1H, $J=13.2$ Hz), 6.8–6.9 (m, 2H), 7.03 (m, 1H), 7.2–7.3 (m, 3H), 7.4–7.6 (m, 6H), 7.9–8.0 (m, 4H). Anal. calcd for $C_{29}H_{23}NO$: C, 86.75; H, 5.77; N, 3.49. Found: C, 86.83; H, 5.83; N, 3.38%.

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