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Phenylalanine derivatives as catalysts in the enantioselective addition of diethylzinc to benzaldehydes

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Abstract—A series of mono and bis β-amino alcohols derived from phenylalanine were synthesised and their application as chiral catalysts in the asymmetric ethylation of aromatic aldehydes in the presence of diethylzinc investigated.

1. Introduction

One of the most common asymmetric reactions studied is that of diethylzinc addition to benzaldehydes. Among the numerous chiral catalysts developed[1–5] for the asymmetric organozinc additions, β-amino alcohols hold a prominent position.[5,6] Our group has been interested in the synthesis and properties of non-natural derivatives of phenylalanine (Phe) such as phenyltrisalanine (Pta) and phenylbisalanine (Pba, Fig. 1).[7–10] In this work, we aimed to determine the efficiency of chiral catalysts of mono-, bis- and tris-β-amino alcohols derived from phenylalanine. It was interesting to find out what effect the presence of several arms in the ligand had on the reaction.

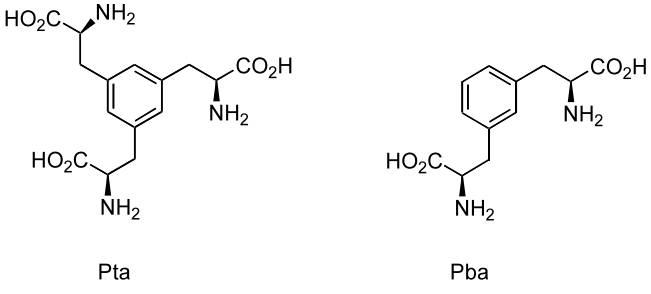

Figure 1. Phenyltrisalanine (Pta) and phenylbisalanine (Pba).

2. Results and discussion

The synthesis of the catalysts was easily accomplished (Scheme 1) following a general procedure based on the alkylation of free terminal amino groups with diverse alkyl halides in DMF at 80°C to give the *N*,*N*′-disubstituted compounds in 30–73% yields after purification by chromatography. The β-amino alcohols were then obtained after reduction with $LiAlH_4$ in 30–91% yields (Scheme 1, for details, see Section 4). The starting material for the tris-armed catalyst was **1**,[7] while the isophthalic aldehyde served as a starting material for the bis-armed analogues. The mono-armed catalysts were derived from commercially available (*S*)-phenylalanine methyl ester.

With the chiral catalysts in hand, the catalysis effect was tested with benzaldehyde as the substrate using standard conditions. The reaction was carried out in dry toluene in the presence of the chiral catalyst at room temperature, for 24 h. The reaction was quenched with 5% aqueous HCl and the product isolated by extraction and purified by chromatography over silica gel. The ee was determined by HPLC analysis using a chiral stationary phase.

The first test was performed with ligand **3a**. As this failed to give any product, despite the use of different reaction conditions (solvents, temperature, reaction time), it was assumed that this ligand formed a complex with the metal such as the one proposed in Figure 2. The structure of the diethylzinc–catalyst complex is

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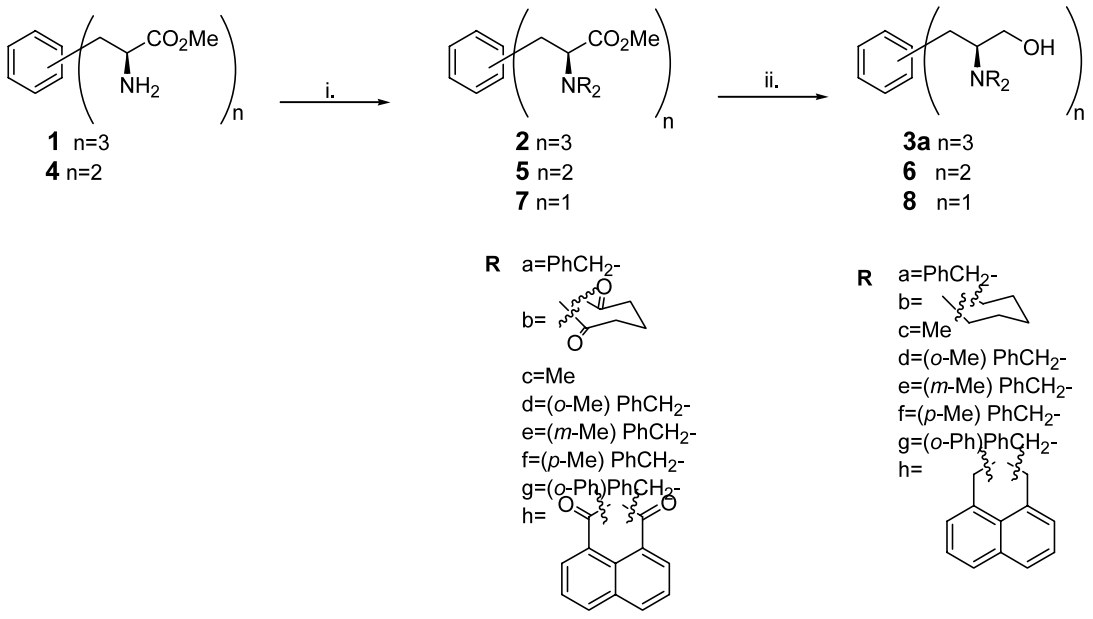


Scheme 1. *Reagents and conditions*: (i) RX, DMF, 80°C, 30–73%; (ii) $LiAlH_4$, THF, 0°C to rt, 30–91%.

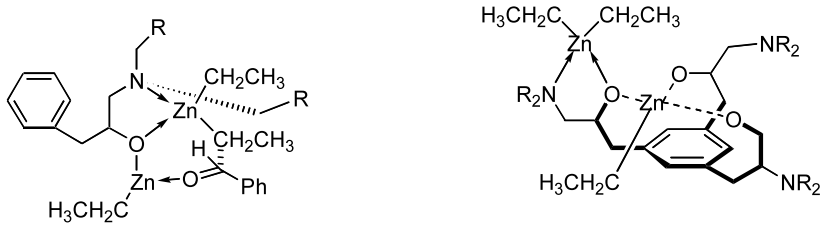


Figure 2. The standard diethylzinc-catalyst complex (left) and the proposed structure for the diethylzinc–**3a** complex (right).

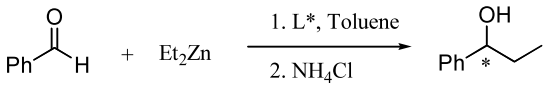
usually described as depicted in Figure 2 (left).[11] In our case, we assume that the complex between **3a** and diethylzinc is as shown in Figure 2 (right). As all three OH groups can coordinate to the Zn, there is no place left for the aldehyde to coordinate.

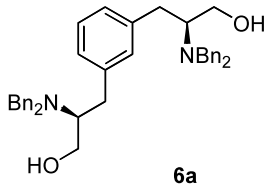
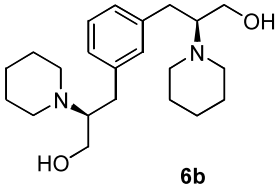
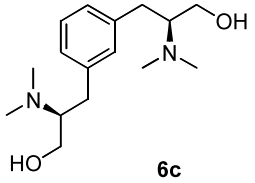
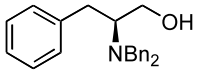
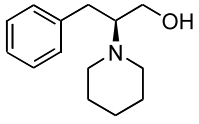
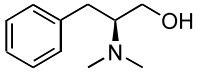
We know from previous coordination studies with Pta[12] that a 1:1 complex forms where the metal ion is placed on top of the aromatic ring, therefore we assume that the same type of complex also forms in this case. NMR studies were undertaken, but only the disappearance of the protons of the OH groups was detected with no shift changes. No crystals of the complex could be formed either.

The ees obtained with the bis- and mono-armed catalysts were promising, namely 65% (76% yield) for **6a** and 68% (51% yield) for **8a** (Table 1). In the initial attempts to improve the results, the order of addition of the reagents was investigated. We discovered that the best ee and yield values were obtained when benzaldehyde was added to a solution containing the chiral catalyst and Et_2Zn. The other two ligand types, **6b–c** and **8b–c**, bearing different substitution patterns, gave poor results (Table 1).

As the results obtained with chiral ligands **6a** and **8a** were the best ones, we decided to tune these structures in order to improve their performance. The first attempt was the introduction of diarylhydroxymethyl. Due to the enhanced stereoselectivity in catalytic reactions, this group has been called the 'magic group' in catalyst design and has frequently been used in recent years.[6,13] Inspired by this, catalyst **9** (Scheme 2) was synthesised in 61% yield by reacting **2a** with PhLi at 0°C in THF. This catalyst was used in the addition reaction, but the presence of the diarylhydroxymethyl groups had a negative effect on the enantioselectivity as only ca. 7% ee was obtained. It was speculated that this was due to the effect of racemisation of the chiral catalyst during the reaction conditions employed in the synthesis. An NMR experiment was performed, where the substrate was titrated with PhLi. The assumption made was that if racemisation took place, the α-hydrogen of the substrate would be removed during the course of the reaction. However, this was not observed on the NMR spectra collected at different time intervals; only the disappearance of the OMe-signal was detected.

Table 1. Enantioselectivity induced by **6a–c** and **8a–c** in the addition of Et_2Zn to benzaldehyde, initial studies

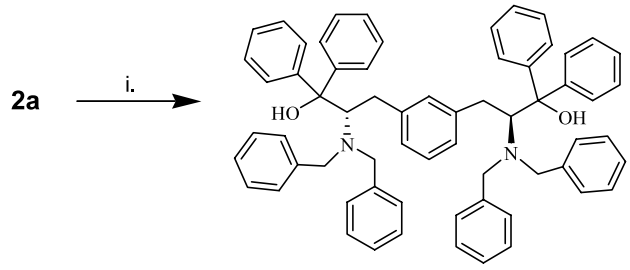


Entry	L*[a]	Time (h)	Yield (%)[b]	ee (%)[c]	Config.[d]
1	 **6a**	24	76	65	*R*
2	 **6b**	24	65	36	*R*
3	 **6c**	24	36	20	*R*
4	 **8a**	24	51	68	*R*
5	 **8b**	24	23	16	*R*
6	 **8c**	24	36	2	*R*

a. The reactions were carried out in toluene at room temperature in the presence of 5 mol% catalyst.
b. Based on isolated compound.
c. Determined using a Chiralcel OD-H column and eluting with hexane/*i*PrOH (97.5:2.5) at the flow rate of 0.5 mL/min.
d. Assigned according to the t_R of the HPLC analysis.

A plausible explanation to the poor result obtained with this catalyst may be the presence of too many phenyl groups. In this case, steric interactions would be significant factors controlling the outcome of the reaction.

The next attempts were concentrated on the substitution pattern on the terminal nitrogens. Thus, phenyl rings bearing different substitution patterns were attached to these terminal nitrogens and their effect on the addition reaction was studied. Initially, a methyl substituent was successively introduced in the *ortho*, *meta* and *para* position. However catalyst **6d** gave only 16% ee and 47% yield (Table 2). Catalyst **6e** gave a better ee (55%) and a better yield (83%) while the best ee (70%) in this series was obtained with catalyst **6f** with a 78% yield. Catalyst **6g**, bearing a Ph-substituent in the *ortho*-position, gave 54% ee. We tried out a different catalyst system, catalyst **6h**, but this only gave 19% ee (Table 2).



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Scheme 2. *Reagents and conditions*: (i) PhLi, THF, 0°C to rt, 12 h, 61%.

The same trend was observed with the mono-armed catalysts, 20% ee with **8d**, 67% ee with **8e** and 72% ee with **8f** (Table 3). The yields of the reaction also followed the same tendency as with the bis-armed catalysts with 82% for **8d**, 98% for **8e** and 69% for **8f**.

When the biphenyl analogue **8g** was tried, it resulted in 54% ee and 64% yield, which is comparable to **6g**. As for catalyst **8h**, 29% ee was obtained and 65% yield, which was more than with the bis-armed catalyst.

The results obtained with both bis- and mono-armed catalyst systems did not seem to follow any particular pattern. As the best results were obtained with the *para*-substituted catalysts, it was tempting to assume that the methyl substituent positioned in the *ortho*-position invoked steric hindrance in the proximity of the reaction centre. When moving this group further from the reaction centre, both the ee and the yield increased. When introducing a Ph-substituent in the *ortho*-position in catalysts **6g** and **8g**, the ees were better than in the *ortho*-methyl substituent cases. An explanation to this result is that the two phenyl rings of the biphenyl group were placed perpendicular to each other, thus an arrangement that did not disturb the reaction centre as much.

As chiral ligands **6f** and **8f** gave the best results, they were used as catalysts in the enantioselective addition to two other types of benzaldehydes, namely *p*-chlorobenzaldehyde and *p*-anisaldehyde. For *p*-chlorobenzaldehyde, the bis-armed catalyst **6f** gave 69% ee and 53% yield (Table 4). The mono-armed catalyst **8f** gave a slightly lower ee value, 61% and lower yield, 35% (Table 4). Both catalysts gave modest ees in the addition reaction to *p*-anisaldehyde, 16% in both cases, with slightly higher yields for the bis-armed catalyst, 31% versus 24%. These results were not unexpected since in the case of the *p*-anisaldehyde, the methoxy group placed in the *para*-position donates electrons to the carbonyl carbon of the aldehyde functionality through an inductive effect. The carbonyl carbon is thus rendered less electrophilic and less prone to react with a nucleophile (the ethylzinc reagent). This phenomenon accounts for the lower ee and yields obtained with this type of aldehyde. The chloro-substituent however has the reverse effect, thus the results should be better with this type of aldehyde.

As previously mentioned, our goal was to investigate the effect of multiple arms in Phe derivatives on the reactivity and enantioselectivity of the chiral catalysts. The intention was to determine what the active complex looked like. We thought that by titrating **6a** with Et_2Zn we might be able to determine the stoichiometry of the active catalyst complex. However, during the performed NMR titration, only the disappearance of the proton of the OH group was observed upon addition of 1 equiv. of Et_2Zn. No shift changes were observed, not even with increased amounts of titrant. Despite our efforts, no crystals of the catalyst–Et_2Zn complex were obtained.

An autocatalysis test was also carried out in order to determine whether the chiral alcohol formed as product was itself acting as a chiral catalyst. When (*R*)-1-phenyl-1-propanol was used to catalyse the Et_2Zn addition to *p*-chlorobenzaldehyde, chosen as substrate as we wanted to be able to differentiate between the catalyst and the formed product, no product was isolated, thus the alcohol did not function as a chiral catalyst.

3. Conclusions

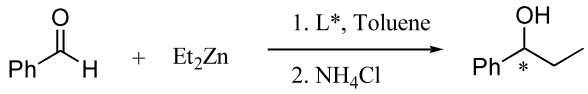
A new series of chiral ligands based on Phe were synthesised and used as catalysts in the addition reaction of Et_2Zn to benzaldehydes. In these reactions, modest to good ee and yield values were obtained. The catalysts that proved the most effective in this type of reaction were those carrying a methyl substituent in the *para* position of the phenyl on the terminal nitrogen. We conclude from our studies that catalysts with C_3-symmetry do not function in this type of reaction and that there is no significant difference between the results obtained with the mono- and bis-armed catalysts. It is probable that only one of the arms in the bis-armed catalysts is involved in the reaction. Further development of this type of catalyst derived from Phe and their use as ligands in other catalytic reactions is in process in our laboratory.

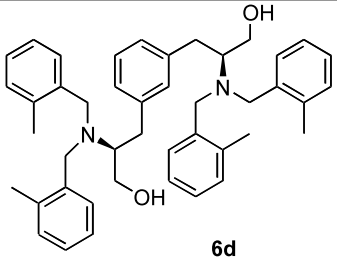
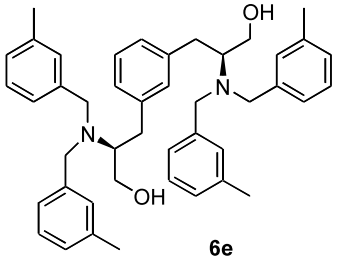
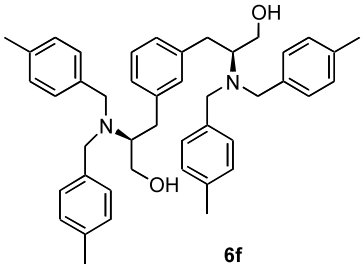
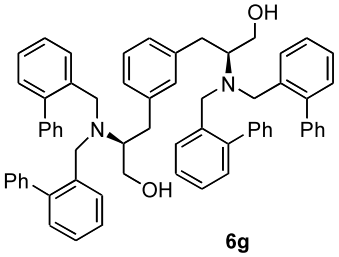
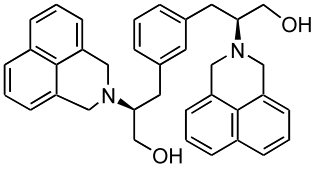
4. Experimental

4.1. General procedures

NMR spectra were recorded on a Bruker DRX 300 and a Bruker DRX 400 instrument in $CDCl_3$ or CD_3OD, at 20°C. For ^1H experiments, residual $CHCl_3$ or MeOH at δ 7.27 and 3.31, respectively, were used as internal standards, while the central peak of the $CDCl_3$ triplet at δ 77.0 and the central peak of the CD_3OD septet at δ 49.5 were used for the ^{13}C experiments. COSY spectra were run for compounds with complicated coupling patterns in order to determine the identity of the different protons. IR spectra were recorded on a Shimadzu 8300 FTIR Instrument. Melting points were taken with a Gallenkamp melting point microscope and are uncorrected. Precoated Merck silica gel 60 F_{254} plates were used for TLC analyses and retention values (TLC R_f) are given in the same solvent as used in the respective

Table 2. Enantioselectivity induced by **6d–h** by addition of Et_2Zn to benzaldehyde

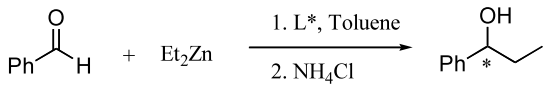


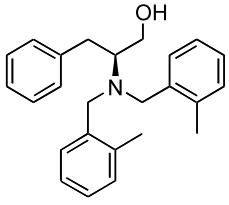
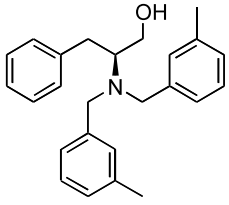
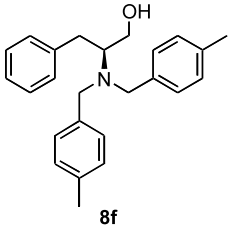
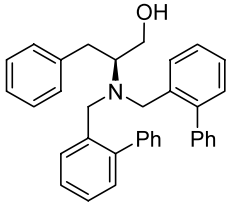
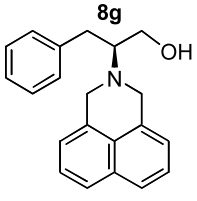
Entry	L* [a]	Time (h)	Yield (%)[b]	ee (%) [c]	Config.[d]
1	 **6d**	24	47	16	*R*
2	 **6e**	24	83	65	*R*
3	 **6f**	24	78	70	*R*
4	 **6g**	24	61	54	*R*
5	 **6h**	24	55	19	*R*

a. The reactions were carried out in toluene at room temperature in the presence of 5 mol% catalyst.
b. Based on isolated compound.
c. Determined using a Chiralcel OD-H column and eluting with hexane/*i*PrOH (97.5:2.5) at the flow rate of 0.5 mL/min.
d. Assigned according to the t_R of the HPLC analysis

chromatography unless otherwise stated. The TLC plates were visualised under UV followed by spraying with a $KMnO_4$ solution[14] followed by heating. {Rh(COD)[(*S*,*S*)-Et-DuPHOS]}$^+$OTf$^-$ was prepared according to literature.[15] The (*S*,*S*)-Et-DuPHOS catalyst was available from Strem Chemicals. (*S*)-Phenylalanine methyl ester was purchased from Aldrich.

Table 3. Enantioselectivity induced by **8d–h** in the addition of Et_2Zn to benzaldehyde

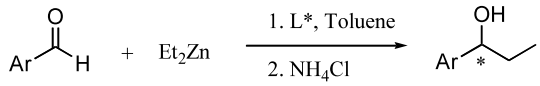


Entry	L* [a]	Time (h)	Yield (%)[b]	ee (%)[c]	Config.[d]
1	 **8d**	24	82	20	*R*
2	 **8e**	24	98	67	*R*
3	 **8f**	24	69	72	*R*
4	 **8g**	24	64	54	*R*
5	 **8h**	24	65	29	*R*

a. The reactions were carried out in toluene at room temperature in the presence of 5 mol% catalyst.
b. Based on isolated compound.
c. Determined using a Chiralcel OD-H column and eluting with hexane/*i*PrOH (97.5:2.5) at the flow rate of 0.5 mL/min.
d. Assigned according to the t_R of the HPLC analysis.

Compound **1** was synthesised as previously described.[7] Compound **8a** was purchased from NSC Technologies (a division of the NutraSweet Co.). Compound **8b** and **8c** were synthesised following the same procedure as for the other compounds. The spectral data were in agreement with literature values.[16–18] Optical rotations were measured with a Perkin–Elmer 241 LC polarimeter at 20°C. Freshly distilled benzaldehyde was used and toluene was dried over molecular sieves (4 Å). HPLC analyses were performed on a Chiralcel OD-H column (0.46 cm×25 cm, 5 μm particle size) with *n*-hexane and *i*PrOH as eluents.

Table 4. Enantioselectivity induced by **6f** and **8f** in the addition of Et_2Zn to aldehydes



Entry	L*[a]	Aldehyde	Time (h)	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	**6f**	*p*-Chlorobenzaldehyde	24	53	69	*R*
2	**8f**	*p*-Chlorobenzaldehyde	24	35	61	*R*
3	**6f**	*p*-Anisaldehyde	24	31	16	*R*
4	**8f**	*p*-Anisaldehyde	24	24	16	*R*

[a] The reactions were carried out in toluene at room temperature in the presence of 5 mol% catalyst.
[b] Based on isolated compound.
[c] Determined using a Chiralcel OD-H column and eluting with hexane/*i*PrOH (95:5) at the flow rate of 0.5 mL/min.
[d] Assigned according to the t_R of the HPLC analysis.

4.2. General procedure for alkylation of the free amino acid methyl ester compounds

Hünig's base (4.6 mmol) was added to a DMF solution (5 mL) of free amine (1.0 mmol) and the mixture stirred for 5 min at room temperature. The alkyl halide (4.6 mmol) was added and the stirring continued at reflux temperature for 18 h. After cooling to ambient temperature, the solvent was removed under reduced pressure. The remains were redissolved in a minute amount of EtOAc and purified by chromatography (SiO_2, heptane/EtOAc, 4:1).

4.2.1. (*S*,*S*,*S*)-2-Dibenzylamino-3-[3,5-bis-(2-dibenzylamino-2-hydroxypropyl)-phenyl]-propanoic acid methyl ester 2. Following the general procedure for alkylation, from 83 mg (0.21 mmol) of **1**, 120 mg (45%) of product were isolated as a colourless oil. IR (ν cm^{-1}): 3024.2, 2947.0, 2839.0, 1728.1; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23–7.16 (m, 30H), 6.52 (s, 3H), 3.90 (d, 6H, $J=14$ Hz), 3.60 (s, 9H), 3.54 (s, 3H, $J=13.9$ Hz), 3.02–2.82 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 139.3, 137.8, 128.6, 128.1, 127.9, 62.4, 54.5, 50.9, 35.5; HRMS (FAB+Na^+) m/z calculated for $C_{60}H_{63}N_3O_6Na$ 944.4610. Found 944.4595 [M+Na].

4.2.2. (*S*,*S*)-2-Amino-3-[3-{(-2-amino-2-methoxycarbonyl)-ethenyl}-phenyl]-acrylic acid methyl ester 4. The didehydroamino acid was synthesised as described[10] from 0.50 g (3.73 mmol) of isophtalic aldehyde, using *N*-benzyloxycarbonyl-2-(dimethoxyphosphinyl)-glycine methyl ester[19] as phosphonate. The product, 790 mg (35%), was obtained as a white powder after chromatography (SiO_2, heptane/EtOAc 2:3, R_f 0.4) and recrystallisation from EtOAc/heptane. Mp 151.8–153.6°C; IR (ν cm^{-1}): 3276.8, 1733.9, 1701.1, 1500.5; ^1H NMR (400 MHz; $CDCl_3$): δ 7.67 (s, 1H), 7.46 (s, 1H), 7.32 (br s, 11H), 6.31 (br s, 2H), 5.09 (s, 4H), 3.82 (s, 6H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 165.5, 135.8, 134.1, 130.4 (br s), 128.8, 128.5 (br), 128.3, 124.7, 67.6, 52.7; HRMS (FAB+Na^+): m/z calculated for $C_{30}H_{28}N_2O_8Na$ 567.1746. Found 567.1734 [M+Na].

The didehydroamino acid obtained in the previous step was submitted to asymmetric hydrogenation with {Rh(COD)[(*S*,*S*)-Et-DuPHOS]}$^+OTf^-$ as catalyst. The substrate, 500 mg (0.92 mmol) was dissolved in 1:1 mixture of MeOH/EtOAc (50 mL) and the solution was purged with N_2 for 30 min. The catalyst (7 μmol) was added and the mixture was hydrogenated at 40 psi at room temperature overnight. The product, 47 mg (94%) was obtained as an oil. $[\alpha]_D^{21}=+30$ (*c* 1.6, $CHCl_3$); IR (ν cm^{-1}): 3346.3, 3033.8, 1718.5; ^1H NMR (400 MHz; $CDCl_3$): δ 7.34 (br s, 10H), 7.21–7.16 (m, 1H), 6.99 (d, 1H, $J=1.6$ Hz), 6.97 (d, 1H, $J=1.5$ Hz), 6.85 (br s, 1H), 5.25 (d, 2H, $J=7.9$ Hz), 5.09 (s, 4H), 4.64 (q, 2H, $J=7.0$ Hz), 3.69 (s, 6H), 3.06 (t, 4H, $J=5.2$ Hz); ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.8, 155.6, 136.1, 130.3, 128.8, 128.5, 128.1, 66.9, 54.7, 52.3, 38.1; HRMS (FAB+Na^+): m/z calculated for $C_{30}H_{32}N_2O_8Na$ 571.2056. Found 571.2056[M+Na].

The product obtained in the previous step was submitted to hydrogenation with Pd/C as catalyst. The substrate, 0.29 g (0.54 mmol) was dissolved in MeOH (25 mL) and the catalyst (50 mg, 0.3 mmol) added. The slurry was hydrogenated at 1 atm, room temperature, overnight. The title compound was obtained, 130 mg (88%), as an oil after filtration through Celite. $[\alpha]_D^{21}=+28$ (*c* 1.6, $CHCl_3$); IR (ν cm^{-1}): 3301.9, 2922.0, 1735.8; ^1H NMR (400 MHz; $CDCl_3$): δ 7.27 (s, 1H), 7.10 (d, 3H, $J=7.6$ Hz), 3.83–3.78 (m, 2H), 3.75 (s, 6H), 3.15–2.86 (dd, 4H, $J=13.7$, 7.6 Hz); ^{13}C NMR (100 MHz; $CDCl_3$): δ 175.2, 137.4, 130.2, 128.7, 127.7, 55.6, 51.9, 40.8; HRMS (FAB+H^+): m/z calculated for $C_{14}H_{23}N_2O_4$ 281.1502. Found 281.1502 [M+H].

4.2.3. (*S*,*S*)-2-Dibenzylamino-3-[3-(2-dibenzylamino-2-methoxycarbonyl-ethyl)-phenyl]-propionic acid methyl ester 5a. Following the general procedure for alkylation, from 100 mg (0.36 mmol) of **4**, 70 mg (30%) of **5a** were isolated as a colourless oil. IR (ν cm^{-1}): 2949.0, 1732.0; ^1H NMR ($CDCl_3$): δ 7.27 (m, 20H), 7.15 (d, 1H, $J=7.6$ Hz), 6.94 (d, 2H, $J=7.6$ Hz), 6.69 (s, 1H), 3.98 (d, 4H, $J=14$ Hz), 3.74 (s, 6H), 3.67 (d, 2H, $J=7.6$ Hz), 3.60 (d, 4H, $J=14$ Hz), 3.04 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 139.2, 127.9, 130.4, 128.6, 128.1, 127.9, 127.3, 126.8, 62.4, 54.9, 51.0, 35.6; HRMS (FAB-H^+) m/z calculated for $C_{42}H_{43}N_2O_4$ 639.3222. Found 639.3230 [M−H].

4.2.4. (*S*,*S*)-2-(2,6-Dioxo-piperidin-1-yl)-3-{3-[2-(2,6-dioxopiperidin-1-yl)-2-methoxycarbonyl-ethyl]-phenyl}-propionic acid methyl ester 5b. To a solution of **4** (150 mg, 0.52 mmol) in CH_2Cl_2 (300 μL) at 0°C was added portion wise glutaric anhydride (70 mg, 0.58 mmol). The solution was then refluxed for 6 h, after which acetyl chloride (2 mL) was added and the reflux maintained for an additional 24 h. The solution was allowed to reach room temperature and the solvent removed under reduced pressure. Water (4 mL) and CH_2Cl_2 (4 mL) were added to the crude product. Saturated K_2CO_3 was added until neutralisation. The aqueous phase was extracted with CH_2Cl_2 (3×4 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude was chromatographed (SiO_2, heptane/EtOAc, 1:9, R_f 0.3) to give **5b** (150 mg, 61%). IR (ν cm^{-1}): 2951.8, 1731.0, 1678.9; ^1H NMR (400 MHz, $CDCl_3$): δ 7.14 (m, 1H), 6.97 (m, 2H), 6.85 (s, 1H), 5.56 (q, 2H, $J=5.2$, 5.4 Hz), 3.37 (s, 6H), 3.42 (m, 2H), 3.22 (m, 2H), 2.53 (m, 8H), 1,76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 169.9, 137.3, 130.5, 128.2, 127.6, 53.0, 52.5, 34.2, 32.5, 16.8; HRMS (FAB+Na^+) m/z calculated for $C_{24}H_{30}N_2O_8Na$ 495.1744. Found 495.1773 [M+Na].

4.2.5. (*S*,*S*)-2-Dimethylamino-3-[3-(2-dimethylamino-2-methoxycarbonyl-ethyl)-phenyl]-propionic acid methyl ester 5c. Following the general procedure of alkylation, from 90 mg (0.32 mmol) of **4**, 20 mg (18%) of **5c** were obtained as a colourless oil after chromatography (SiO_2, heptane/EtOAc 7:3, R_f 0.7). IR (ν cm^{-1}): 2961, 1729; ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (m, 1H), 7.05 (m, 3H), 3.62 (s, 8H), 3.04 (d, 4H, $J=7.6$ Hz), 2.53 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 137.3, 129.9, 128.8, 127.6, 68.9, 51.5, 41.4, 35.4; HRMS (FAB+H^+) m/z calculated for $C_{18}H_{29}N_2O_4$ 337.2128. Found 337.2140 [M+H].

4.2.6. (*S*,*S*)-2-[Bis-(2-methyl-benzyl)-amino]-3-(3-{2-[bis-(2-methyl-benzyl)-amino]-2-methoxycarbonyl-ethyl}-phenyl)-propionic acid methyl ester 5d. Following the general procedure of alkylation, from 100 mg (0.36 mmol) of **4**, 180 mg (73%) of the title compound were obtained as a brown oil. IR (ν cm^{-1}): 2964.4, 1734.9; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.11 (m, 17H), 6.91 (dd, 2H, $J=1.5$, 7.1 Hz), 6.63 (s, 1H), 3.92 (d, 4H, $J=20.2$ Hz), 3.75 (s, 6H), 3.79–3.66 (m, 6H), 3.22–2.94 (m, 4H), 2.25 (s, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.4, 138.0, 137.2, 136.5, 130.3, 130.2, 130.1, 129.9, 129.8, 127.9, 127.6, 127.4, 127.1, 126.8, 125.9, 125.5, 62.8, 52.4, 50.9, 34.9, 19.0; HRMS (FAB+H^+) m/z calculated for $C_{46}H_{53}N_2O_4$ 697.4006. Found 697.4007 [M+H].

4.2.7. (*S*,*S*)-2-[Bis-(3-methyl-benzyl)-amino]-3-(3-{2-[bis-(3-methyl-benzyl)-amino]-2-methoxycarbonyl-ethyl}-phenyl)-propionic acid methyl ester 5e. Following the general procedure of alkylation, from 100 mg (0.36 mmol) of **4**, 150 mg (62%) of **5e** were isolated. IR (ν cm^{-1}): 2964.4, 1734.9; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.11 (m, 17H), 6.91 (dd, 2H, $J=1.5$, 7.1 Hz), 6.63 (s, 1H), 3.92 (d, 4H, $J=20.2$ Hz), 3.75 (s, 6H), 3.79–3.66 (m, 6H), 3.22–2.94 (m, 4H), 2.25 (s, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.4, 138.0, 137.2, 136.5, 130.3, 130.2, 130.1, 129.9, 129.8, 127.9, 127.6, 127.4, 127.1, 126.8, 125.9, 125.5, 62.8, 52.4, 50.9, 34.9, 19.0; HRMS (FAB+H^+) m/z calculated for $C_{46}H_{53}N_2O_4$ 697.4006. Found 697.4007 [M+H].

4.2.8. (*S*,*S*)-2-[Bis-(4-methyl-benzyl)-amino]-3-(3-{2-[bis-(4-methyl-benzyl)-amino]-2-methoxycarbonyl-ethyl}-phenyl)-propionic acid methyl ester 5f. Following the general procedure of alkylation, from 90 mg (0.29 mmol) of **4**, 110 mg (52%) of **5f** were isolated as a colourless oil. IR (ν cm^{-1}): 2964.4, 1734.9; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.11 (m, 17H), 6.91 (dd, 2H, $J=1.5$, 7.1 Hz), 6.63 (s, 1H), 3.92 (d, 4H, $J=20.2$ Hz), 3.75 (s, 6H), 3.79–3.66 (m, 6H), 3.22–2.94 (m, 4H), 2.25 (s, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.4, 138.0, 137.2, 136.5, 130.3, 130.2, 130.1, 129.9, 129.8, 127.9, 127.6, 127.4, 127.1, 126.8, 125.9, 125.5, 62.8, 52.4, 50.9, 34.9, 19.0; HRMS (FAB+H^+) m/z calculated for $C_{46}H_{53}N_2O_4$ 697.4006. Found 697.4007 [M+H].

4.2.9. (*S*,*S*)-2-(Bis-biphenyl-2-ylmethyl-amino)-3-{3-[2-(bis-biphenyl-2-ylmethyl-amino)-2-methoxycarbonyl-ethyl]-phenyl}-propionic acid methyl ester 5g. Following the general procedure of alkylation, from 100 mg (0.36 mmol) of **4**, 200 mg (60%) of **5g** were isolated as an oil. IR (ν cm^{-1}): 3023.3, 1729.1; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47–7.27 (m, 37H), 6.89 (d, 2H, $J=7.6$ Hz), 6.69 (s, 1H), 3.73 (q, 8H, $J=39.6$ Hz), 3.49 (t, 2H, $J=7.1$ Hz) 3.29 (s, 6H), 3.00–2.63 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.3, 145.9, 142.1, 141.2, 138.1, 137.7, 136.3, 133.5, 130.7, 130.6, 130.2, 130.0, 129.8, 129.3, 128.9, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.5, 127.3, 127.2, 126.7, 126.4, 62.9, 51.4, 50.4, 35.4, 31.8; HRMS (FAB+H^+) m/z calculated for $C_{66}H_{61}N_2O_4$ 945.4632. Found 945.4636 [M+H].

4.2.10. (*S*,*S*)-2-(1*H*,3*H*-Benzo[de]isoquinolin-2-yl)-3-{3-[2-(1*H*,3*H*-bezo[de]isoquinolin-2-yl)-2-hydroperoxycarbonyl-ethyl]-phenyl}-propionic acid methyl ester 5h.[†] Following the general procedure of alkylation, from 100 mg (0.36 mmol) of **4**, 50 mg (21%) of white solid was obtained after chromatography (SiO_2, heptane/EtOAc, 1:1, TLC CH_2Cl_2/MeOH 30:1, R_f 0.4). Mp 126.8–129.1°C; IR (ν cm^{-1}): 2950.9, 1739.9; ^1H NMR (300 MHz, $CDCl_3$): δ 8.44 (dd, 4H, $J=1.0$, 7.3 Hz), 8.16 (dd, 4H, $J=1.0$, 8.4 Hz), 7.68 (t, 4H, $J=7.4$ Hz), 7.12 (s, 1H), 6.92 (m, 3H), 5.93 (q, 2H, $J=5.9$, 9.3 Hz), 3.68 (s, 6H), 3.60–3.21 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.1, 163.5, 137.5, 137.4, 135.3, 134.1, 133.3, 131.4, 130.4, 128.1, 128.08, 127.4, 127.3, 126.8, 122.0, 54.1, 52.3, 34.8; HRMS (FAB+H^+) m/z calculated for $C_{39}H_{29}N_2O_8$ 641.1846. Found 641.1921 [M+H].

[†] The methyl ester product was difficult to purify and the final product contained traces of starting material, 1,8-naphthalic anhydride. The product was used in the $LiAlH_4$ reduction after which the chiral catalyst was easily purified.

4.2.11. (*S*)-2-[Bis-(2-methyl-benzyl)-amino]-3-phenyl-propionic acid methyl ester 7d. Following the general procedure of alkylation, from 100 mg (0.56 mmol) of phenylalanine methyl ester, 160 mg (72%) of **7d** were obtained as a colourless oil. IR (ν cm^{-1}): 3026.1, 2949.0, 1734.9; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.07 (m, 13H), 3.97 (d, 2H, $J=13.7$ Hz), 3.81 (br s, 4H, OMe+α-*H*), 3.77 (s, 1H), 3.21 (m, 2H), 2.29 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.4, 138.2, 137.3, 136.5, 130.1, 129.9, 129.2, 128.1, 127.2, 126.9, 126.1, 125.5, 62.8, 52.4, 50.9, 35.1, 19.1; HRMS (FAB+H$^+$) m/z calculated for $C_{26}H_{30}NO_2$ 388.2277. Found 388.2289 [M+H].

4.2.12. (*S*)-2-[Bis-(3-methyl-benzyl)-amino]-3-phenyl-proionic acid methyl ester 7e. Following the general procedure of alkylation, from 100 mg (0.56 mmol) of phenylalanine methyl ester, 110 mg (50%) of **7e** were obtained as a colourless oil. IR (ν cm^{-1}): 3026.1, 2949.0, 1734.9; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.04 (m, 13H), 4.02 (d, 2H, $J=13.9$ Hz), 3.83 (s, 3H), 3.80 (m, 1H), 3.60 (d, 2H, $J=14$ Hz), 3.24–3.06 (m, 2H), 2.38 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.8, 139.2, 138.1, 137.5, 129.5, 129.4, 128.0, 127.9, 127.5, 126.2, 125.7, 62.1, 54.3, 51.0, 35.7, 21.4; HRMS (FAB+H$^+$) m/z calculated for $C_{26}H_{30}NO_2$ 388.2277. Found 388.2289 [M+H].

4.2.13. (*S*)-2-[Bis-(4-methyl-benzyl)-amino]-3-phenyl-proionic acid methyl ester 7f. Following the general procedure of alkylation, from 100 mg (0.56 mmol) of phenylalanine methyl ester, 170 mg (79%) of **7f** were obtained as a yellow oil. IR (ν cm^{-1}): 3026.1, 2949.0, 1734.9; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.16 (m, 13H), 4.07 (d, 2H, $J=13.8$ Hz), 3.85 (m, 4H, OMe+α-*H*), 3.66 (d, 2H, $J=13.9$ Hz), 3.31–3.10 (m, 2H), 2.46 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.7, 138.1, 136.2, 136.1, 129.8, 129.7, 129.6, 129.3, 129.2, 129.0, 128.9, 128.8, 128.7, 128.5, 128.3, 128.2, 127.9, 126.1, 62.1, 53.9, 50.9, 35.6, 21.0; HRMS (FAB+H$^+$) m/z calculated for $C_{26}H_{30}NO_2$ 388.2277. Found 388.2289 [M+H].

4.2.14. (*S*)-2-(Bis-biphenyl-2-ylmethyl-amino)-3-phenyl-propionic acid methyl ester 7g. Following the general procedure of alkylation, from 100 mg (0.56 mmol) of phenylalanine methyl ester, 240 mg (84%) of **7g** were obtained as a yellow oil. IR (ν cm^{-1}): 3059.9, 1732.9; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.10 (m, 23H), 3.98 (d, 2H, $J=14.5$ Hz), 3.70 (m, 3H, C*H*$_2$Ph+α-*H*), 3.41 (s, 3H), 3.15–2.75 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 172.5, 142.4, 141.4, 138.5, 136.5, 133.7, 130.8, 130.2, 129.9, 129.5, 129.3, 129.2, 128.9, 128.6, 128.4, 128.3, 127.9, 127.9, 127.7, 127.5, 126.9, 126.6, 126.3, 63.1, 51.6, 50.7, 35.6; HRMS (FAB+H$^+$) m/z calculated for $C_{36}H_{33}NO_2$ 512.2590. Found 512.2595 [M+H].

4.2.15. (*S*)-2-(1*H*,3*H*-Benzo[de]isoquinolin-2-yl)-3-phenyl-propionic acid methyl ester 7h.[†] Following the general procedure of alkylation, from 100 mg (0.56 mmol) of phenylalanine methyl ester, 100 mg (51%) of **7h** were obtained as a pink semi-solid. IR (ν cm^{-1}): 3029.9, 1738.7, 1661.6; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (dd, 2H, $J=1.0$, 7.4 Hz), 8.18 (dd, 2H, $J=1.1$, 8.4 Hz), 7.70 (t, 2H, $J=7.3$ Hz), 7.24–7.05 (m, 5H), 6.06 (q, 1H, $J=1.8$ Hz), 3.76 (s, 3H), 3.73–3.45 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.2, 153.6, 137.3, 135.3, 134.2, 133.3, 131.5, 131.4, 129.2, 128.2, 128.0, 127.4, 126.8, 126.4, 121.9, 54.2, 34.9, 22.6; HRMS (FAB+H$^+$) m/z calculated for $C_{22}H_{17}NO_4$ 360.1237 Found 360.1265 [M+H].

4.3. (*S*,*S*)-2-Dibenzylamino-3-[3-(2-dibenzylamino-3-hydroxy-3,3-diphenyl-propyl)-phenyl]-1,1-diphenyl-propan-1-ol 9

PhLi (39 mg, 0.46 mmol) was added to a solution of **2a** (40 mg, 0.12 mmol) in dry THF (5 mL) under a nitrogen atmosphere. The reaction was stirred at room temperature for 18 h. Saturated NH_4Cl solution was added to pH ~3. The aqueous layer was extracted with diethyl ether (3×20 mL) followed by drying over Na_2SO_4 and removal of the solvent under reduced pressure. The crude was chromatographed (SiO_2, heptane/EtOAc 1:4, R_f 0.2) to give **9** (65 mg, 61%) as a white semi-amorphous mass. $[\alpha]_D^{21}=-20.5$ (c 1.7, EtOH); IR (ν cm^{-1}): 3388.7, 1645.17; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (m, 4H), 7.40–7.00 (m, 40H), 5.19 (m, 2H), 3.36 (m, 12H, C*H*$_2$Ph+β-*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 145.6, 143.8, 141.2, 138.9, 129.6, 129.1, 128.3, 128.1, 127.9, 127.8, 127.3, 127.2, 127.1, 55.5, 31.7, 22.7, 14.1; HRMS (FAB+H$^+$) m/z calculated for $C_{64}H_{60}N_2O_2Na$ 911.4553. Found 911.4550[M+Na].

4.4. General procedure for reduction of the methyl ester with $LiAlH_4$

Dry THF (15 mL) was added to $LiAlH_4$ (10 mmol) at 0°C and the resulting slurry stirred for 10 min. The methyl ester (1.0 mmol) was dissolved in dry THF (3 mL) and then slowly added to the slurry at 0°C. The reaction mixture was stirred for 4 h at room temperature and then quenched by the addition of 0.1 M HCl (10 mL) followed by further stirring for 1 h. The mixture was filtered through Celite and the aqueous phase extracted with diethyl ether (2×30 mL) followed by drying (Na_2SO_4) and the solvent removed under reduced pressure. The crude was purified by chromatography (diethyl ether/pentane, 4:1).

4.4.1. (*S*,*S*,*S*)-2-Dibenzylamino-3-[3,5-bis-(2-dibenzylamino-2-hydroxy-propyl)-phenyl]-propan-1-ol 3a. Following the general procedure for reduction with $LiAlH_4$, from 60 mg (0.09 mmol) of **2**, 26 mg (50%) of the title compound were obtained as a colourless oil. $[\alpha]_D^{21}=+16$ (c 1.2, EtOH); IR (ν cm^{-1}): 3386.8, 2935.5, 2856.4, 1600.8; ^{1}H NMR (400 MHz, CD_3OD): δ 7.22 (m, 30H), 6.67 (s, 3H), 4.59 (s, 3H), 3.71 (m, 12H), 3.44 (m, 3H), 2.92 (m, 6H), 2.56 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 141.8, 130.4, 128.7, 128.4, 62.9, 62.4, 55.2, 34.8, 30.6; HRMS (FAB+Na$^+$) m/z calculated for $C_{57}H_{63}N_3O_3Na$ 860.4767. Found 860.4758 [M+Na].

4.4.2. (*S*,*S*)-2-Dibenzylamino-3-[3-(2-dibenzylamino-3-hydroxypropyl)-phenyl]-propan-1-ol 6a. Following the general procedure for reduction with $LiAlH_4$, from 100 mg (0.16 mmol) of **5a**, 70 mg (80%) of **6a** were obtained as a colourless oil. $[\alpha]_D^{21} = +16.3$ (*c* 1.1, EtOH); IR (*v* cm^{-1}): 3301.9, 2911.0; ^1H NMR (400 MHz, CD_3OD): δ 7.34 (d, 1H, $J = 6.0$ Hz), 7.22 (m, 20H), 6.93 (d, 2H, $J = 7.5$ Hz), 6.82 (s, 1H), 3.71 (m, 8H), 3.45 (m, 2H), 2.95 (m, 4H), 2.61 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 141.9, 141.8, 130.4, 129.7, 128.4, 62.9, 62.4, 55.2, 34.9; HRMS (FAB+Na^+) *m*/*z* calculated for $C_{40}H_{45}N_2O_2$ 607.3301. Found 607.3299 [M+Na].

4.4.3. (*S*,*S*)-3-[3-(3-Hydroxy-2-piperidin-1-yl-propyl)-phenyl)-phenyl]-2-piperidin-1-yl-propan-1-ol 6b. Following the general procedure for reduction with $LiAlH_4$, from 120 mg (0.25 mmol) of **5b**, 30 mg (30%) of **6b** were obtained as a yellow oil. $[\alpha]_D^{21} = +13.1$ (*c* 1.9, EtOH); IR (*v* cm^{-1}): 3401.2, 2930.6; ^1H NMR (400 MHz, CD_3OD): δ 7.25–7.03 (m, 5H, α-*H*+CH_2OH), 2.72 (m, 13H), 1.52 (m, 12H); ^{13}C NMR (100 MHz, CD_3OD): δ 169.6, 159.1, 157.5, 155.9, 97.5, 88.9, 79.2, 61.5, 55.4, 53.7; HRMS (FAB+H^+) *m*/*z* calculated for $C_{22}H_{37}N_2O_2$ 361.2856. Found 361.2845 [M+H].

4.4.4. (*S*,*S*)-2-Dimethylamino-3-[3-(2-dimethylamino-3-hydroxypropyl)-phenyl]-propan-1-ol 6c. Following the general procedure for reduction with $LiAlH_4$, from 30 mg (0.09 mmol) of **5c**, 35 mg (72%) of **6c** were obtained as a yellow oil. The product could not be chromatographed because it decomposed on the column. $[\alpha]_D^{21} = +0.2$ (*c* 3.2, EtOH); IR (*v* cm^{-1}): 2359.7, 2330.8; ^1H NMR (400 MHz, CD_3OD): δ 7.34–7.05 (m, 4H), 3.50 (m, 4H), 2.81 (m, 2H), 2.71 (m, 4H), 2.40 (s, 12H); ^{13}C NMR (100 MHz, CD_3OD): δ 141.6, 131.3, 129.8, 128.1, 69.0, 61.3, 41.5, 33.1; HRMS (FAB+H^+) *m*/*z* calculated for $C_{16}H_{29}N_2O_2$ 281.2230. Found 281.2239 [M+H].

4.4.5. (*S*,*S*)-2-[Bis-(2-methyl-benzyl)-amino]-3-(3-{2-[bis-(2-methyl-benzyl)-amino]-3-hydroxypropyl}-phenyl)-propan-1-ol 6d. Following the general procedure for reduction with $LiAlH_4$, from 110 mg (0.16 mmol) of **5d**, 50 mg (50%) of **6d** were obtained as a colourless oil. $[\alpha]_D^{21} = +29.8$ (*c* 1.6, EtOH); IR (*v* cm^{-1}): 3427.3, 2915.2; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–7.18 (m, 19H), 6.99 (dd, 2H, $J = 1.5$, 6.1 Hz), 6.91 (s, 1H), 4.73 (s, 1H, O*H*), 3.80 (m, 8H), 3.57 (t, 2H, $J = 10.7$ Hz), 3.29 (m, 4H), 3.09 (m, 2H), 2.51 (m, 2H), 2.29 (s, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 139.4, 137.0, 136.3, 130.6, 130.4, 130.2, 129.9, 128.8, 127.7, 127.4, 127.37, 126.7, 126.0, 125.8, 125.5, 63.4, 60.9, 60.4, 51.0, 31.1, 30.3, 29.7, 19.1; HRMS (FAB+H^+) *m*/*z* calculated for $C_{44}H_{53}N_2O_2$ 641.4029. Found 641.4091 [M+H].

4.4.6. (*S*,*S*)-2-[Bis-(3-methyl-benzyl)-amino]-3-(3-{2-[bis-(3-methyl-benzyl)-amino]-3-hydroxypropyl}-phenyl)-propan-1-ol 6e. Following the general procedure for reduction with $LiAlH_4$, from 70 mg (0.11 mmol) of **5e**, 40 mg (59%) of the title compound were obtained as a colourless oil. $[\alpha]_D^{21} = +23.2$ (*c* 1.9, EtOH); IR (*v* cm^{-1}): 3427.3, 2915.2; ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–7.08 (m, 19H), 6.95 (dd, 2H, $J = 1.6$, 6.0 Hz), 6.85 (s, 1H), 4.68 (s, 1H, O*H*), 3.69 (m, 10H, CH_2Ph+α-*H*), 3.32 (m, 2H), 3.08 (m, 6H), 2.36 (s, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.5, 138.5, 138.1, 130.0, 129.8, 128.7, 128.4, 128.0, 126.8, 126.1, 60.9, 60.3, 53.3, 31.6, 21.4; HRMS (FAB+H^+) *m*/*z* calculated for $C_{44}H_{53}N_2O_2$ 641.4029. Found 641.4091 [M+H].

4.4.7. (*S*,*S*)-2-[Bis-(4-methyl-benzyl)-amino]-3-(3-{2-[bis-(4-methyl-benzyl)-amino]-3-hydroxypropyl}-phenyl)-propan-1-ol 6f. Following the general procedure for reduction with $LiAlH_4$, from 110 mg (0.16 mmol) of **5f**, 90 mg (91%) of **6f** were obtained as a colourless oil. $[\alpha]_D^{21} = +17.9$ (*c* 1.4, EtOH); IR (*v* cm^{-1}): 3427.3, 2915.2; ^1H NMR (300 MHz, $CDCl_3$): δ 7.19–7.04 (m, 19H), 6.85 (dd, 2H, $J = 1.5$, 7.6 Hz), 6.75 (s, 1H), 3.58 (m, 8H), 3.40 (t, 2H, $J = 3.8$ Hz), 3.20 (dd, 2H, $J = 3.9$, 10.4 Hz), 2.98 (d, 6H, $J = 11.8$ Hz), 2.26 (m, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 139.5, 136.9, 135.9, 129.2, 128.9, 126.82, 126.8, 60.3, 60.2, 52.8, 31.6, 21.1; HRMS (FAB+H^+) *m*/*z* calculated for $C_{44}H_{53}N_2O_2$ 641.4029. Found 641.4091 [M+H]. Anal. calcd for $C_{44}H_{52}N_2O_2$: C, 82.46; H, 8.18; N, 4.37. Found: C, 82.32; H, 8.11; N, 4.26%.

4.4.8. (*S*,*S*)-2-(Bis-biphenyl-2-ylmethyl-amino)-3-{3-[2-(bis-biphenyl-2-ylmethyl-amino)-3-hyroxypropyl]-phenyl}-propan-1-ol 6g. Following the general procedure for reduction with $LiAlH_4$, from 140 mg (0.15 mmol) of **5g**, 70 mg (51%) of **6g** were obtained as a white powder. Mp 84.4–86.2°C; $[\alpha]_D^{21} = +16$ (*c* 1.2, EtOH); IR (*v* cm^{-1}): 3388.7, 3022.2, 2858.3; ^1H NMR (300 MHz, $CDCl_3$): δ 7.24–7.21 (m, 36H), 6.95 (t, 1H, $J = 7.6$ Hz), 6.47 (d, 2H, $J = 7.6$ Hz), 6.32 (s, 1H), 3.65 (m, 8H), 3.13 (t, 2H, $J = 10.3$ Hz), 3.03 (m, 2H), 2.67 (m, 2H), 2.48 (m, 2H), 1.99 (q, 2H, $J = 13.3$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 142.2, 141.2, 138.8, 136.0, 130.2, 129.8, 129.7, 129.2, 128.3, 128.1, 127.6, 127.0, 126.8, 126.3, 61.3, 60.4, 50.4, 30.9; HRMS (FAB+H^+) *m*/*z* calculated for $C_{64}H_{61}N_2O_2$ 889.4734. Found 889.4745 [M+H].

4.4.9. (*S*,*S*)-2-(1*H*,3*H*-Benzo[de]isoquinolin-2-yl)-3-{3-[2-(1*H*,3*H*-benzo[de]isoquinolin-2-yl)-3-hydroxypropyl]-phenyl}-propan-1-ol 6h. Following the general procedure for reduction with $LiAlH_4$, from 47 mg (0.073 mmol) of **5h**, 20 mg (41%) of **6h** were obtained as a colourless oil. $[\alpha]_D^{21} = -20.8$ (*c* 1.6, $CHCl_3$); IR (*v* cm^{-1}): 3442.7, 2926.8, 1700.0, 1657.7; ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (m, 2H), 7.73 (d, 4H, $J = 8.0$ Hz), 7.42 (q, 2H, $J = 6.9$, 7.8 Hz), 7.19 (m, 3H), 7.09 (d, 1H, $J = 6.9$ Hz), 6.94 (d, 1H, $J = 6.6$ Hz), 5.75–5.68 (m, 1H), 4.27–3.96 (m, 6H), 3.40–3.16 (m, 6H), 3.01–2.41 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 138.5, 134.1, 133.7, 133.5, 131.4, 129.8, 128.6, 128.1, 128.05, 127.3, 127.1, 127.0, 126.1, 125.6, 121.8, 66.5, 63.6, 59.9, 54.5, 51.9; HRMS (FAB+H^+) *m*/*z* calculated for $C_{36}H_{36}N_2O_2$ 529.2856. Found 529.5856 [M+H].

4.4.10. (*S*)-2-[Bis-(2-methyl-benzyl)-amino]-3-phenyl-propan-1-ol 8d. Following the general procedure for reduction with $LiAlH_4$, from 100 mg, 0.26 mmol) of **7d**, 90 mg (99%) of **8d** were isolated as a colourless oil. $[\alpha]_D^{21} = +43.8$ (*c* 8.0, $CHCl_3$); IR (*v* cm^{-1}): 3388.7, 2922.9; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–7.17 (m, 13H)

3.98 (d, 2H, $J=13.1$ Hz), 3.68 (d, 2H, $J=13.1$ Hz), 3.61 (d, 1H, $J=10$ Hz), 3.36 (m, 2H), 3.16 (m, 1H), 2.59 (q, 1H, $J=10.5$, 13.2 Hz), 2.32 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 139.1, 136.9, 136.3, 130.5, 130.4, 130.2, 128.9, 128.5, 127.6, 127.3, 126.2, 125.8, 125.5, 60.8, 60.3, 50.8, 31.1, 19.0; HRMS (FAB+H$^+$) m/z calculated for $C_{25}H_{30}NO$ 360.2328. Found 360.2333 [M+H].

4.4.11. (*S*)-2-[Bis-(3-methyl-benzyl)-amino]-3-phenyl-propan-1-ol 8e. Following the general procedure for reduction with $LiAlH_4$, from 100 mg (0.26 mmol) of **7e**, 90 mg (97%) of **8e** were isolated as a colourless oil. $[\alpha]_D^{21}=+20.3$ (*c* 7.2, EtOH); IR (ν cm^{-1}): 3388.7, 2922.9; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.13 (m, 13H), 3.97 (d, 2H, $J=13.2$ Hz), 3.54 (m, 3H, C*H*$_2$Ph+α-*H*), 3.42 (q, 1H, $J=4.4$, 10.7 Hz), 3.16 (m, 2H), 2.41 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 139.2, 138.9, 137.9, 129.8, 128.9, 128.4, 128.3, 127.9, 126.1, 126.0, 125.5, 60.7, 60.2, 53.1, 31.6, 21.4; HRMS (FAB+H$^+$) m/z calculated for $C_{25}H_{30}NO$ 360.2328. Found 360.2333 [M+H].

4.4.12. (*S*)-2-[Bis-(4-methyl-benzyl)-amino]-3-phenyl-propan-1-ol 8f. Following the general procedure for reduction with $LiAlH_4$, from 170 mg (0.44 mmol) of **7f**, 150 mg (94%) of **8f** were obtained as a colourless oil. $[\alpha]_D^{21}=+12.7$ (*c* 11.3, $CHCl_3$); IR (ν cm^{-1}): 3388.7, 2922.9; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.19 (m, 13H), 3.97 (d, 2H, $J=13.2$ Hz), 3.58 (d, 1H, $J=10.5$ Hz), 3.52 (d, 2H, $J=13.2$ Hz), 3.41 (m, 1H), 3.17 (m, 2H), 2.42 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 139.1, 136.7, 135.9, 129.1, 129.05, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 126.9, 126.1, 125.4, 60.4, 60.1, 52.7, 30.2, 21.0; HRMS (FAB+H$^+$) m/z calculated for $C_{25}H_{30}NO$ 360.2328. Found 360.2333 [M+H]. Anal. calcd for $C_{25}H_{29}NO$: C, 83.52; H, 8.13; N, 3.90. Found: C, 83.39; H, 8.08; N, 3.84%.

4.4.13. (*S*)-2-(Bis-biphenyl-2-ylmethyl-amino)-3-phenyl-propan-1-ol 8g. Following the general procedure for reduction with $LiAlH_4$, from 200 mg (0.39 mmol) of **7g**, 200 mg (99%) of **8g** were obtained as a yellow-white semi-solid. $[\alpha]_D^{21}=+16.7$ (*c* 24, $CHCl_3$); IR (ν cm^{-1}): 3389.7, 3025.1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53–6.83 (m, 23H), 3.93 (d, 2H, $J=13.7$ Hz), 3.62 (d, 2H, $J=13.7$ Hz), 3.27 (m, 2H), 2.81 (m, 1H), 2.66 (dd, 1H, $J=3.6$, 13.2 Hz), 2.19 (q, 1H, $J=10.1$, 13.2 Hz); ^{13}C NMR (75.5 Hz, $CDCl_3$): δ 142.1, 141.1, 138.9, 136.1, 130.2, 129.9, 129.8, 129.2, 129.0, 128.8, 128.6, 128.3, 128.2, 128.1, 128.0, 127.5, 127.4, 127.1, 126.9, 126.8, 125.8, 125.4, 62.8, 61.5, 50.3, 30.2; HRMS (FAB+H$^+$) m/z calculated for $C_{35}H_{34}NO$ 484.2641. Found 484.2635 [M+H].

4.4.14. (*S*)-2-(1*H*,3*H*-Benzo[de]isoquinolin-2-yl)-3-phenyl-propan-1-ol 8h. Following the general procedure for reduction with $LiAlH_4$, from 70 mg (0.20 mmol) of **7h**, 40 mg (64%) of **8h** were obtained as a colourless semi-solid. $[\alpha]_D^{21}=-13.4$ (*c* 1.1, $CHCl_3$); IR (ν cm^{-1}): 3423.4, 3036.7, 1660.6; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77–7.20 (m, 11H), 4.30 (d, 2H, $J=14.3$ Hz), 4.07 (d, 2H, $J=13.9$ Hz), 3.60 (m, 2H), 3.41–3.13 (m, 3H), 2.61 (m, 1H, O*H*); ^{13}C NMR (75.5 Hz, $CDCl_3$): δ 138.9, 133.9, 133.7, 133.2, 129.1, 128.9, 128.6, 128.3, 128.1, 126.9, 126.3, 126.1, 125.5, 121.7, 66.7, 60.0, 51.9, 32.0; HRMS (FAB+H$^+$) m/z calculated for $C_{21}H_{22}NO$ 304.1702. Found 304.1692 [M+H].

4.5. General procedure for the chiral catalyst-promoted addition of Et_2Zn to aldehydes

To a solution of the chiral catalyst (0.05 equiv.) in dry toluene (3 mL/0.95 mmol benzaldehyde) under nitrogen atmosphere was added a solution of Et_2Zn (1.73 mL, 1.1 M in toluene, 2 equiv.) via syringe. After stirring for 10 min, freshly distilled benzaldehyde (1 equiv.) was added into the mixture via syringe. The resulting mixture was stirred for 24 h at room temperature and the reaction quenched by the addition of NH_4Cl solution (4 mL) on an ice bath. The aqueous phase was extracted with diethyl ether (3×6 mL) washed with $NaHSO_3$ (3×8 mL), dried over Na_2SO_4 followed by the removal of the solvent under reduced pressure. The crude was chromatographed (pentane/diethyl ether, 6:4) to give the pure product.

4.6. General conditions for HPLC analysis of chiral alcohols

Method A: Chiralcel OD-H column eluted with *n*-hexane/*i*PrOH (97.5:2.5) at 0.5 mL/min using an UV detector operating at 254 nm.

Method B: Chiralcel OD-H column eluted with *n*-hexane/*i*PrOH (95:5) at 0.5 mL/min using an UV detector operating at 254 nm.

1-Phenyl-1-propanol
Method A: $t_R=23.2$ min for (*R*) and $t_R=26.2$ min for (*S*)
1-(4′-Chlorophenyl)-1-propanol
Method B: $t_R=14.5$ min for (*R*) and $t_R=15.3$ min for (*S*)
1-(4′-Methoxyphenyl)-1-propanol
Method B: $t_R=19.1$ min for (*R*) and $t_R=22.7$ min for (*S*).

References

1. Oguni, N.; Omi, T. *Tetrahedron Lett*. **1984**, *25*, 2823.
2. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc*. **1986**, *108*, 6071.
3. Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 49.
4. Soai, K.; Niwa, S. *Chem. Rev*. **1992**, *92*, 833.
5. Pu, L.; Yu, H.-B. *Chem. Rev*. **2001**, *101*, 757 and references cited therein.
6. Dai, W.-M.; Zhu, H.-J.; Hao, X.-J. *Tetrahedron: Asymmetry* **2000**, *11*, 2315.
7. Ionescu, R. D.; Frejd, T. *Chem. Commun*. **2001**, 1088.
8. Ritzén, A.; Basu, B.; Chattopadhyay, S. K.; Dossa, F.; Frejd, T. *Tetrahedron: Asymmetry* **1998**, *9*, 503.
9. Ritzén, A.; Basu, B.; Wållberg, A.; Frejd, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3491.

10. Ritzén, A.; Frejd, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3419.
11. Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264.
12. Ionescu, R. D., unpublished results.
13. Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.
14. Sarvary, I.; Almquist, F.; Frejd, T. *Chem. Eur. J.* **2001**, *7*, 2158.
15. Burk, M. J.; Feaser, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.
16. Micouin, L.; Quirion, J.-C.; Husson, H.-P. *Synth. Commun.* **1996**, *26*, 1605.
17. Kapil, R. S. *Indian J. Chem.* **1966**, *4*, 177.
18. Corey, E. J.; McCaully, R. J.; Sachev, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 2476.
19. Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159.