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Chiral amino alcohols bound to diimines, diamines and dendrimers as chiral ligands for the enantioselective ethylation of *N*-diphenylphosphinylimines

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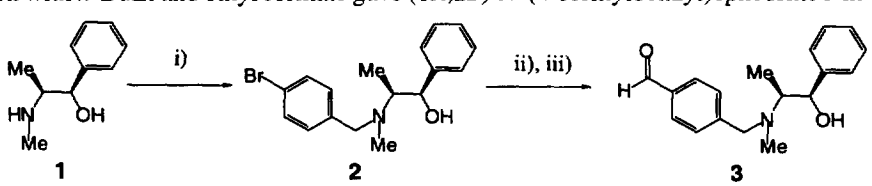
Abstract: Chiral diimines, diamines and dendrimers possessing 2, 4 and 8 ephedrine derivatives are utilized as chiral ligands for the enantioselective addition of diethylzinc to *N*-diphenylphosphinylimines to afford enantiomerically enriched *N*-diphenylphosphinylamines in up to 93% e.e. © 1997 Elsevier Science Ltd. All rights reserved.

Dendrimers form a class of compounds with hyper-branched chains and generally consist of a spherical structure possessing terminal functional groups.[1] Therefore it is possible to prepare chiral dendrimers by attaching chiral monomeric ligands to the functional groups at their terminal positions. However, chiral dendrimers[2] have rarely been utilized in asymmetric synthesis.[3] We previously reported an enantioselective alkylation of *N*-diphenylphosphinylimine with dialkylzincs using either monomeric[4] or polymeric[5] chiral amino alcohols as chiral ligands. In the reaction, the chiral amino alcohol plays the role of not only chiral ligand but promoter of the nucleophilicity of dialkylzincs.[6] During the study, we took an interest in the preparation of chiral dendrimers and their use in the enantioselective alkylation of *N*-diphenylphosphinylimine as a chiral ligand.

We report here the preparation of chiral diimines, diamines and dendrimers possessing ephedrine derivatives and their use as chiral ligands in the enantioselective addition of diethylzinc (Et_2Zn) to *N*-diphenylphosphinylimines.

We plan to connect a chiral amino alcohol moiety and ethylenediamine or Starburst (PAMAM) Dendrimers by the formation of imine. Chiral amino alcohol **3** possessing a formyl group, was synthesized from (1*R*,2*S*)-ephedrine **1** (Scheme 1). Reaction of **1** with 4-bromobenzyl bromide in the presence of potassium carbonate afforded *N*-4-bromobenzylephedrine **2** in 64% yield. The subsequent formylation with *n*-BuLi and ethyl formate gave (1*R*,2*S*)-*N*-(4-formylbenzyl)ephedrine **3** in 46% yield.



Scheme 1. (i) 4-bromobenzyl bromide, K_2CO_3; (ii) *n*-BuLi; (iii) ethyl formate.

When ethylenediamine **4** and **3** reacted in refluxing toluene with a Dean–Stark trap, chiral diimine **5a** was obtained in 91% yield. Reduction of **5a** with sodium borohydride ($NaBH_4$) afforded chiral diamine **5b** in 98% yield (Scheme 2).

Starburst (PAMAM) Dendrimer (Generation 0) **6** with four surface primary amino groups was treated with amino alcohol **3** to afford in 71% yield a chiral imino dendrimer **7a** containing four

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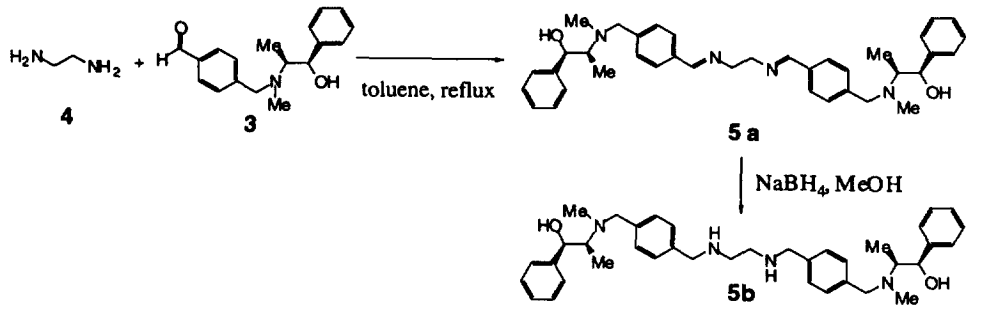
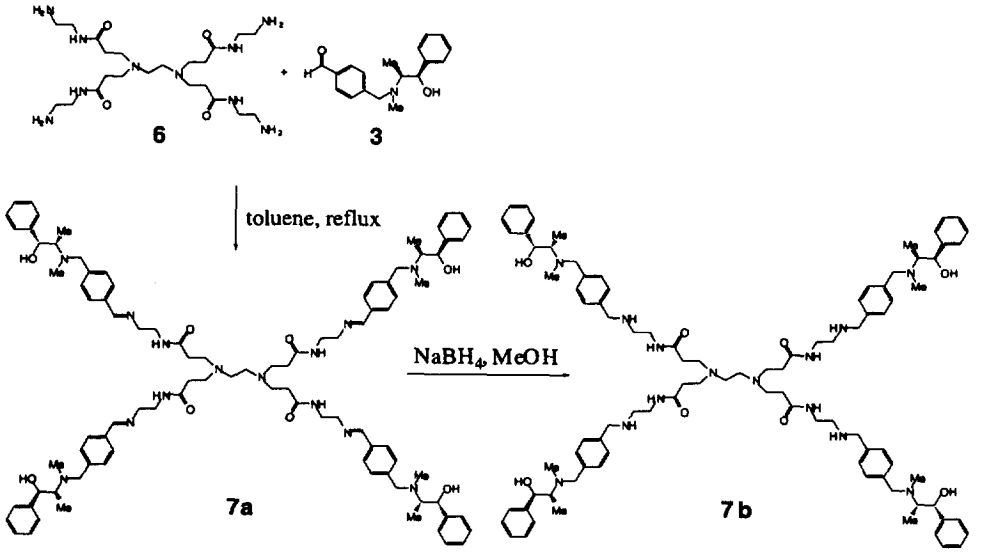


Scheme 2.

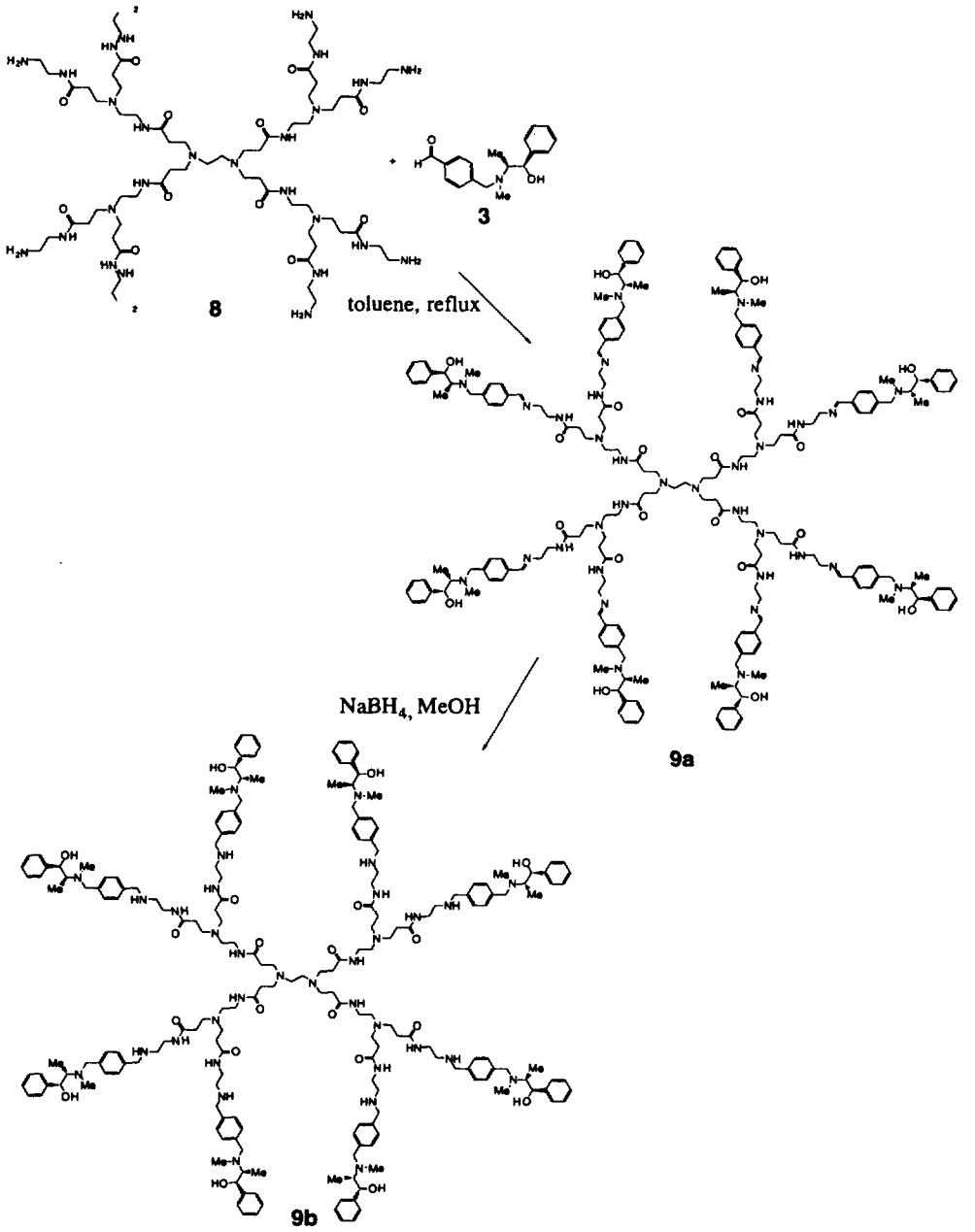
chiral amino alcohol moieties on its terminal positions (Scheme 3). The subsequent reduction of imine groups of **7a** using $NaBH_4$ afforded the corresponding chiral amino dendrimer **7b** in 98% yield.



Scheme 3.

In a similar manner, starting from Starburst (PAMAM) Dendrimer (Generation 1) **8** with eight surface primary amino groups and chiral amino alcohol **3**, chiral imino dendrimer **9a** with eight surface amino alcohols was synthesized in 82% yield (Scheme 4). Reduction of the imino groups of **9a** with $NaBH_4$ afforded chiral amino dendrimer **9b** possessing eight surface amino alcohols in quantitative yield.

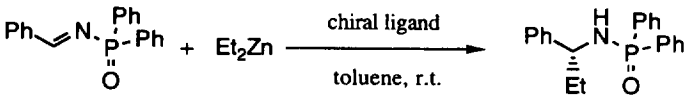
In the presence of **5a,b**, **7a,b**, and **9a,b** as chiral ligands, an enantioselective addition of Et_2Zn to *N*-diphenylphosphinylimine **10a** was examined in toluene at room temperature. The results are shown in Table 1. When chiral diimine **5a** (50 mol%) was employed as the chiral ligand, enantiomerically enriched *N*-diphenylphosphinylamine (*R*)-**11a** with 92% e.e. was obtained in 54% yield (Table 1, entry 1). Because dialkylzinc hardly adds to *N*-alkylimine even in the presence of amino alcohols, the *N*-alkylimine type chiral ligand **5a** was not alkylated during the ethylation reaction of *N*-diphenylphosphinylimine **10a**. The reaction using chiral diamine **5b** as the chiral ligand afforded (*R*)-**11a** with 92% e.e. (entry 2). Chiral ligand **5b** was recovered after quenching. These e.e.s are as high as those observed in the enantioselective ethylation of the same imine **10a** using chiral (1*R*,2*S*)-*N*-benzylephedrine (91% e.e.).[5c] Thus, chiral diimine **5a** and diamine **5b** with C_2 axes were found to be highly enantioselective chiral ligands in the alkylation of *N*-diphenylphosphinylimine.[7]



Scheme 4.

On the other hand, in the presence of chiral imino dendrimeric ligand **7a** (50 mol%), Et_2Zn added to **10a** afforded (*R*)-**11a** with moderate enantioselectivity (43% e.e.) (entry 3). The reaction using chiral amino dendrimer **7b** as a chiral ligand gave (*R*)-**11a** with a similar e.e. (entry 4). Both **7a** and **7b** were soluble in toluene and worked as homogeneous chiral ligands during the reaction. The enantioselectivity of chiral imino dendrimeric ligand **9a** (50 mol%) (entry 5) was comparable to that of **7a** and **7b**. The use of a lesser amount of chiral amino dendrimer **9b** (25 mol%) resulted in the decrease of the yield and e.e. of (*R*)-**11a** (entry 6).

Table 1. Enantioselective ethylation of *N*-diphenylphosphinylimine **10a** using various chiral ligands



10a (*R*)-**11a**

entry	chiral ligand	(mol%)	time / d	(*R*)-**11a** yield / %	e.e. / %
1	**5a**	50	2	54	92
2	**5b**	50	2	46	92
3	**7a**	50	2	32	43
4	**7b**	50	2	18	40
5	**9a**	50	2	12	39
6	**9b**	25	3	8	30

Molar ratio imine : Et_2Zn = 1 : 6

There was very little difference in the enantioselectivities between the imino type and the corresponding amino type chiral ligands (**5a** and **5b**, **7a** and **7b**). Because the imino and amino groups are located in the core part of the molecule, the difference in their structure may not affect the enantioselective reaction promoted by the terminal ephedrine derivatives. Unlike cross linked solid polystyrene resin, dendrimeric chiral ligands **7a,b** and **9a,b** have flexible conformations in organic solvents. Thus, unlike in the reaction using monomeric ligand, the four or eight parts of in situ formed ethylzinc alkoxides of amino alcohols (active chiral sites) cannot operate independently and cannot form an appropriate reaction field for the highly enantioselective addition of Et_2Zn because of the intramolecular interaction among them.

The generality of *N*-diphenylphosphinylimine is exemplified in the enantioselective ethylation of various *N*-diphenylphosphinylimines (**10a–d**) in the presence of 50 mol% of chiral ligands **5a**, **5b** and **7a** (Table 2). Imines **10a,c,d** were ethylated to afford **11a,c,d** with very high e.e.s in the presence of either chiral **5a** or **5b**. The e.e.s of the obtained **11d** with the *p*-tolyl substituent using **5a** and **5b** reached 93% e.e. (entries 4 and 8). On the other hand, the enantioselectivities of **7a** were moderate, affording **11d** with 56% e.e. (entry 12). It should be noted that enantiomerically enriched **11** is known to be converted into the corresponding enantiomerically enriched amine by acidic hydrolysis.[8]

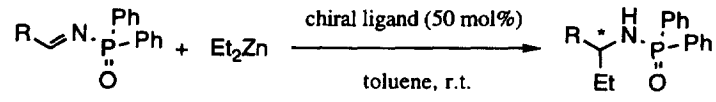
As described, we prepared chiral diimine **5a** and diamine **5b** from chiral amino alcohol **3** and chiral dendrimers **7a,b** and **9a,b** by loading **3** on Starburst (PAMAM) Dendrimers. These compounds were used as chiral ligands for the enantioselective addition of diethylzinc to *N*-diphenylphosphinylimines **10**. In the presence of chiral diimine **5a** and diamine **5b**, *N*-diphenylphosphinylamines **11** with >90% e.e. were obtained. Dendrimeric chiral ligands **7a,b** and **9a,b** afforded **11** with moderate e.e.s. To the best of our knowledge, the present method is the first example of the use of dendrimeric chiral ligands in the enantioselective alkylation of imines.[9]

Experimental

General

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DPX300 spectrometer. IR spectra were recorded on a Horiba FT210 spectrometer. Optical rotations were measured using a JASCO DIP-1000 polarimeter. High resolution mass spectra were measured on JEOL JMS-SX102A. Hexane, toluene, and dichloromethane were distilled from CaH_2, and THF and diethyl ether distilled from $LiAlH_4$ before use. Starburst (PAMAM) Dendrimers were purchased from Sigma Aldrich. *N*-Diphenylphosphinylimines **10a–d** were synthesized according to the literature procedure.[10] All reactions were carried out under an argon atmosphere. HPLC analysis was performed using a chiral column.

Table 2. Enantioselective ethylation of various *N*-diphenylphosphinylimines **10a–d**



10a-d **11a-d**

	imine **10**				product **11**		
entry	R		chiral ligand	time / d		yield / %	e.e. / %
1	phenyl	**10a**	**5a**	2	**11a**	54	92
2	1-naphthyl	**10b**	**5a**	2	**11b**	27	74
3	2-naphthyl	**10c**	**5a**	2	**11c**	52	90
4	*p*-tolyl	**10d**	**5a**	2	**11d**	54	93
5	phenyl	**10a**	**5b**	2	**11a**	46	92
6	1-naphthyl	**10b**	**5b**	2	**11b**	11	71
7	2-naphthyl	**10c**	**5b**	3	**11c**	41	89
8	*p*-tolyl	**10d**	**5b**	2	**11d**	38	93
9	phenyl	**10a**	**7a**	2	**11a**	32	43
10	1-naphthyl	**10b**	**7a**	3	**11b**	10	11
11	2-naphthyl	**10c**	**7a**	3	**11c**	25	47
12	*p*-tolyl	**10d**	**7a**	4	**11d**	22	56

Molar ratio imine : Et_2Zn = 1 : 6

(1R,2S)-N-(4'-Bromobenzyl)ephedrine 2

A mixture of an acetonitrile solution (100 ml) of 4-bromobenzyl bromide (83.3 mmol, 20.8 g), (1*R*,2*S*)-ephedrine (100 mmol, 18.8 g), and potassium carbonate (200 mmol, 27.6 g) was refluxed for 3 h, and then 100 ml of 2 M aq. KOH was added. The acetonitrile layer was separated, the aqueous layer was extracted with dichloromethane (20 ml×3) and the combined organic layer was washed with sat. aq. NaCl. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification of the crude by recrystallization (hexane) gave **2** (53.2 mmol, 17.8g, 64% yield). Mp 55.5°C; $[\alpha]_D^{26}$ +9.9 (*c* 1.0, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ=1.03 (d, 3H, *J*=6.8 Hz), 2.20 (s, 3H), 2.94 (dq, 1H, J_d=5.2, J_q=6.8 Hz), 3.05–3.25 (bs, 1H), 3.56 (s, 2H), 4.86 (d, 1H, *J*=5.2 Hz), 7.08 (d, 2H, *J*=8.2 Hz), 7.28–7.43 (m, 7H, *J*=8.2 Hz); IR (KBr) 3300 (OH), 1068 (Ph–Br) cm^{-1}; HRMS (EI+) found m/z 332.0649, calcd for $C_{17}H_{19}BrNO$: (M−1), 332.0650.

(1R,2S)-N-(4'-Formylbenzyl)ephedrine 3

To a THF solution (3 ml) of (1*R*,2*S*)-**2** (1.5 mmol, 0.502 g), a 1.63 M hexane solution of *n*-butyllithium (3.3 mmol, 2.0 ml) was added dropwise at −100°C and the mixture was stirred for 20 min, then ethyl formate (3.3 mmol, 0.244 g, 0.27 ml) was added. The reaction mixture was stirred for 30 min at −100°C. The reaction was quenched by adding 4 M dry HCl in ethyl acetate (4 mmol, 1 ml) at −100°C. Then 20 ml of 1 M aq. NaOH was added and the reaction mixture was left to warm to room temperature. The mixture was filtered and the filtrate was extracted with dichloromethane (10 ml×4). The extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification of the crude on silica gel TLC (developing solvent ethyl acetate:hexane=1:4, then acetone:hexane=1:4) gave **3** (0.68 mmol, 0.194 g, 46% yield). Mp 80.0°C; $[\alpha]_D^{25}$ +10.9 (*c* 1.0, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ=1.08 (d, 3H, *J*=6.8 Hz), 2.23 (s, 3H), 2.94 (dq, 1H, *J*d=5.3, *J*q=6.8 Hz), 3.30–3.45 (bs, 1H), 3.68 (s, 2H), 4.85 (d, 1H, *J*=5.3 Hz), 7.28–7.35 (m, 7H, *J*=7.9 Hz), 7.79 (d, 2H, *J*=7.9 Hz), 9.97 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ=10.1, 39.1, 59.1, 64.2, 74.7, 126.7, 127.6, 128.5, 129.4, 130.2, 135.8, 143.2, 147.5, 192.5; IR (neat) 3437 (OH), 3140 (Ph), 1701 (C=O) cm^{-1}; HRMS (EI+) found m/z 282.1484, calcd for $C_{18}H_{21}NO_2$: (M−1), 282.1494.

N,N′-*Bis{4-[N″-(1′S,2′R)-2′-hydroxy-1′-methyl-2′-phenylethyl-N″-methyl]aminomethyl-benzylidene}ethylenediamine* **5a**

A mixture of a toluene solution (10 ml) of ethylenediamine (0.47 mmol, 0.028 g, 0.03 ml) and (1*R*,2*S*)-**3** (0.95 mmol, 0.270 g) was refluxed for 8 h with a Dean–Stark trap. The remaining solution was evaporated under reduced pressure. The residue was washed three times with a hot solution of ethyl acetate and hexane (1:10, v/v) and the solvent was dried *in vacuo*. The product **5a** (0.43 mmol, 0.253 g, 91% yield) was obtained. $[\alpha]_D^{23}$ +16.4 (*c* 1.5, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ=1.00 (d, 3H×2, *J*=6.8 Hz), 2.18 (s, 3H×2), 2.91 (dq, 1H×2, J_q=5.0, J_d=6.8 Hz), 3.61 (bs, 4H+1H×2), 3.96 (s, 2H×2), 4.85 (d, 1H×2, *J*=5.0 Hz), 7.24–7.34 (m, 7H×2), 7.62 (d, 2H×2, *J*=8.1 Hz), 8.27 (s, 1H×2); ^{13}C-NMR ($CDCl_3$) δ=10.3, 39.1, 59.3, 62.1, 63.9, 74.2, 126.6, 127.5, 128.5, 128.5, 129.2, 135.4, 142.9, 162.; IR (neat) 3417 (OH), 1647 (C=N) cm^{-1}; HRMS (EI+) found m/z 591.3705, calcd for $C_{38}H_{46}O_2N_4$: (M+1), 591.3699.

N,N′-*Bis{4-[N″-(1′S,2′R)-2′-hydroxy-1′-methyl-2′-phenylethyl-N″-methyl]aminomethyl-benzyl}ethylenediamine* **5b**

To a solution of **5a** (0.45 mmol, 0.263 g) in dichloromethane (5 ml) and methanol (2 ml) was added sodium borohydride (4.5 mmol, 0.171 g), and the mixture was stirred for 2 h. The remaining solution was evaporated under reduced pressure. The mixture was filtered through Celite and washed with dichloromethane. The filtrate was evaporated under reduced pressure, then dried *in vacuo*. The product **5b** (0.44 mmol, 0.261 g, 98% yield) was obtained. $[\alpha]_D^{28}$ +10.5 (*c* 1.1, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ=0.97 (d, 3H×2, *J*=6.8 Hz), 1.65 (br, 1H×2), 2.17 (s, 3H×2), 2.76 (s, 4H), 2.92 (dq, 1H×2, J_q=4.8, J_d=6.8 Hz), 3.58 (br, (2H+1H)×2), 3.75 (s, 2H×2), 4.87 (d, 1H×2, *J*=4.8 Hz), 7.17–7.33 (m, 9H×2); ^{13}C-NMR ($CDCl_3$) δ=10.4, 39.1, 49.2, 54.0, 59.3, 63.8, 74.0, 126.6, 127.4, 128.4, 128.5, 129.1, 138.5, 139.6, 142.9; IR (neat) 1041, 2792 (NH), 3317 (OH) cm^{-1}; HRMS (EI+) found m/z 595.4026, calcd for $C_{38}H_{50}O_2N_4$: (M+1), 595.4012.

N,N,N′,N′-*Tetrakis{3-N″-{2′-N‴-{4″-[N⁗-(1‴S,2‴R)-2‴-hydroxy-1‴-methyl-2‴-phenylethyl-N⁗-methyl]aminomethylbenzylidene}aminoethyl}amino-3-oxopropyl}ethylenediamine* **7a**

A mixture of a toluene solution (8 ml) of dendrimer (Generation 0) **6** (0.236 mmol, 0.121 g) and (1*R*,2*S*)-**3** (0.945 mmol, 0.268 g) was refluxed for 8 h with a Dean–Stark trap. The remaining solution was evaporated under reduced pressure. The residue was washed three times with hot ethyl acetate and the solvent was dried *in vacuo*. Chiral dendrimer **7a** (0.168 mmol, 0.266 g, 71% yield) was obtained. $[\alpha]_D^{23}$ +10.1 (*c* 1.0, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ=1.01 (d, 3H×4, *J*=6.7 Hz), 1.87 (br, 1H×4), 2.18–2.70 (m, 32H), 2.91 (dq, 1H×4, J_q=4.9, J_d=6.7 Hz), 3.40–3.80 (m, 28H), 4.86 (d, 1H×4, *J*=4.9 Hz), 7.22–7.63 (m, 9H×4), 8.24 (s, 1H×4); ^{13}C-NMR ($CDCl_3$) δ=10.1, 34.4, 39.2, 40.6, 50.9, 51.9, 59.2, 60.8, 63.9, 74.4, 126.3, 126.6, 127.5, 128.4, 128.6, 129.3, 135.1, 143.0, 143.4, 163.1, 173.1; IR (neat) 1651, (C=N), 3443 (OH) cm^{-1}; HRMS (FAB+) found m/z 1577.9838, calcd for $C_{94}H_{124}N_{14}O_8$: (M+1), 1577.9805.

N,N,N′,N′-*Tetrakis{3-N″-{2′-N‴-{4″-[N⁗-(1‴S,2‴R)-2‴-hydroxy-1‴-methyl-2‴-phenylethyl-N⁗-methyl]aminomethylbenzyl}aminoethyl}amino-3-oxopropyl}ethylenediamine* **7b**

Chiral dendrimer **7b** was synthesized from chiral dendrimer **7a** (0.05 mmol, 0.079 g) according to the same procedure as described in the synthesis of **5b**. Yield of the product **7b** (0.049 mmol, 0.078 g) was 98%. $[\alpha]_D^{21}$ +4.3 (*c* 1.0, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ=0.99 (d, 3H×4, *J*=6.5 Hz), 2.10–2.95 (m, 52H), 3.09–3.40 (m, (1H+1H)×4, *J*=6.5 Hz), 3.56–4.14 (m, 16H), 4.85 (br, 1H×4), 7.19–7.31 (m, (9H+1H)×4); ^{13}C-NMR ($CDCl_3$) δ=9.7, 34.1, 38.6, 39.1, 48.3, 50.5, 53.3, 58.7, 63.1, 73.7, 125.8, 126.2, 126.9, 127.9, 128.1, 128.8, 138.4, 138.6, 142.6, 173.0; IR (neat) 1034, 2784 (NH), 3417 (OH) cm^{-1}; HRMS (FAB+) found m/z 1586.0359, calcd for $C_{94}H_{132}N_{14}O_8$: (M+1), 1586.0431.

N,N,N′,N′-Tetrakis{3-N″-{2′-N‴,N⁗-bis{3″-N⁗′-{2‴-N⁗′-{4⁗′-[N⁗′′-(1⁗′S,2⁗′R)-2⁗′-hydroxy-1⁗′-methyl-2⁗′-phenylethyl-N⁗′′-methyl]aminomethylbenzylidene}aminoethyl}-amino- 3″-oxopropyl}aminoethyl}-amino-3-oxopropyl}ethylenediamine ***9a***

Chiral dendrimer **9a** was synthesized from dendrimer (Generation 1) **8** (0.15 mmol, 0.214 g) and (1*R*,2*S*)-**3** according to the same procedure as described in the synthesis of **7a**. Yield of the product **9a** (0.12 mmol, 0.438 g) was 82%. $[\alpha]_D^{25}$ +11.1 (*c* 1.0, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ=1.01 (d, 3H×8, *J*=6.5 Hz), 2.17–2.80 (m, 84H), 2.89 (dq, 1H×8, J_q=3.8, J_d=6.5 Hz), 3.16 (br, 1H×8), 3.62–3.95 (m, 56H), 4.84 (d, 1H×8, *J*=3.8 Hz), 7.21–7.62 (m, 84H), 8.23 (s, 1H×8); ^{13}C-NMR ($CDCl_3$) δ=10.0, 34.4, 39.2, 40.7, 45.6, 50.7, 51.1, 52.8, 59.1, 60.8, 64.0, 74.5, 126.3, 126.7, 127.4, 128.4, 128.6, 129.3, 135.0, 143.3, 143.5, 163.3, 173.1 (two other signals are not separated); IR (neat) 1658 (C=N), 3432 (OH) cm^{-1}; HRMS (FAB+) found m/z 3551.2, 3552.3, 3553.0, calcd for $C_{206}H_{280}N_{34}O_{20}$: (M+1), 3551.2, (M+2), 3552.2, (M+3), 3553.2.

N,N,N′,N′-Tetrakis{3-N″-{2′-N‴,N⁗-bis{3″-N⁗′-{2‴-N⁗′-{4⁗′-[N⁗′′-(1⁗′S,2⁗′R)-2⁗′-hydroxy-1⁗′-methyl-2⁗′-phenylethyl-N⁗′′-methyl]aminomethylbenzyl}aminoethyl}-amino-3″-oxopropyl}aminoethyl}amino-3-oxopropyl}ethylenediamine ***9b***

Chiral dendrimer **9b** was synthesized from chiral dendrimer **9a** (0.11 mmol, 0.388 g) according to the same procedure as described in the synthesis of **5b**. Yield of the product **9b** (0.11 mmol, 0.394 g) was quantitative. $[\alpha]_D^{23}$ +6.9 (*c* 1.1, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ=0.99 (d, 3H×8, *J*=6.6 Hz), 2.17 (s, 3H×8), 2.27 (br, 24H), 2.47 (br, 1H×8), 2.69 (br, 36H), 2.90 (dq, 1H×8, J_q=4.1, J_d=6.6 Hz), 3.12–3.78 (m, 80H), 4.84 (d, 1H×8, *J*=4.1 Hz), 7.19–7.36 (m, 84H); ^{13}C-NMR ($CDCl_3$) δ=10.0, 34.6, 39.1, 39.4, 48.6, 50.6, 51.1, 53.6, 59.2, 63.6, 74.2, 126.6, 127.3, 128.4, 128.6, 129.2,138.9, 143.2, 173.2 (six other signals are not separated); IR (neat) 1034, 2823 (NH), 3432 (OH) cm^{-1}; HRMS (FAB+) found m/z 3567.2, 3568.4, 3569.0, calcd for $C_{206}H_{296}N_{34}O_{20}$: (M+1), 3567.3, (M+2) 3568.3, (M+3), 3569.3.

Typical procedure for the enantioselective ethylation of N*-diphenylphosphinylimine* ***10a*** *by using chiral ligand* ***5a***

A toluene solution (1 M) of diethylzinc (0.6 mmol, 0.6 ml) was added dropwise to a mixture of toluene solution (1 ml) of **5a** (0.05 mmol, 0.030 g) and imine **10a** (0.1 mmol, 0.031 g). The reaction mixture was stirred for 2 days at room temperature, and then quenched by addition of sat. aq. $NaHCO_3$. The mixture was filtered and the filtrate was extracted with dichloromethane (10 ml×3). The extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification of the residue on silica gel TLC (developing solvent acetone:hexane=1:1) gave (*R*)-**11a** (0.060 mmol, 0.018 g, 54% yield). Enantiomeric enrichment was determined to be 92% e.e. by HPLC analysis using a chiral column [Daicel Chiralcel OD: 4×250 mm, 254 nm UV detector, room temperature, eluent: 3% 2-propanol in hexane, flow rate: 1.0 ml/min, retention time (min): 13.1 for the major-(*R*)-**11a**, 24.5 for the minor-(*S*)-**11a**; 25.1 for the major-**11b**, 34.5 for the minor-**11b**; 25.1 for the major-**11c**, 36.6 for the minor-**11c**, 18.1 for the major-**11d**, 23.3 for the minor-**11d**].

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