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Multiple Dendritic Catalysts for Asymmetric Transfer Hydrogenation

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The first and second generation multiple dendritic ligands based on chiral diamine were synthesized in a convergent approach and were well-characterized by NMR and MS techniques. Their ruthenium complexes prepared in situ had good solubility in the reaction medium (azeotrope of formic acid and triethylamine) and demonstrated high catalytic activity and enantioselectivity comparable to monomeric catalysts in the asymmetric transfer hydrogenation of ketones and imines. Quantitative yields and for some cases a slightly higher enantioselectivity (up to 98.7% ee) were obtained in the dendritic catalysis. Considering the high local catalyst concentrations at the periphery, diones were tested for the possible synergic reactivity between catalytic units at the surface, while no apparent differences were noted.

Introduction

Dendrimers are perfect monodisperse macromolecules with a regular and highly branched three-dimensional architecture. One of the important developments in this field of chemistry is the synthesis of catalytically active dendritic systems,[1] within which two general strategies are evolved: one (or more) catalytic site(s) in the core of dendrimer, the other, multiple catalytic sites at the periphery of the dendrimer. As an interface between homogeneous and heterogeneous catalysts, dendritic catalysts have received considerable attention;[2] however, the application of chiral organometallic dendrimers in asymmetric synthesis is a field still in its infancy.[3]

Recently we[4] reported the synthesis of chiral TsDPEN analogue enclosed dendritic ligands and the application of their Ru(II) complexes in the asymmetric transfer hydrogenation of acetophenone. High catalytic activity and enantioselectivity were observed, and the higher generation catalysts could be reused several times without apparent loss of activity. However, in contrast to such sterically crowded core-functionalized systems, the metal complexes deposited at the surface of a dendrimer would allow better accessibility to the substrate, thus higher turnover numbers could be expected. On the other hand, considering the relatively higher local catalyst concentration, the quest for potential cooperation among metal complexes is still ongoing.[5] Herein, we would like to report the synthesis and application of dendritic catalysts with up to 12 chiral diamine based ligands at the periphery.

Results and Discussion

Ligand Synthesis. In the construction of the dendritic ligands, both ether and amide linkages were used so that the relatively polar constitutions would favor the solution

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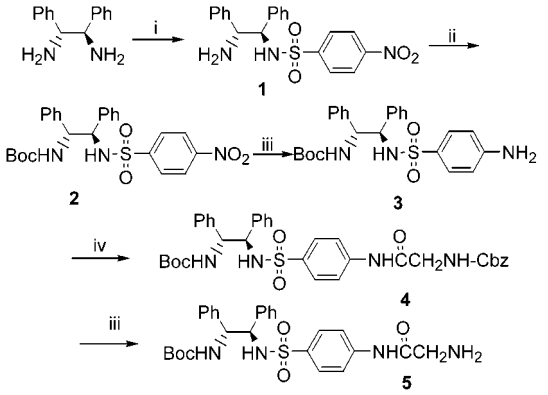
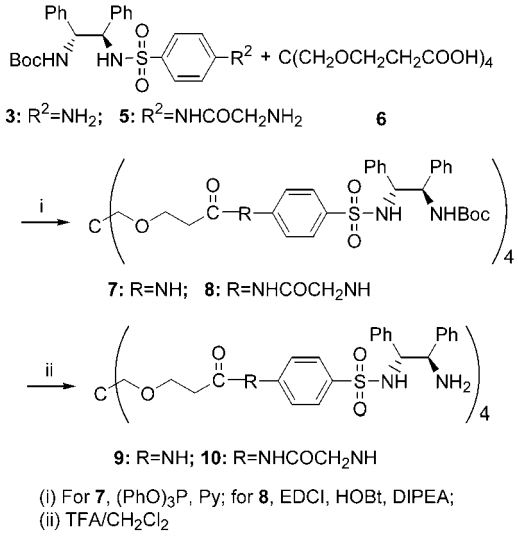
SCHEME 1. Synthesis of Functionalized Monomeric Ligands



(i) NosCl, NEt_3; (ii) $(Boc)_2O$, DIPEA; (iii) Pd/C, $HCOONH_4$; (iv) Cbz-Gly, IBCF, NMM

SCHEME 2. Preparation of G-1 Dendritic Ligands



(i) For **7**, $(PhO)_3P$, Py; for **8**, EDCI, HOBt, DIPEA; (ii) TFA/CH_2Cl_2

of the dendritic catalysts in the reaction medium (azeotrope of formic acid and triethylamine). Thus, amino-functionalized monomer (*R*,*R*)-**3** was initially prepared from (*R*,*R*)-DPEN (1,2-diphenylethylenediamine) in three steps in 81% overall yield. However, it was found that the sulfonated group dramatically decreased the reactivity of the aromatic amino group in **3**, and therefore the amido linkage with the carboxylic group could not be formed with EDCI-HOBt as the condensation reagent. For the convenience of synthesis of dendrimers, a glycine residue was previously introduced using more active IBCF/NMM (mixed anhydride) or $P(OPh)_3$ in pyridine[6] as the coupling reagents. After hydrogenolysis of the Cbz group under transfer hydrogenation conditions, the other aliphatic amino-functionalized monomer **5** was obtained in high yields (Scheme 1).

For the synthesis of the first generation dendrimers (Scheme 2), tetrakis(2-carboxyethoxymethyl) methane **6** with four carboxylic groups was selected as the core unit. After heating with 4.5 equiv of **3** and excess $P(OPh)_3$ in pyridine at 95 °C for 24 h, a white solid **7** was obtained, which was almost insoluble in any solvents (including DMF and DMSO). Fortunately, after deprotection with TFA, pure ligand **9** could be obtained in 40% yield in two steps through flash chromatography on silica gel eluting with DCM and methanol. On the other hand, the introduction of a glycine residue could greatly improve the solubility, and thus the coupling product **8** from **5** and **6** could be easily recrystallized from methanol. Subsequently, dendritic ligand **10** was received after deprotection of **8** with TFA in 84% overall yield.

In a similar convergent strategy, the second generation dendrimer bearing 12 chiral ligands was synthesized by coupling the poly(ether-amido) dendron previously developed by Newkome et al. (Scheme 3).[7] It was found that esterlysis of cyano groups in ethanol could be more conveniently conducted with H_2SO_4 rather than HCl gas. Thus, triacid **13** coupled with slightly excess **5** using EDCI-HOBt as coupling reagent afforded **14** in 81% yield, and after deprotection of the Cbz group, the air-dried crude solid **15** was directly condensed with tetraacid **6** under above conditions without further purification. The crude macromolecule **16** was insoluble in pure methanol, DCM, THF, or acetone at ambient temperature, but very soluble in DCM or acetone containing methanol. After flash chromatography on silica gel, the obtained solid was further recrystallized from methanol to give pure **16** in 34% yield. The dendritic ligand **17** could be obtained after deprotection of all Boc groups of **16** with TFA in DCM.

The high degree of symmetry in these dendrimers enabled facile confirmation of both structure and purity by NMR techniques. For example, in the ^1H NMR spectrum of dendritic ligand **9**, the core protons observed the resonance signals at 2.43 (t), 3.23 (s), and 3.49 (t) ppm were clearly distinguishable from the resonances arising from the wedges (DPEN ligands) at 4.10 (d) and 4.46 (t) ppm. Integration of the respective areas of the core protons and methine protons of DPEN ligands confirmed the complete coupling of the central core **6** and ligand **3**. A quite similar spectrum had been obtained from dendritic ligand **10**. For the second-generation dendrimers **17**, although some resonance signals were not well resolved, the complete cascade reactions could also be verified through comparison of integration areas of the core protons at 2.37 (br s), 3.18 (br s), and 3.49 (br s) ppm and methine protons of DPEN ligands at 4.06 (d) and 4.42 (d) ppm. Moreover, ^{13}C NMR spectra were also in good agreement with those of the signed structures.

Furthermore, the structures of these dendrimers were further verified by ESI HRMS or MALDI-TOF MS (Table 1). All of the spectra displayed a very prominent peak corresponding to the dendrimers complexed with protons or sodium cation except no signal was collected in dendrimer **16**. In case of **10**, a peak complexed with two protons (*m*/2*e*) was identified, while for dendritic ligand **17**, a peak complexed with six protons (*m*/6*e*) was observed.[8] Moreover, MALDI-TOF MS was also applied for confirming the structure of dendrimer **17**. Although no signal could be observed from **16**, an apparent peak of $[M + Na]^+$ was determined for dendritic ligand **17**, and

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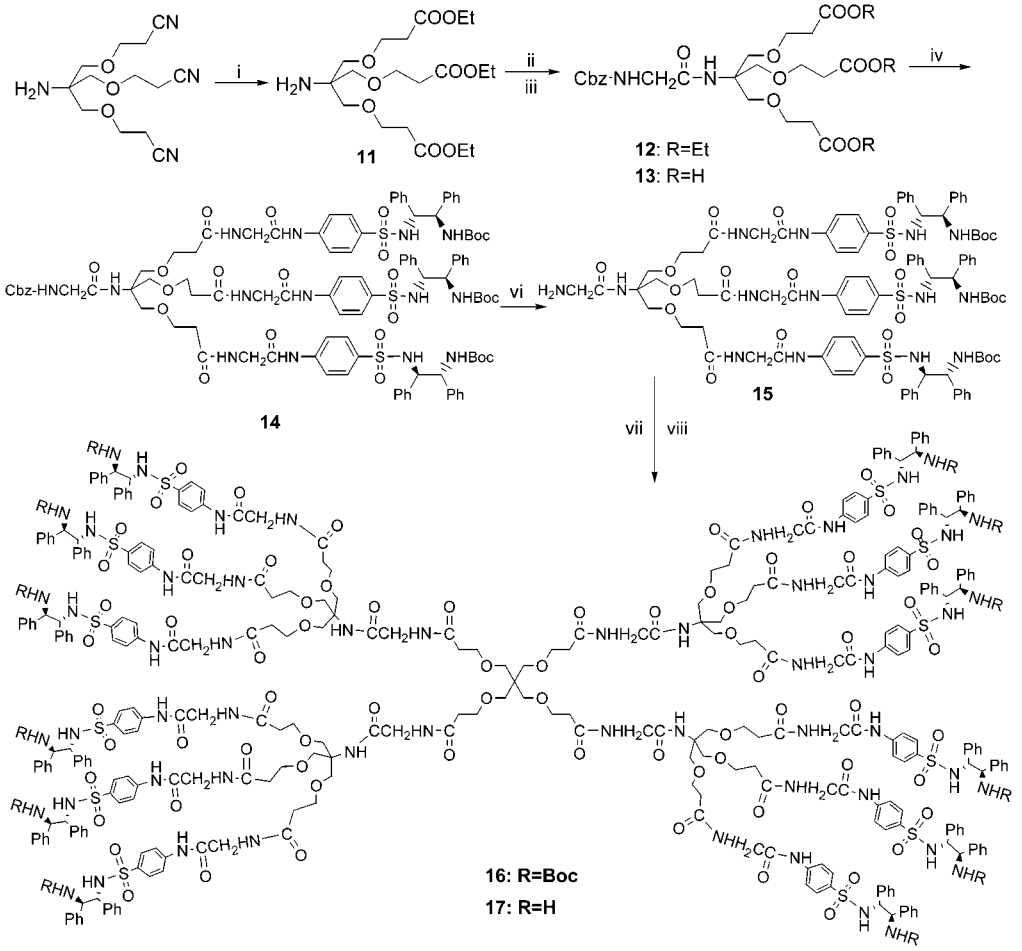
SCHEME 3. Preparation of the G-2 Dendritic Ligand



(i) C_2H_5OH, H_2SO_4; (ii) Cbz-Gly, IBCF, NMM; (iii) NaOH, CH_3OH/H_2O; (iv) **5**,EDCI/HOBt, DIPEA; (vi) $HCOONH_4$, Pd/C; (vii) **6**, EDCI/HOBt, DIPEA; (viii) TFA, DCM, then NH_3

TABLE 1. MS Data of Dendrimers

dendrimer	*M* (calcd)	*M* (ms)
Cbz-NH-triester(**12**)	612.3	613.5 (M + H)[a]
Cbz-NH-triacid (**13**)	528.2	529.4 (M + H)[a]
Cbz-NH-triNHBoc (**14**)	2045.7840	2069.9189 (M + Na)[b]
NH_2-triNHBoc (**15**)	1911.7433	1913.7955 (M + H)[b]
G-1-NH_2 (**9**)	1820.6576	1821.6863 (M + H)[b]
G-1-Gly-NHBoc (**8**)	2448.9532	2471.8755 (M + Na)[b]
G-1 -Gly-NH_2 (**10**)	2048.7435	1025.3853 (M + 2H) [b]
G-2-NHBoc (**16**)	8003.14	—[b–d]
G-2-NH_2 (**17**)	6802.5070	1135.4286 (M + 6H)[b] 6829 (M + Na)[c]

[a] API MS. [b] ESI HRMS. [c] MALDI-TOF MS. [d] No data was collected.

TABLE 2. Chiroptical[a] Data for Dendrimers

dendrimer	$[\alpha]^{23}_D$[b]	$[\phi]^{23}_D$[c]
Cbz-NH-triNHBoc (**14**)	+39.0	797.9
NH_2−triNHBoc (**15**)	+34.5	659.5
G-1-NH_2 (**9**)	+62.1	1130
G-1-Gly-NHBoc (**8**)	+14.4	352.6
G-1-Gly-NH_2 (**10**)	+37.6	770.3
G-2-NHBoc (**16**)	+18.8	1504
G-2-NH_2 (**17**)	+45.6	3102

[a] Rotations measured in THF for **14** and **15**, the others in CH_3OH/DCM (1:1). [b] Specific rotation in 10^{-1} deg cm^2 g^{-1}. [c] Molar rotation in 10^{-1} deg cm^2 mol^{-1}.

the observed molecular mass gave the molecular weight calculation at only 0.06% of the theoretical value.[9]

The chiroptical data for the dendrimers were summarized in Table 2. Interestingly, the molar rotation of amino-deprotected dendrimers was double that of the amino-protected derivatives (Table 2, **8** vs **10** and **16** vs **17**), and was increased from the first- to the second-generation dendrimers (Table 2, **10** vs **17**).

Asymmetric Transfer Hydrogenation. Ru(II) complexes of (*R*,*R*)-TsDPEN (**18**) and (*R*,*R*)-*N*-(4-acetylaminophenylsulfonyl)-1,2-diphenylethylenediamine (**19**) were selected as monomeric catalysts for comparison. Initial experiments were conducted to test the catalytic activity of ruthenium(II) complexes of the dendritic ligands, and in the transfer hydrogenation reaction, acetophenone was used as the model substrate and the azeotrope of formic acid and triethylamine as the hydrogen source.[10] The average turnover frequencies (TOFs, in relation to per mole of Ru(II) complex) and enantioselectivity compared to monomeric catalysts **18** and **19** were summarized in Table 3.

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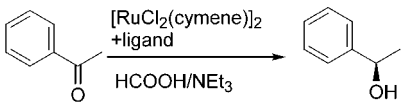
TABLE 3. Comparison of Dendritic and Monomeric Catalysts in Asymmetric Transfer Hydrogenation of Acetophenone[a]



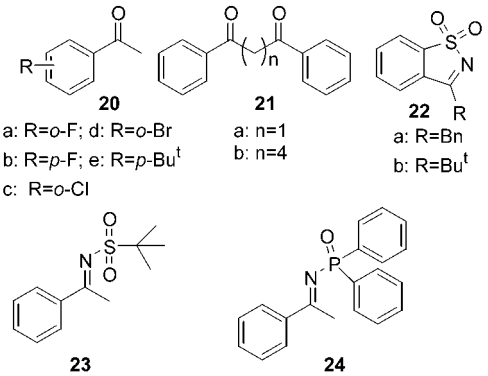
entry	ligand	conv (%)[b]	TOF (h^{-1})[c]	ee (%)[d]
1	**18**	>99	14.8	97.7
2	**19**	>99	13.2	97.1
3	**9**	99	13.8	97.6
4	**10**	99	12.6	96.4
5	**17**	97	10.6	97.1

[a] Reactions were conducted at 28 °C for 20 h, S/C = 100. [b] Conversions were determined by GC. [c] The average TOFs were calculated over the 5 h reaction time. [d] Determined by GC with a Chrompack CP Chirasil-dex column (25 m × 0.25 mm).

It was found that the macromolecular catalysts showed no significant difference in activity and enantioselectivity as compared with the monomeric catalysts **18** and **19**. Good retention of catalytic activity and high enantioselectivity were observed in these dendritic catalysis. However, the glycine spacer had mild negative effects on the catalytic activity (entries 3 vs 4).

For exploring the scope and limitations of this reaction catalyzed by the dendritic catalysts, a variety of ketones and imines were applied in the asymmetric transfer hydrogenation with HCOOH-NEt_3. In general, excellent conversion and enantioselectivity were achieved (Table 4). Halogen-substituted acetophenones **20a**−**d** tended to lower the enantioselectivity, especially at the para-site of the benzene ring with fluorine (entry 2), and an electronic donating group at the para-site of the benzene ring of acetophenone would decrease the reactivity (entries 7 and 8).[10] Considering the multimeric nature of the dendritic catalysts, diones **21a**,**b**[11] were tested for the possible synergy between catalytic units at the surface of the dendritic catalysts.[5] Although excellent enantioselectivity (entries 9−12) was obtained, no apparent difference was noted for the diastereoselectivity and the reaction proceeded slowly. Probably the space between the metal complexes was still too far for such possible cooperation. Interestingly, useful chiral sultam auxiliaries could be obtained quantitatively from imines **22a**,**b**[12] catalyzed by the dendritic catalysts with excellent enantiomeric purity (up to 98.7%), in which a promoted activity was also observed for **22a** as compared with the monomeric catalyst **18** (entries 13−16). Moreover, the dendritic catalyst **9** was more enantioselective than the monomeric catalyst **18** in the reduction of *N*-*tert*-butylsulfonylketimine[13] **23** with high yield, moderate enantioselectivity, and similar reaction rate (entries 20 vs 21). However, *N*-diphenylphosphinyl ketimine **24** was found to be inactive under the same conditions and decomposed during the reaction.[14]

TABLE 4. Asymmetric Transfer Hydrogenation of Ketones and Imines[a]



entry	sub	ligand	time (h)	conv (%)[b]	ee (%)[c]	conf[d]
1	**20a**	**9**	24	97	93.2	*R*
2	**20b**	**9**	24	>99	89.4	*R*
3	**20c**	**9**	24	>99	94.7	*R*
4	**20c**	**17**	24	>99	95.5	*R*
5	**20d**	**9**	24	>99	94.6	*R*
6	**20d**	**10**	24	99	94.2	*R*
7	**20e**	**9**	45	>99	97.2	*R*
8	**20e**	**17**	55	98	96.3	*R*
9[e]	**21a**	**9**	72	71[f]	>99[g,h]	*R*,*R*
10[e]	**21a**	**17**	72	70[f]	>99[g,i]	*R*,*R*
11[e]	**21b**	**9**	72	69[f]	>99[j,k]	*R*,*R*
12[e]	**21b**	**17**	72	67[f]	>99[j,m]	*R*,*R*
13[n]	**22a**	**18**	3	99[f]	96.1[g]	*R*
14[n]	**22a**	**9**	2	99[f]	98.7[g]	*R*
15[n]	**22a**	**10**	2	99[f]	96.1[g]	*R*
16[n]	**22a**	**17**	2	99[f]	95.9[g]	*R*
17[n]	**22b**	**18**	5	98[f]	98.3[g]	*R*
18[n]	**22b**	**9**	5	98[f]	98.3[g]	*R*
19[n]	**22b**	**17**	6	97[f]	98.4[g]	*R*
20[n]	**23**	**18**	24	93	45.0[g]	*R*
21[n]	**23**	**9**	25	92	51.8[g]	*R*

[a] Reactions were conducted at 28 °C, S/C=100. [b] Based on GC analysis. [c] Determined by GC with a Chrompack CP Chirasil-dex column (25 m × 0.25 mm). [d] Determined by comparison of optical rotations with literature values. [e] Reaction was carried out in 2 M DMF solutions at 40 °C. [f] Isolated yield. [g] Determined by HPLC with a Daicel Chiralcel OD column. [h] 98.1% de. [i] 94.7% de. [j] Determined by HPLC with a Daicel Chiralcel OB and ChiralPak AD column. [k] 84.2% de. [m] 82.6% de. [n] Reaction was carried out in 0.5 M DCM solutions at 28 °C.

In conclusion, multiple dendritic ligands based on (*R*,*R*)-1,2-diphenylethylenediamine were synthesized and well characterized. Their ruthenium(II) complexes demonstrated high catalytic activity and enantioselectivity in the asymmetric transfer hydrogenation of ketones and imines. Further work is being conducted to immobilize these highly active dendritic catalysts on polymers to facilitate the recycling,[15] and to investigate their applications in other asymmetric catalysis.

Experimental Section

General Methods. Melting points were determined in open capillaries and were uncorrected. NMR spectra were recorded with tetramethylsilane as the internal standard. Chiral 1,2-

(11) The results catalyzed by (*S*,*S*)-TsDPEN-RuCl(cymene) in HCOOH/NEt_3 for 40 h: **21a**: 96%, >99% ee, 97.8%de; **21b**: 98%, >99% ee, 84.2% de. See: Chen, Y.-C.; Deng, J.-G.; Wu, T.-F.; Cui, X.; Jiang, Y.-Z.; Choi, M. C. K.; Chan, A. C. S. *Chin. J. Chem*. **2001**, *19*, 807.

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(14) Spindler, F.; Blaser, H.-U. *Adv. Synth. Catal*. **2001**, *343*, 68.

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diphenylethylenediamine was prepared in our laboratory, $[\alpha]_D^{20}$ +106.7 (*c* 1.0, CH_3OH, *R,R*-isomer). All other reagents were used without purification as commercially available.

(*R,R*)-*N*-(4-Nitrophenylsulfonyl)-1,2-diphenylethylenediamine (1). To a solution of (*R,R*)-DPEN (3.5 g, 16.5 mmol) and NEt_3 (3 mL, 21 mmol) in DCM (50 mL) cooled in an ice-bath was added dropwise 4-nitrophenylsulfonyl chloride (3.7 g, 16.7 mmol) in DCM (15 mL). After the ice-bath was removed, the mixture was stirred at ambient temperature overnight and concentrated in vacuo. The residue was triturated with water, and the resulting solid was filtered and dried in air. Subsequently, the crude solid was refluxed in ethyl acetate (30 mL) for 2 h, cooled, and filtered to give monosulfonylated diamine **1** (5.5 g, 84%): mp 211−212 °C; $[\alpha]_D^{23}$ +21.8 (*c* 0.48, THF); ^{1}H NMR (DMSO, 300 MHz) δ 3.98 (d, J = 6.9 Hz, 1H), 4.38 (d, J = 6.9 Hz, 1H), 6.96−7.12 (m, 10H), 7.61 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 60.6, 65.3, 124.1, 127.0, 127.7, 127.9, 128.0, 128.1, 139.6, 142.4, 147.1, 149.1; IR (KBr) 3429, 3348, 3254, 1526, 1352, 1157 cm^{-1}; API-ES MS (*m/z*) 420.2 $[M + Na]^+$ (5), 398.2 $[M + H]^+$ (100).

(*R,R*)-*N*-Boc-*N*′-(4-Nitrophenylsulfonyl)-1,2-diphenylethylenediamine (2). A solution of (*R,R*)-**1** (5.3 g, 13.4 mmol), $(Boc)_2O$ (3.4 g, 15.6 mmol), and DIPEA (3.0 mL, 17.0 mmol) in DCM (40 mL) was stirred at ambient temperature for 24 h and then washed successfully with 0.5 M citric acid, water, saturated sodium bicarbonate, and brine and dried over Na_2SO_4. After concentration, the residue was triturated with petroleum ether and filtered to afford **2** as a light yellow powder (6.56 g, 99%): mp 213 °C dec; $[\alpha]_D^{23}$ +54.3 (*c* 0.52, THF); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52 (s, 9H), 4.74−4.84 (m, 2H), 5.25 (d, J = 5.1 Hz, 1H), 6.76−7.21 (m, 10H), 7.60 (d, J = 6.9 Hz, 2H), 8.49 (d, J = 6.9 Hz, 2H); ^{13}C NMR (DMSO, 75 MHz) δ 28.2, 60.1, 65.0, 81.2, 123.4, 127.2, 127.4, 127.6, 127.8, 128.2, 128.7, 137.0, 146.8, 149.2, 157.5; IR (KBr) 3481, 3388, 3319, 1689, 1527, 1351, 1165 cm^{-1}; API-ES MS (*m/z*) 496 $[M - H]^-$ (100). Anal. Calcd for $C_{25}H_{27}N_3O_6S$: C, 60.35; H, 5.47; N, 8.45; S, 6.44. Found: C, 59.83; H, 5.47; N, 8.30; S, 6.27.

(*R,R*)-*N*-Boc-*N*′-(4-Aminophenylsulfonyl)-1,2-diphenylethylenediamine (3). To a suspension of Pd/C (10%, 500 mg) in methanol were added (*R,R*)-**2** (6.3 g, 12.6 mmol) and ammonium formate (4 g, 64 mmol). The mixture was stirred at room temperature under argon for 1 h, filtered through Celite, and washed with methanol. After concentration, water (40 mL) was added and the resulting solid was filtered, washed with water, and dried in air to afford **3** as a white powder (5.86 g, 99%): mp 199.5 °C dec; $[\alpha]_D^{23}$ +32.9 (*c* 0.33, THF); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 4.50 (t, J = 8.4 Hz, 1H), 4.79 (t, J = 9.0 Hz, 1H), 5.30 (d, J = 7.8 Hz, 1H), 5.89 (s, 1H), 6.44 (d, J = 8.7 Hz, 2H), 6.79−7.17 (m, 10H), 7.34 (d, J = 8.7 Hz, 2H); ^{13}C NMR (DMSO, 75 MHz) δ 28.5, 59.6, 62.2, 78.4, 93.8, 126.8, 126.9, 127.0, 127.5, 127.8, 128.1, 128.3, 140.2, 141.0, 152.2, 155.3; IR (KBr) 3463, 3381, 1690, 1521, 1156 cm^{-1}; API-ES MS (*m/z*) 506.2 $[M + K]^+$ (5), 490.3 $[M + Na]^+$ (60), 368.3 $[M - 99\ (Boc)]^+$ (100). Anal. Calcd for $C_{25}H_{29}N_3O_4S$: C, 64.22; H, 6.25; N, 8.99; S, 6.86. Found: C, 63.77; H, 6.14; N, 8.77; S, 6.86.

(*R,R*)-(4). To a stirred solution of (*R,R*)-**3** (3.83 g, 8.2 mmol), *N*-Cbz-glycine (2.6 g, 12.4 mmol), and NMM (1.6 mL, 14 mmol) in dry THF cooled in an ice−salt bath was added slowly IBCF (1.6 mL, 11.8 mmol). After 5 min, the ice bath was removed and the mixture was stirred at ambient temperature for 24 h. After THF was removed in vacuo, water was added to the residue and then the aqueous phase was extracted with EtOAc (50 mL). The organic phase was washed successfully with 0.5 M citric acid, water, saturated sodium bicarbonate, and brine and dried over Na_2SO_4. After concentration, the solid was recrystallized from acetone and hexane to give a white powder (5.12 g, 95%): mp 204 °C dec; $[\alpha]_D^{23}$ +34.6 (*c* 0.37, THF); ^{1}H NMR (DMSO, 300 MHz) δ 1.26 (s, 9H), 3.81 (d, J = 3.0 Hz, 2H), 4.64 (d, J = 4.8 Hz, 1H), 4.78 (t, J = 4.5 Hz, 1H), 5.05 (s, 2H), 6.84−7.57 (m, 19H), 10.17 (s, 1H); ^{13}C NMR (DMSO, 75 MHz) δ 28.5, 44.5, 59.5, 62.5, 65.9, 78.4, 118.5, 127.0, 127.1, 127.5, 127.9, 128.1, 128.2, 128.7, 135.7, 137.3, 139.8, 140.8, 142.0, 155.3, 157.0, 168.8; IR (KBr) 3366, 3301, 1690, 1521, 1156 cm^{-1}; API-ES MS (*m/z*) 659.3 $[M + H]^+$ (7), 559.2 $[M - 99\ (Boc)]^+$ (3). Anal. Calcd for $C_{35}H_{38}N_4O_7S$: C, 63.81; H, 5.81; N, 8.50; S, 4.87. Found: C, 63.65; H, 5.98; N, 8.50; S, 4.71.

(*R,R*)-(5). The hydrogenolysis of (*R,R*)-**4** was performed with the same procedure as **2** to afford **5** as a white powder (3.5 g, 91%): mp 216 °C dec; $[\alpha]_D^{23}$ +45.0 (*c* 0.30, THF); ^{1}H NMR (DMSO, 300 MHz) δ 1.26 (s, 9H), 3.49 (s, 2H), 4.64 (d, J = 6.3 Hz, 1H), 4.80 (d, J = 5.4 Hz, 1H), 7.01−7.23 (m, 10H), 7.33 (d, J = 9.6 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 8.32 (s, 1H); ^{13}C NMR (DMSO, 75 MHz) δ 28.5, 43.1, 59.5, 62.5, 78.4, 118.6, 126.9, 127.1, 127.4, 127.5, 127.9, 128.1, 135.9, 139.8, 140.8, 141.7, 155.3, 166.2; IR (KBr) 3389, 3296, 3194, 3112, 3031, 1689, 1595, 1156 cm^{-1}; API-ES MS (*m/z*) 547.3 $[M + Na]^+$ (6), 425.3 $[M - 99\ (Boc)]^+$ (100).

(*R,R*)-G-1-NH$_2$ (9). Tetrakis(carboxyethoxymethyl)methane **6** (50 mg, 0.12 mmol), (*R,R*)-**3** (230 mg, 0.49 mmol), and $(PhO)_3P$ (0.16 mL, 0.62 mmol) were dissolved in pyridine (5 mL). The solution was heated at 95 °C for 24 h, cooled, and then poured into ice water (30 mL). The resulting solid was filtered, washed successively with 0.5 M citric acid, water, saturated sodium hydrogen carbonate and water, and dried in air to afford crude **7**, which was almost insoluble in any solvent (CH_3OH, DCM, THF, DMSO, and DMF). Thus, to a suspension of the crude **7** in DCM was added TFA (2 mL) in an ice bath. The mixture was stirred and the solid was dissolved rapidly. After 1 h, the solvent was removed in vacuo and water (10 mL) was added. The mixture was neutralized with ammonia and stirred at room temperature for 2 h. The resulting solid was collected by filtration, washed with water, and then dissolved in CH_3OH−DCM (20 mL, v/v, 1:2). The solution was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel with MeOH−DCM (1:15, 1:10, 1:4) to give ligand **9** as a white solid (86 mg, 40% yield in two steps): $[\alpha]_D^{23}$ +62.1 [*c* 0.13, CH_3OH/DCM (v/v, 1:1)]; ^{1}H NMR (CD_3OD, 400 MHz) δ 2.43 (t, J = 5.6 Hz, 8H), 3.23 (s, 8H), 3.49 (t, J = 5.6 Hz, 8H), 4.10 (d, J = 9.2 Hz, 4H), 4.46 (t, J = 9.2 Hz, 4H), 6.76−6.78 (m, 8H), 6.84−6.90 (m, 12H), 7.07−7.13 (m, 20H), 7.38−7.43 (m, 16H); ^{13}C NMR (CD_3OD, 50 MHz) δ 38.7, 46.7, 61.9, 65.7, 68.4, 70.5, 120.1, 128.3, 128.6, 128.8, 128.9,129.0, 129.4, 136.6, 139.1, 140.4, 143.4, 172.7; IR (KBr) 3430, 3369, 3192, 3063, 1677, 1592, 1534, 1317, 1155, 1093 cm^{-1}; ESI HRMS calcd for $C_{97}H_{104}N_{12}O_{16}S_4$ + H 1821.6654, obsd 1821.6863.

(*R,R*)-G-1-Gly-NHBoc (8). To a stirred solution of tetraacid **6** (42 mg, 0.099 mmol), (*R,R*)-**5** (230 mg, 0.44 mmol), EDCI (100 mg, 0.52 mmol), and HOBt (85 mg, 0.55 mmol) in DCM and DMF (10 mL/3 mL) cooled in an ice bath was added NEt_3 (70 μL, 0.76 mmol). After the ice bath was removed, the mixture was stirred at ambient temperature overnight. DCM was removed under reduced pressure and water (30 mL) was added to the residue. The resulting solid was filtered, washed successively with 0.5 M citric acid, water, saturated sodium hydrogen carbonate, and water, and dried in air. The crude product was recrystallized from methanol twice to give **8** as a white powder (190 mg). An additional crop of **8** (36 mg) was obtained from the mother liquid by further purification on Sephadex LH-20 with methanol as elutent (total 226 mg, 93% yield): mp 182 °C dec; $[\alpha]_D^{23}$ +14.4 [*c* 0.12, CH_3OH/DCM (v/v, 1:1)]; ^{1}H NMR (CD_3COCD_3, 400 MHz) δ 1.35 (s, 36H), 2.51 (t, J = 6.0 Hz, 8H), 3.38 (s, 8H), 3.64 (t, J = 6.0 Hz, 8H), 4.10 (s, 8H), 4.71 (d, J = 8.4 Hz, 4H), 4.95 (t, J = 8.4 Hz, 4H), 7.02−7.17 (m, 40H), 7.42 (d, J = 8.0 Hz, 8H), 7.53 (d, J = 8.8 Hz, 8H); ^{13}C NMR (CD_3COCD_3 + DMSO, 75 MHz) δ 33.2, 41.4, 48.4, 50.6, 64.7, 67.8, 72.6, 74.5, 83.4, 123.6, 132.0, 132.1, 132.4, 132.6, 132.9, 133.2, 141.0, 145.0, 145.8, 147.1, 160.5, 173.6, 176.7; IR (KBr) 3374, 3116, 3064, 1690, 1533, 1156 cm^{-1}; ESI HRMS calcd for $C_{125}H_{148}N_{16}O_{28}S_4$ + Na 2471.9430, obsd 2471.8755.

(*R*,*R*)-G-1-Gly-NH_2 (10). Compound **8** was deprotected by the same procedure as **7**. After neutralization with ammonia, **10** was obtained as a white powder (125 mg, 92% yield): $[\alpha]_D^{23}$ +37.6 [*c* 0.16, CH_3OH/DCM (v/v, 1:1)]; ^1H NMR (CD_3OD + $CDCl_3$, 400 MHz) δ 2.47 (t, J = 5.6 Hz, 8H), 3.34 (s, 8H), 3.61 (t, J = 5.6 Hz, 8H), 3.99 (s, 8H), 4.04 (d, J = 8.8 Hz, 4H), 4.42 (t, J = 8.8 Hz, 4H), 6.76−6.78 (m, 8H), 6.85−6.91 (m, 12H), 7.07−7.11 (m, 20H), 7.39−7.41 (m, 16H); ^{13}C NMR (CD_3OD + $CDCl_3$, 50 MHz) δ 37.2, 44.1, 46.3, 61.7, 65.8, 68.2, 70.4, 119.9, 128.0, 128.2, 128.3, 128.4, 128.8, 129.1, 136.3, 139.2, 140.9, 142.8, 169.4, 174.3; IR (KBr) 3367, 3194, 3111, 3063, 1650, 1536, 1154 cm^{-1}; ESI HRMS calcd for $C_{105}H_{116}N_{16}O_{20}S_4$ + 2H (*m*/*2e*) 1025.3978, obsd 1025.3853.

CbzNH-triester (12) was prepared by coupling amino triester **11** and *N*-Cbz-glycine with MA (mixed anhydride) with the same procedure for the preparation of **4**. Purification by flash chromatography on silica gel afforded **12** as an oil (680 mg, 84%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.2 Hz, 9H), 2.53 (t, J = 6.3 Hz, 6H), 3.50−3.71 (m, 12H), 3.87 (d, J = 5.1 Hz, 2H), 4.15 (q, J = 8.7 Hz, 6H), 5.14 (s, 2H), 5.59 (s, 1H), 6.38 (s, 1H), 7.34−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 34.8, 45.1, 59.8, 60.4, 66.7, 69.0, 127.9, 128.0, 128.4, 136.4, 156.5, 169.8, 171.6; IR (KBr) 3358, 3034, 1726, 1523, 1374, 1245, 1188, 1112 cm^{-1}; API MS (*m*/*z*) 613.5 $[M + H]^+$.

CbzNH-triacid (13). To a solution of triester **12** (500 mg, 0.82 mmol) in CH_3OH-H_2O (10 mL/10 mL) was added a solution of NaOH (0.13 g, 3.2 mmol) in water (3 mL). The mixture was stirred overnight, and then methanol was removed. The aqueous solution was acidified with 1 M HCl, extracted with EtOAc (2 × 20 mL), washed with brine, and dried over Na_2SO_4. After concentration, recrystallization from EtOAc/hexane afforded **13** as a white needle (360 mg, 85%): mp 103−105 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.56 (br s, 6H), 3.46 (br s, COOH), 3.72−3.83 (m, 14H), 5.16 (s, 2H), 7.36−7.38 (m, 5H); IR (KBr) 3339, 3299, 3034, 1713, 1637, 1546, 1210, 1120, 1088 cm^{-1}; API MS (*m*/*z*) 529.4 $[M + H]^+$.

(*R*,*R*)-CbzNH-triNHBoc (14) was prepared by a similar procedure as given above with **8**. Purification by flash chromatography with acetone−DCM (v/v, 1.5:1, 4:1 and 10:1) afforded **14** as a white powder (520 mg, 81%): $[\alpha]_D^{23}$ +39.0 (*c* 0.31, THF); ^1H NMR (CD_3COCD_3, 400 MHz) δ 1.34 (s, 27H), 2.47 (t, J = 5.6 Hz, 6H), 3.67 (t, J = 5.2 Hz, 6H), 3.71 (s, 6H), 3.83 (d, J = 6.0 Hz, 2H), 4.08 (d, J = 6.0 Hz, 6H), 4.69 (d, J = 8.4 Hz, 3H), 4.92 (t, J = 8.4 Hz, 3H), 5.08 (s, 2H), 7.00−7.77 (m, 30H), 7.41 (d, J = 8.4 Hz, 6H), 7.52 (d, J = 8.8 Hz, 6H), 9.55 (s, 3H); ^{13}C NMR (CD_3COCD_3 + DMSO, 75 MHz) δ 28.7, 33.7, 45.3, 46.3, 61.6, 62.1, 64.7, 68.1, 69.6, 71.1, 80.3, 111.7, 120.6, 121.4, 126.5, 128.9, 129.0, 129.3, 129.5, 129.6, 129.8, 130.1, 130.4, 130.6, 138.0, 139.5, 142.0, 142.8, 144.1, 157.4, 159.0, 170.5, 171.5, 173.6; IR (KBr) 3370, 3342, 3064, 1690, 1532, 1157, 1094 cm^{-1}; ESI HRMS calcd for $C_{104}H_{121}N_{14}O_{24}S_3$ + Na 2068.7738, obsd 2069.9189.

(*R*,*R*)-NH_2-triNHBoc (15). Hydrogenolysis of **14** was performed with a similar procedure as given above with **4** to afford **15** (240 mg, 85%): $[\alpha]_D^{23}$ +34.5 (*c* 0.20, THF); ^1H NMR (CD_3OD, 400 MHz) δ 1.39 (s, 27H), 2.49 (t, J = 5.6 Hz, 6H), 3.20 (s, 2H), 3.67 (t, J = 5.6 Hz, 6H), 3.73 (s, 6H), 4.00 (s, 6H), 4.57 (d, J = 8.8 Hz, 3H), 6.88−7.09 (m, 30), 7.36−7.42 (m, 12H) (the other three NCH groups are overlapped by the H_2O of CD_3OD); IR (KBr) 3406, 3372, 3063, 1689, 1532, 1157, 1093 cm^{-1}; ESI HRMS calcd for $C_{96}H_{115}N_{14}O_{22}S_3$ + H 1912.7511, obsd 1913.7955.

(*R*,*R*)-G-2-NHBoc (16). Compound **15** was coupled with tetraacid **6** according to a similar procedure as given above with **8** to afford a crude product, which was insoluble in pure CH_3OH, DCM, THF, or acetone at ambient temperature, but very soluble in DCM or acetone containing CH_3OH. Flash chromatography with CH_3OH−DCM (v/v, from 1:25 to 1:20) and recrystallization with methanol afforded **16** as a white powder (160 mg, 34% yield): mp 186 °C dec; $[\alpha]_D^{23}$ +18.8 [*c* 0.14, CH_3OH/DCM (v/v, 1:1)]; ^1H NMR (CD_3COCD_3 + CD_3OD, 400 MHz) δ 1.34 (s, 108H), 2.51 (br s, 32H), 3.25 (s, 8H), 3.61−3.73 (m, 56H), 3.97 (s, 8H), 4.11 (br s, 24H), 4.70 (d, J = 7.6 Hz, 12H), 4.91−4.93 (m, 12H), 6.99 (br s, 8H), 7.05−7.15 (m, 120H), 7.40 (d, J = 8.4 Hz, 24H), 7.51 (d, J = 8.8 Hz, 24H); ^{13}C NMR (CD_3COCD_3 + CD_3OD, 50 MHz) δ 28.6, 37.0, 44.2, 47.9, 48.3, 48.8, 49.2, 49.6, 60.7, 61.1, 63.8, 68.2, 70.0, 79.7, 119.6, 127.9, 128.3, 128.4, 128.6, 128.8, 131.9, 139.8, 140.8, 142.7, 156.7, 169.2, 170.4, 173.4; IR (KBr) 3338, 1688, 1533, 1317, 1253, 1157, 1093 cm^{-1}. No data were collected in ESI HRMS and MALDI-TOF MS.

(*R*,*R*)-G-2-NH_2 (17). Compound **16** was deprotected by a similar procedure as given above with **7**. After neutralization with ammonia, the mixture was stirred at room temperature for 3 h. The resulting solid was filtered, washed with water, dissolved in CH_3OH−DCM (20 mL, v/v, 1/1), and then dried over Na_2SO_4. After concentration, the residue was triturated with pure DCM to afford **17** as a white powder (90 mg, 88%): $[\alpha]_D^{23}$ +45.6 [*c* 0.12, CH_3OH/DCM (v/v, 1:1)]; ^1H NMR (CD_3OD + $CDCl_3$, 400 MHz) δ 2.37 (br s, 8H), 2.46 (br s, 24H), 3.18 (br s, 8H), 3.49 (br s, 8H), 3.63−3.67 (m, 48H), 3.83 (s, 8H), 3.99 (s, 24H), 4.06 (d, J = 6.4 Hz, 12H), 4.42 (d, J = 8.8 Hz, 12H), 6.76−6.78 (m, 24H), 6.86−6.88 (m, 36H), 7.06−7.12 (m, 60H), 7.37 (br s, 48H); ^{13}C NMR (CD_3OD + $CDCl_3$, 50 MHz) δ 37.1, 44.0, 61.1, 61.5, 65.6, 68.1, 70.0, 119.8, 127.5, 128.1, 128.4, 128.7, 129.0, 129.4, 136.1, 139.0, 140.7, 142.6, 169.4, 170.7, 173.7, 174.0; IR (KBr) 3401, 3369, 3350, 3278, 3106, 3063, 1651, 1534, 1318, 1155, 1094 cm^{-1}; ESI HRMS calcd for $C_{341}H_{388}N_{56}O_{72}S_{12}$ + 6H (*m*/*6e*) 1134.7590, obsd 1135.4286; MALDI-TOF MS calcd for $C_{341}H_{388}N_{56}O_{72}S_{12}$ + Na 6825, obsd 6829.

Asymmetric Transfer Hydrogenation: General Procedure for Asymmetric Transfer Hydrogenation of Ketones and Imines. A solution of $[RuCl_2(cymene)]_2$ (1.3 mg, 0.002 mmol), dendritic ligand (0.0044 mmol of DPEN), and NEt_3 (1.3 μL, 0.008 mmol) in methanol was heated at 65 °C for 2 h. After methanol was removed in vacuo, ketone **20** (0.4 mmol) and an azeotrope of formic acid and triethylamine (0.2 mL) were added in turn. The mixture was stirred at 28 °C and monitored by TLC. After completion, the mixture was diluted with diethyl ether (3 mL), washed with brine, and dried over Na_2SO_4. The ether solution was passed through a short column (silica gel) and concentrated in vacuo to afford the (*R*)-alcohol.

The transfer hydrogenation of diones **21** and imines **22**−**24** was conducted in 2 M DMF and 0.5 M DCM solutions, respectively.

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Supporting Information Available: GC, HPLC, and $[\alpha]_D$ values of the reduction products and spectra of dendritic ligands **9**, **10**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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