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Dendritic Amplification of Stereoselectivity of a Prolinamide-Catalyzed Direct Aldol Reaction

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Abstract. Isomeric "*compact*" and "*expanded*" dendrimers functionalized with L-prolinamide catalytic units at the periphery were compared as catalysts to monomer controls in the organocatalytic direct aldol condensation. A positive dendritic effect that amplifies the stereoselectivity of the direct aldol condensation was observed for dendrimers **3** and **4**, compared with lower molecular weight catalysts L-prolinanilide **1** and G1 dendron **2**. The difference in the compactness between **3** and **4** appears to have less impact on the stereoselectivity than the preorganized multivalency of the dendritic catalysts.

INTRODUCTION

The apparent structural similarity of dendrimers to globular proteins has stimulated intense interest in exploiting the three-dimensional nature of their structures to enhance catalytic efficiency.[1] In particular, dendrimers with peripheral catalytic groups have received the most attention because the spatially well-defined and specific number of active sites on their surfaces afford a predictable catalytic activity that is not significantly different from that of the monomeric counterpart. This property ideally suits dendritic systems as soluble supports to aid in catalyst recovery/separation without decreasing the activity or selectivity of the catalyst, as often occurs with polymer-supported catalysts.[2] However, the search for a dendritic catalyst that amplifies the intrinsic efficiency of the parent catalyst in a manner that resembles natural enzymes remains elusive.[3] In pursuit of that objective, we recently reported the first example of a dendritic catalyst that directs the stereoselectivity of a Rh-catalyzed hydrogenation by dynamically transferring the conformational chirality of the folded structure to the catalytic center at the core.[4] Although extensive research efforts over the last decade have revealed a number of positive dendritic effects in dendrimers displaying peripheral catalytic groups, they remain relatively uncommon.[5] Generation-dependent increases in enantioselectivity have been noted for a Pd-catalyzed allylic amination,[6] a direct aldol reaction catalyzed by a polymer-supported dendritic proline,[7] and more recently, in a Rh-catalyzed hydrogenation.[8] It is noteworthy that prior studies using unsupported proline-terminated dendrimers as organocatalysts for the direct aldol reaction revealed generation-independent enantioselectivities that were actually slightly lower compared with L-proline.[9] These studies generally suggest that the dendritic effects observed in dendritic catalysts arise from the increased congestion

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and local proximity of catalytic groups at the periphery, rather than from folding or topological effects.

We have previously developed a series of folded dendrons based on pyridine-2,6-dicarboxamides that adopt a dynamic helical secondary structure.[10] Dendrimers derived from this repeat unit experience non-bonded packing interactions that couple the motions of the terminal groups, causing the conformational equilibrium of the helical termini to shift toward a single helical sense with increasing generation. We compared the conformational properties of a series of "*compact*" and "*expanded*" dendrimers produced by linking the dendrons to 1,3,5-benzenetricarbonyl chloride, as the central core, via either a 2- or 4-aminobenzamide linkage, respectively. [11] These relatively minor modifications of the dendron/core linkage in the structure of these folded dendrimers afforded large variations in hydrodynamic volumes. Further, the "*compact*" dendrimer exhibited a much more thermally stable helical bias than the "*expanded*" dendrimer. The dendron precursor did not exhibit a helically-biased conformation. Herein, we explore whether the non-bonded interactions that induce these conformational properties would be capable of enhancing the stereoselectivity of a direct aldol reaction catalyzed by L-proline-terminated analogues of these dendrimers.[12]

RESULTS AND DISCUSSION

Synthesis of Dendrimer Catalysts

Accordingly, we constructed two isomeric dendrimers with peripheral L-prolinamide groups, analogous to the "*expanded*" and "*compact*" systems, to probe the impact of conformational preorganization on the proline-catalyzed direct aldol reaction. Dendrons displaying terminal L-prolinamide groups were linked to a central core via 3-aminobenzamide (*meta*) and 2-aminobenzamide (*ortho*) linkage to create "*expanded*" (**3**) and "*compact*" (**4**) dendrimer catalysts, respectively. These structures differ from the previously studied dendrimers in ref 11 in two aspects: (1) the "*expanded*" dendrimer (**3**) was constructed using a 3-aminobenzamide linkage due to synthetic difficulties associated with the tendency of the 4-aminobenzamide analogue to aggregate, and (2) the L-proline termini were linked to the pyridine-2,6-dicarboxamide branch point via an *o*-phenylenediamine rather than an anthranilamide linkage. Along with these new dendrimers, L-prolinanilide **1**[13] and prolinamide dendron **2** were prepared as controls for comparison to the dendrimer catalysts (Fig. 1).

The preparation of the Boc-protected dendrons was accomplished in one pot by sequentially acylating *o*-

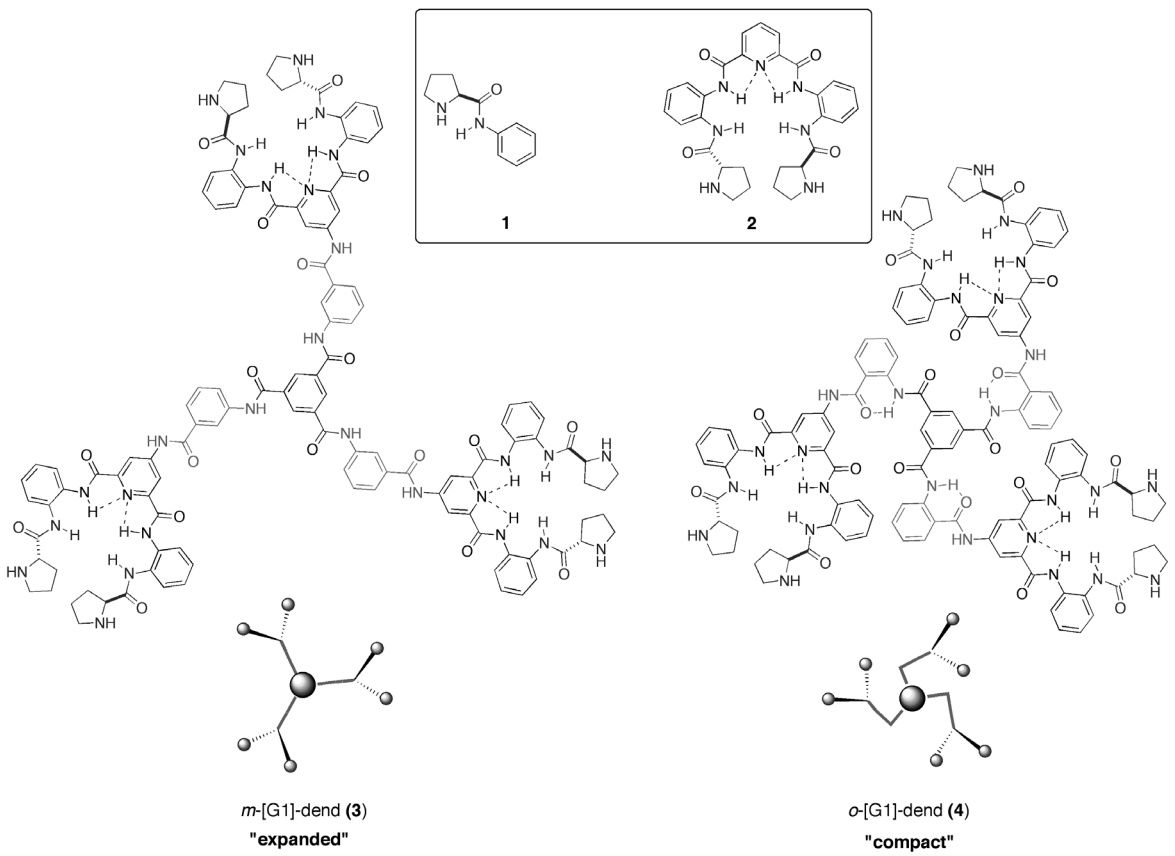
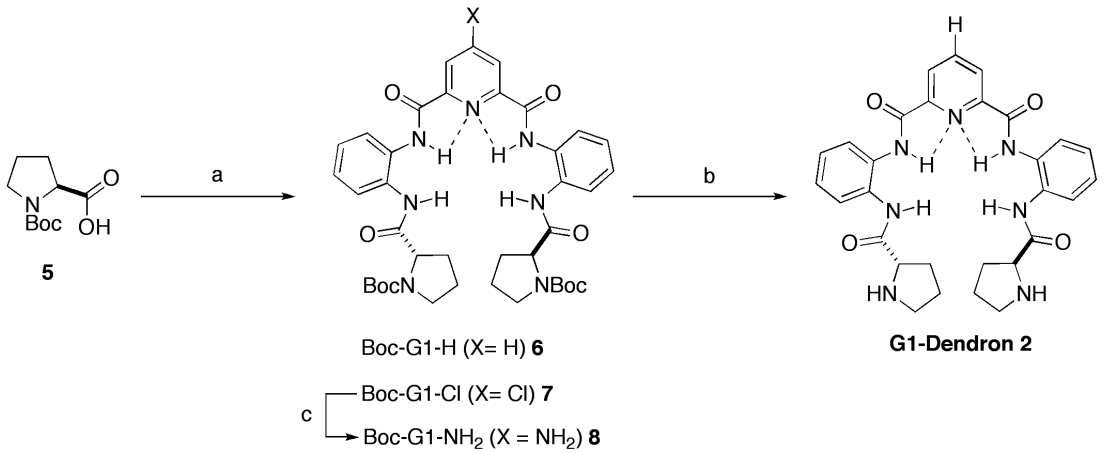


Fig. 1. Structures of prolinamide organocatalysts.



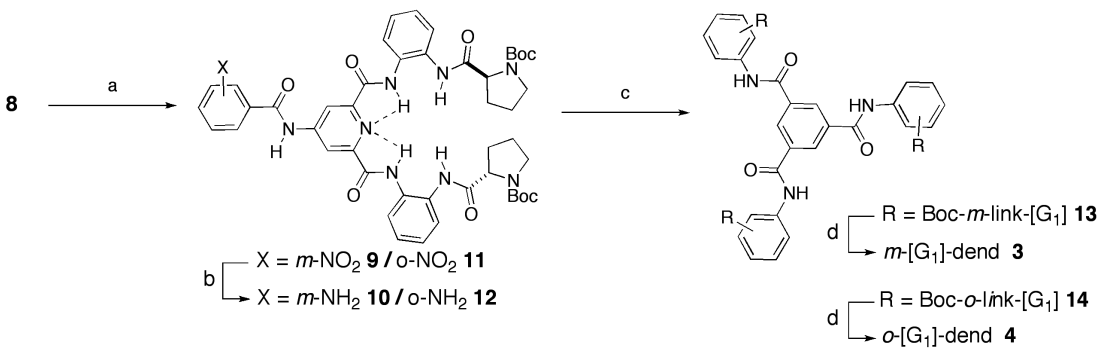
Scheme 1. (a) 1—Ethyl chloroformate, Et_3N, THF, 0 ºC; 2—*o*-phenylenediamine, THF, –20 ºC; 3—2,6-pyridinedicarbonyl dichloride for **6** or 4-Cl-2,6-pyridinedicarbonyl dichloride for **7**, Et_3N, CH_2Cl_2, 0 ºC, 81% for **6,** 89% for **7**. (b) TFA, anisole, CH_2Cl_2, quant. (c) 1) NaN_3, DMF, 50°C; 2) Pd/C, H_2, EtOH, 88% (2 steps).

phenylenediamine with Boc-L-Pro-OH/ethyl chloroformate and either pyridine-2,6-dicarbonyl chloride or 4-chloropyridine-2,6-dicarbonyl chloride, affording Boc-G1-H (**6**) and Boc-G1-Cl (**7**) in 81% and 89% yields, respectively (Scheme 1). Displacement of the 4-chloro group with NaN_3, followed by catalytic hydrogenation over Pd/C, produced Boc-G1-NH_2 (**8**) in 88% overall yield in two steps. Deprotection of **6** with TFA/anisole afforded catalyst **2** in quantitative yield.

The *meta*- and *ortho*-aminobenzamide linkages were installed by reacting the 4-amino function of **8** with 2- or 3-nitrobenzoyl chloride, followed by catalytic hydrogenation over Pd/C, affording Boc-G1-meta-NH_2 (**10**) and Boc-G1-ortho-NH_2 (**12**) (Scheme 2). The isomeric tripodal dendrimers, *m*-[G_1]-dend (**3**) and *o*-[G_1]-dend (**4**), were obtained by reacting the aminobenzamides **10** and **11** with 0.33 equiv of 1,3,5-benzenetricarbonyl chloride in 67% yield for **13** and in 55% yield for **14**, followed by deprotection with trifluoroacetic acid/anisole in CH_2Cl_2.

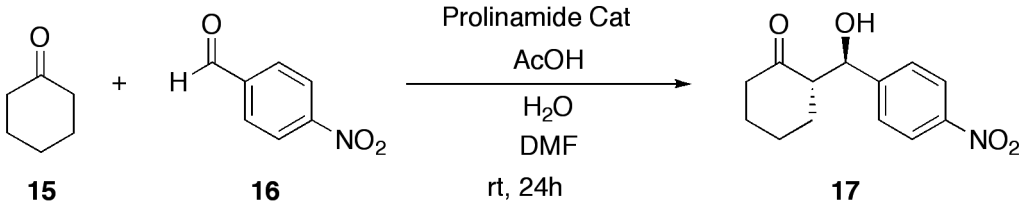
Catalysis of Direct Aldol Reaction

We investigated the aldol reaction between 4-nitrobenzaldehyde and cyclopentanone or cyclohexanone using catalysts **1–4** to reveal any potential dendritic effects on the stereoselectivity. The aldol reactions were performed in DMF for 24 h in the presence of excess ketone (27 equiv), catalytic acetic acid (1.0 equiv per catalytic unit), and water (1000 mol%).[14] Under these conditions, the aldol condensations proceeded smoothly for both ketones in 85–100% yields providing the aldol products as a mixture of *syn* and *anti* diastereomers. L-prolinanilide **1**, serving as a monomeric control, provided the *anti*-aldol product in 64% ee for



Scheme 2. (a) 3-Nitrobenzoyl chloride for **9** or 2-nitrobenzoyl chloride for **11**, pyridine, DMAP, CH_2Cl_2, 0 ºC, 84% for **9**, 48% for **11**. (b) Pd/C, H_2, EtOH, 97% for **10**, 85% for **12**. (c) benzene-1,3,5-tricarbonyl trichloride, pyridine, CH_2Cl_2, 0 ºC, 67% for **13**, 55% for **14**. (d) TFA, anisole, CH_2Cl_2, quant. for **3**/**4**.

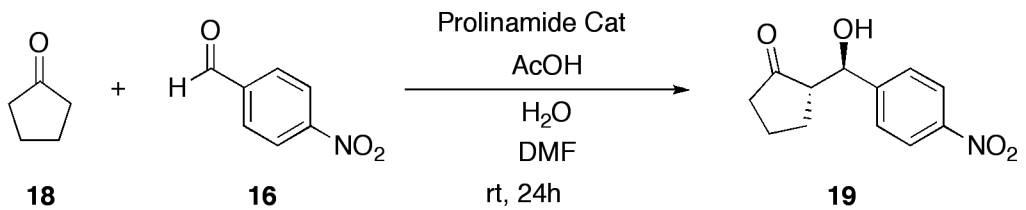
Table 1. Direct aldol reaction of 4-nitrobenzaldehyde with cyclohexanone catalyzed by prolinamide organocatalysts[a]



entry	catalyst	mol%	yield (%)[b]	dr[c] *anti*:*syn*	% ee[d] *anti*/*syn*
1	L-prolinanilide (**1**)	20	99	5.3:1	64/28
2	G1-dendron (**2**)	10	90	4.4:1	59/48
3	*m*-[G1]-dend (**3**)	3.3	98	20:1	96/43
4	*o*-[G1]-dend (**4**)	3.3	100	12.5:1	91/13

[a]Reactions were performed at rt in DMF in the presence of acetic acid (1 equiv per prolinamide), 1000 mol% H_2O, and 27 equiv of ketone for 24 h. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC.

Table 2. Direct aldol reaction of 4-nitrobenzaldehyde with cyclopentanone catalyzed by prolinamide organocatalysts[a]



entry	catalyst	mol%	yield (%)[b]	dr[c] *anti*:*syn*	% ee[d] *anti*/*syn*
1	L-prolinanilide (**1**)	8	98	1:2.2	33/6
2	G1-dendron (**2**)	4	87	1:2.9	63/14
3	*m*-[G1]-dend (**3**)	1.33	88	1.3:1	90/64
4	*o*-[G1]-dend (**4**)	1.33	85	1.5:1	88/62

[a]Reactions were performed at rt in DMF in the presence of acetic acid (1 equiv per prolinamide), 1000 mol% H_2O and 27 equiv of ketone for 24 h. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC.

cyclohexanone and 36% ee for cyclopentanone (Tables 1 and 2).[15] For both ketones, the enantioselectivities generally increased going from **1** → G1 dendron **2** → dendrimers **3**/**4**, indicating a strongly positive dendritic effect (Fig. 2). The enantioselectivities of the *syn* diastereomer experienced moderate increases going from **1** → **3**/**4**, with the exception of catalyst **4**, which provided a particularly low 13% ee for cyclohexanone. However, the selectivities were significantly lower compared with the *anti* diastereomer. It is noteworthy that whereas the *anti*/*syn* ratio increased from **1** → **3**/**4** for cyclohexanone, the ratio reversed from *syn*-selective with **1** and **2** to *anti*-selective with dendrimers **3** and **4** for cyclopentanone.

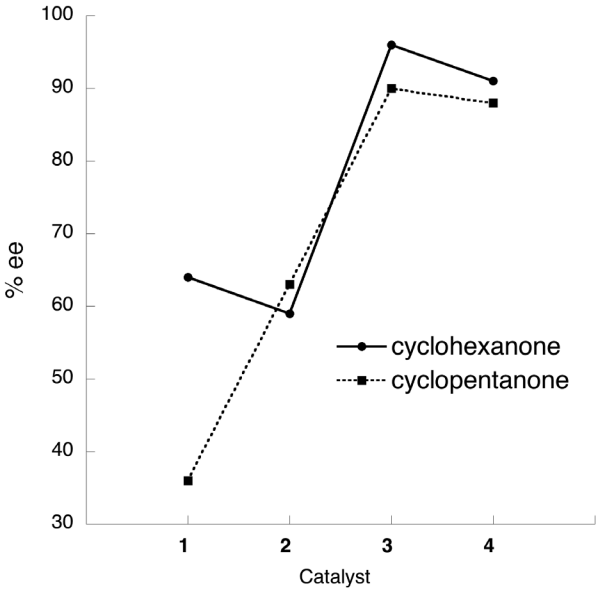


Fig. 2. Plot of the % ee of the *anti* diastereomer produced in the aldol condensation between 4-nitrobenzaldehyde and cyclohexanone/cyclopentanone as function of catalyst structure.

CONCLUSION

Overall, the enantioselectivity of the aldol reactions of both ketones improved going from L-prolinanilide **1** and dendron **2** to the dendrimeric catalysts **3**/**4**. Although prior conformational studies on closely related dendrimers suggest that *o*-[G_1]-dend (**4**) would maintain a more compact and thermally stable secondary structure than *m*-[G_1]-dend (**3**), both dendrimers in that study showed higher helical bias than the precursor dendron.[11] The increases in selectivity for the L-prolinamide dendrimers parallel the conformational differences between the dendrons and dendrimers in the previous study. However, the similar catalytic behavior of **3** and **4** contrasts with the difference in conformational bias between the "*compact*" and "*expanded*" dendrimers. Although the source of the dendritic effect remains under investigation, these observations suggest that the overall compactness of the dendritic catalysts has lower impact on the selectivity than the preorganized multivalency of the L-prolinamide catalytic groups on the dendrimer surface.

EXPERIMENTAL

General Methods

Melting points were determined in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1600 instrument. Fourier transform-infrared spectrometry was performed on an FTIR spectrometer (Thermo Nicolet, Madison, WI). ^{1}H NMR was recorded at 400 or 500 MHz and ^{13}C NMR at 100 or 125 MHz on a Bruker DPX-400 or DPX-500 instrument as indicated. EI or FAB mass spectra were recorded at The Ohio State University Chemical Instrumentation Center. Matrix-assisted laser desorption ionization-time of flight MS (MALDI-TOF MS) spectrometry was performed using 2,5-dihydroxybenzoic acid as the matrix in tetrahydrofuran (THF). All reactions were performed in oven- or flame-dried glassware under a nitrogen atmosphere unless otherwise noted. *N*,*N*-Dimethylformamide (DMF) was dried by distillation from activated 4 Å molecular sieves; THF was distilled from sodium/benzophenone ketyl; dichloromethane was distilled from calcium hydride; pyridine was distilled from calcium hydride; triethylamine was distilled from calcium hydride; chloroform was distilled from calcium carbonate. Boc-Pro-OH was purchased from Novabiochem and used without further purification. Chromatographic separations were performed on silica gel 60 (230–400 mesh, 60 Å) using the indicated solvents.

Boc-G1-H (6). To a solution of Boc-Pro-OH (**5**) (2.15 g, 10.0 mmol) in anhydrous THF (50 mL) was added Et_3N (2.79 mL, 20.0 mmol) at room temperature under N_2 atmosphere. The reaction mixture was stirred for 30 min and cooled to 0 ºC. Ethyl chloroformate (0.956 mL, 10.0 mmol) was added to the reaction mixture dropwise and the reaction was stirred and warmed to rt over 3 h. The reaction was cooled to –20 ºC, and then *o*-phenylenediamine (973 mg, 9.0 mmol) in anhydrous THF (4.5 mL) was added to the reaction mixture quickly. The resulting mixture was stirred while warming to rt gradually over 12 h. After the complete consumption of diamine starting material (~12 h), the reaction was cooled to 0 ºC. An additional amount of Et_3N (4.18 mL, 30.0 mmol) was added. To this reaction mixture was added a solution of 2,6-pyridinedicarbonyl chloride (1.02 g, 5.0 mmol) in CH_2Cl_2 (5 mL) dropwise over 5 min. The resulting reaction mixture was stirred while warming to rt over 12 h. The solvent was removed in vacuo. The residue was redissolved in $CHCl_3$ (50 mL) and washed with cold 1 M HCl (30 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 × 20 mL). The combined organics were treated with solid $NaHCO_3$ until pH ~7, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (0%-50% EtOAc/ether) to give Boc-G1-H **6** (5.41 g, 7.29 mmol, 81% based on diamine) as a white solid. mp 155–158 ºC ($CHCl_3$); ^{1}H NMR (400 MHz, 80 ºC, DMSO-d_6) δ 1.23 (s, 18 H), 1.53–1.70 (m, 4 H), 1.82–1.90 (m, 2 H), 1.97–2.06 (m, 2 H), 3.09–3.22 (m, 4 H), 4.18 (dd, J = 8.5 Hz, 4.4 Hz, 2 H), 7.28–7.33 (m, 4 H), 7.63–7.65 (m, 2 H), 7.81–7.83 (m, 2 H), 8.34 (dd, J = 8.7 Hz, 6.9Hz, 1 H), 8.43 (d, J = 7.5 Hz, 2 H), 9.5 (s, 2 H), 10.88 (s, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 30.1, 46.1, 60.3, 78.3, 124.3, 124.7, 124.8, 124.9, 125.3, 129.7, 130.6, 130.5, 139.6, 148.2, 153.1, 161.2, 171.6; IR (KBr) 3478, 3263, 3075, 2967, 2914, 2870, 2350, 1691, 1602, 1526, 1491, 1450, 1391, 1360, 1306, 1253, 1159, 1118, 1003 cm^{-1}. HRMS calcd for $C_{39}H_{47}N_7O_8$ (M+Na) 764.3384. Found 764.3380.

G1-dendron (2). To a solution of Boc-G1-H (**6**) (3.7 g, 5.0 mmol) in CH_2Cl_2 (20 mL) was added anisole (2.7 mL,

25 mmol) at rt. The mixture was cooled to 0 °C and TFA (7.43 mL, 100 mmol) was added dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The volatiles were removed in vacuo. To the residue was added diethyl ether (25 mL) and the solid precipitate was isolated by filtration. The precipitate was redissolved in $CHCl_3$ (100 mL), washed with saturated aqueous $NaHCO_3$ (50 mL), dried over Na_2SO_4, and concentrated in vacuo to give G1-dendron **2** (2.6 g, 4.8 mmol, 96%) as a white solid. mp 115–118 ºC ($CHCl_3$); ^{1}H NMR (400 MHz, 80 ºC, DMSO-d_6) δ 1.46–1.53 (m, 4 H), 1.67–1.74 (m, 2 H), 1.83–1.92 (m, 2 H), 2.57–2.62 (m, 2 H), 2.70–2.75 (m, 2 H), 2.99 (brs, 2 H), 3.64 (dd, *J* = 8.9 Hz, 5.3 Hz, 2 H), 7.21–7.33 (m, 4 H), 7.63–7.60 (dd, *J* = 7.8 Hz, 1.4 Hz, 2 H), 7.9 (dd, *J* = 8.0 Hz, 1.4 Hz, 2 H), 8.34 (dd, *J* = 8.6 Hz, 6.8 Hz, 1 H), 8.42 (d, *J* = 7.2 Hz, 2 H), 10.04 (brs, 2 H), 10.93 (brs, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.1, 29.7, 45.9, 60.4, 69.4, 122.2, 123.8, 124.4, 126.0, 128.1, 132.4, 139.5, 148.1, 161.5, 173.4; IR (KBr) 3464, 3346, 3256, 2959, 2869, 2356, 1682, 1592, 1516, 1480, 1300, 1226, 1135, 1106 cm^{-1}; HRMS calcd for $C_{29}H_{31}N_7O_4$ (M+Na) 564.2332. Found 564.2335.

Boc-G1-Cl (7). To a solution of Boc-Pro-OH (**5**) (2.15 g, 10.0 mmol) in anhydrous THF (50 mL) was added Et_3N (2.79 mL, 20.0 mmol) at room temperature under N_2 atmosphere. The reaction mixture was stirred for 30 min and cooled to 0 ºC. Ethyl chloroformate (0.956 mL, 10.0 mmol) was added to the reaction mixture dropwise and the reaction was stirred and warmed to rt over 3 h. The reaction was cooled to –20 ºC, and then *o*-phenylenediamine (973 mg, 9.0 mmol) in anhydrous THF (4.5 mL) was added to the reaction mixture quickly. The resulting mixture was stirred while warming to rt gradually over 12 h. After the complete consumption of diamine starting material (~12 h), the reaction was cooled to 0 ºC. An additional amount of Et_3N (4.18 mL, 30.0 mmol) was added. To this reaction mixture was added a solution of 4-chloro-2,6-pyridinedicarbonyl dichloride (1.02 g, 5.0 mmol) in CH_2Cl_2 (5 mL) dropwise over 5 min. The r sulting reaction mixture was stirred while warming to rt over 12 h. The solvent was removed in vacuo. The residue was redissolved in $CHCl_3$ (50 mL) and washed with cold 1 M HCl (30 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 × 20 mL). The combined organics were treated with solid $NaHCO_3$ until pH ~7, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (0%–50% EtOAc/ether) to give Boc-G1-Cl **7** (6.21 g, 8.0 mmol, 89% based on diamine) as a white solid. mp 174–178 ºC ($CHCl_3$); ^{1}H NMR (400 MHz, 80 ºC, DMSO-d_6) δ 1.23 (s, 18 H), 1.57–1.71 (m, 4 H), 1.84–1.92 (m, 2 H), 1.98–2.06 (m, 2 H), 3.09–3.23 (m, 4 H), 4.19 (dd, *J* = 8.4 Hz, 4.4 Hz, 2 H), 7.29–7.34 (m, 4 H), 7.64–7.66 (m, 2 H), 7.76–7.79 (m, 2 H), 8.41 (s, 2 H), 9.51 (s, 2 H), 10.88 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 30.1, 46.1, 60.2, 78.4, 78.7, 124.3, 124.4, 124.9, 125.6, 129.3, 130.8, 146.6, 149.9, 153.1, 160.1, 171.5; IR (KBr) 3492, 3241, 3068, 2973, 2921, 2869, 2349, 1690, 1600, 1534, 1482, 1452, 1395, 1317, 1255, 1162, 1118, 1010 cm^{-1}; HRMS calcd for $C_{39}H_{46}ClN_7O_8$ (M+Na) 798.2994. Found 798.2996.

Boc-G1-NH$_2$ (8). Boc-G1-Cl (**7**) (1.88 g, 2.42 mmol) was dissolved in anhydrous DMF (16.7 mL). To this solution was added NaN_3 (2.17 g, 33.3 mmol). After stirring at 50 ºC for 48 h, the solvent was removed under reduced pressure. The residue was redissolved in water (50 mL) and $CHCl_3$ (30 mL). The organic layer was extracted, washed with brine (20 mL), and dried over Na_2SO_4. After concentration in vacuo, the residue was redissolved in anhydrous EtOH. 10% Pd/C (189 mg) was added to this mixture and the reaction was hydrogenated under H_2 at atmospheric pressure for 12 h. The catalyst was removed by filtration through a pad of Celite. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (1–5% MeOH/$CHCl_3$ to give Boc-G1-NH$_2$ **8** (1.61 g, 2.13 mmol, 88% over 2 steps) as an off-white solid. mp 176–180 ºC ($CHCl_3$); ^{1}H NMR (400 MHz, 80 ºC, DMSO-d_6) δ 1.24 (s, 18 H), 1.53–1.70 (m, 4 H), 1.77–1.85 (m, 2 H), 1.94–2.00 (m, 2 H), 3.09–3.19 (m, 4 H), 4.19 (dd, *J* = 8.6 Hz, 4.5 Hz, 2 H), 6.65 (s, 2 H), 7.23–7.30 (m, 4 H), 7.53 (s, 2 H), 7.55–7.58 (m, 2 H), 7.78–7.80 (m, 2 H), 9.53 (s, 2 H), 10.70 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.9, 27.5, 30.0, 46.0, 60.2, 78.4, 108.7, 124.4, 124.89, 124.92, 130.14, 130.18, 148.6, 153.0, 157.1, 162.1, 171.6; IR (KBr) 3449, 3353, 3250, 2973, 2921, 2869, 2358, 1695, 1603, 1520, 1482, 1447, 1395, 1365, 1300, 1257, 1162, 1123 cm^{-1}; HRMS calcd for $C_{39}H_{48}N_8O_8$ (M+Na) 779.3487. Found 779.3459.

Boc-G1-meta-NO$_2$ (9). To a solution of Boc-G1-NH$_2$ (**8**) (0.844 g, 1.12 mmol) in dry CH_2Cl_2 (11 mL) were added DMAP (14 mg, 0.11 mmol) and pyridine (3.0 mL). The reaction mixture was cooled to 0 ºC in an ice bath. To this mixture was added a solution of 3-nitrobenzoyl chloride (208 mg, 1.12 mmol) in CH_2Cl_2 (1.0 mL) dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with cold aqueous 1 M HCl (30 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 × 20 mL). The combined organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography on silica gel (1–3% MeOH/$CHCl_3$) to afford Boc-G1-meta-NO$_2$ **9** (848 mg, 0.936 mmol, 84%) as an off-white solid. mp 180–183 ºC ($CHCl_3$); ^{1}H NMR (400 MHz, 80 ºC, DMSO-d_6) δ 1.25 (s, 18 H), 1.54–1.72 (m, 4 H), 1.83–1.90 (m, 2 H), 1.97–2.07 (m, 2 H), 3.11–3.22 (m, 4 H), 4.19 (dd, *J* = 8.3 Hz, 4.6 Hz, 2 H), 7.28–7.34 (m, 4 H), 7.61–7.64 (m, 2 H), 7.82–7.85 (m, 2 H), 7.90 (t, *J* = 8.4 Hz, 1 H), 8.47 (m, 2 H), 8.91 (s, 2 H), 8.22 (t, *J* = 2.0 Hz, 1 H), 9.58 (s, 2 H), 10.88 (s, 2 H), 11.25 (s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.9, 28.4, 30.9, 47.0, 61.4, 79.3, 115.5, 123.1, 125.3, 125.7, 125.9, 126.2, 127.2, 130.8, 131.4, 134.8, 135.7, 148.6, 149.7, 150.3, 154.0, 162.1, 165.0, 172.5; IR (KBr) 3473, 3270, 2973, 1685, 1597, 1523, 1397, 1286, 1249, 1161 cm^{-1}; HRMS calcd for $C_{46}H_{51}N_9O_{11}$ (M+Na) 928.3606. Found 928.3617.

Boc-G1-meta-NH$_2$ (10). Boc-G1-meta-NO$_2$ (**9**) (760 mg, 0.839 mmol) was dissolved in anhydrous EtOH (25 mL). 10% Pd/C (76 mg) was added to this mixture and the reaction was hydrogenated under H_2 at atmospheric pressure for 5 h. The catalyst was removed by filtration through a pad of Celite. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (1–5% MeOH/$CHCl_3$) to

give Boc-G1-meta-NH_2 **10** (712 mg, 0.813 mmol, 97%) as an off-white solid. mp 175–177 ºC ($CHCl_3$); ^{1}H NMR (400 MHz, 80 ºC, DMSO-d_6) δ 1.23 (s, 18H), 1.54–1.68 (m, 4 H), 1.80–1.87 (m, 2 H), 1.95–2.05 (m, 2 H), 3.10–3.20 (m, 4 H), 4.15 (dd, *J* = 8.5 Hz, 4.7 Hz, 2 H), 5.15 (brs, 2 H), 6.85–6.88 (m, 1 H), 7.21–7.24 (m, 2 H), 7.27–7.32 (m, 3 H), 7.58–7.62 (m, 2 H), 7.79–7.82 (m, 2 H), 8.87 (s, 2 H), 9.52 (s, 2 H), 10.76 (s, 1 H), 10.82 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.9, 28.4, 30.9, 47.0, 61.1, 79.3, 114.0, 115.2, 115.9, 118.5, 125.3, 125.7, 125.8, 126.1, 129.4, 130.8, 131.4, 135.2, 149.1, 150.1, 150.3, 154.0, 162.3, 167.8, 172.5; IR (KBr) 3474, 3260, 2964, 1680, 1592, 1518, 1481, 1444, 1393, 1305, 1230, 1156 cm^{-1}; HRMS calcd for $C_{46}H_{53}N_9O_9$ (M+Na) 898.3864. Found 898.3876.

Boc-G1-ortho-NO_2 (11). To a solution of Boc-G1-NH_2 (**8**) (0.50 g, 0.66 mmol) in dry CH_2Cl_2 (3.3 mL) were added DMAP (16 mg, 0.13 mmol) and pyridine (3.3 mL). The reaction mixture was cooled to 0 ºC in an ice bath. To this mixture was added a solution of 2-nitrobenzoyl chloride (122 mg, 0.66 mmol) in CH_2Cl_2 (0.7 mL) dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and washed with cold 1 M HCl (15 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 × 10 mL). The combined organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography on silica gel (1–3% MeOH/$CHCl_3$) to afford Boc-G1-ortho-NO_2 **11** (289 mg, 0.319 mmol, 48%) as an off-white solid. mp 182–185 ºC ($CHCl_3$); ^{1}H NMR (400 MHz, 80 ºC, DMSO-d_6) δ 1.26 (s, 18 H), 1.55–1.71 (m, 4 H), 1.84–1.91 (m, 2 H), 1.98–2.07 (m, 2 H), 3.12–3.23 (m, 4 H), 4.19 (dd, *J* = 8.7 Hz, 4.4 Hz, 2 H), 7.23–7.34 (m, 4 H), 7.62–7.64 (m, 2 H), 7.82–7.84 (m, 2 H), 7.87 (td, *J* = 7.6 Hz, 1.7 Hz, 2 H), 7.94 (td, *J* = 7.5 Hz, 1.1 Hz, 1 H), 8.22 (dd, *J* = 8.2 Hz, 1.0 Hz, 1 H), 8.72 (s, 2 H), 9.56 (s, 2 H), 10.87 (s, 2 H), 11.38 (s, 1 H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 23.0, 27.5, 30.0, 46.1, 60.3, 78.4, 114.0, 123.9, 124.4, 124.8, 125.0, 125.3, 128.8, 129.8, 130.6, 131.1, 131.2, 133.8, 146.0, 148.6, 149.5, 153.1, 161.2, 165.0, 171.6; IR (KBr) 3447, 3355, 3086, 2978, 2931, 2347, 1681, 1596, 1531, 1481, 1393, 1367, 1349, 1296, 1256, 1160, 1128 cm^{-1}; HRMS calcd for $C_{46}H_{51}N_9O_{11}$ (M+Na) 928.3600. Found 928.3609.

Boc-G1-ortho-NH_2 (12). Boc-G1-ortho-NO_2 (**11**) (289 mg, 0.320 mmol) was dissolved in anhydrous EtOH (6 mL). 10% Pd/C (29 mg) was added to this mixture and the reaction was hydrogenated under H_2 at atmospheric pressure for 12 h. The catalyst was removed by filtration through a pad of Celite. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (1–3% MeOH/$CHCl_3$) to give Boc-G1-ortho-NH_2 **12** (237 mg, 0.271 mmol, 85%) as an off-white solid. mp 174–178 ºC ($CHCl_3$); ^{1}H NMR (400 MHz, 80 ºC, DMSO–d_6) δ 1.24 (s, 18 H), 1.54–1.70 (m, 4 H), 1.79–1.88 (m, 2 H), 1.95–2.05 (m, 2 H), 3.10–3.20 (m, 4 H), 4.16 (dd, *J* = 9.0 Hz, 4.4 Hz, 2 H), 6.42 (brs, 2 H), 6.65 (td, 7.0 Hz, 1.4 Hz, 1 H), 6.84 (dd, *J* = 8.4 Hz, 1.1 Hz, 1 H), 7.23–7.34 (m, 5 H), 7.59–7.61 (m, 2 H), 7.78–7.82 (m, 3 H), 8.84 (s, 2 H), 9.53 (s, 2 H), 10.82 (s, 2 H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 23.0, 27.5, 30.0, 46.1, 60.2, 69.5, 78.3, 113.3, 114.4, 116.5, 124.4, 124.7, 124.9, 125.2, 128.5, 129.9, 130.5, 132.6, 149.1, 149.4, 150.2, 153.1, 161.4, 168.3, 171.6; IR (KBr) 3440, 3258, 2973, 2877, 2358, 1677, 1594, 1517, 1478, 1447, 1391, 1361, 1292, 1235, 1157, 1123 cm^{-1}; HRMS calcd for $C_{46}H_{53}N_9O_9$ (M+Na) 898.3864. Found 898.3859.

Boc-*m*-[G_1]-dend (13). To a solution of Boc-G1-meta-NH_2 (**10**) (175 mg, 0.20 mmol) in dry CH_2Cl_2 (0.4 mL) were added pyridine (0.4 mL). The reaction mixture was cooled to 0 ºC in an ice bath. To this mixture was added a solution of freshly prepared benzene-1,3,5-tricarbonyl trichloride (18 mg, 0.066 mmol) in CH_2Cl_2 (0.4 mL) dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and washed with cold 1 M HCl (10 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 × 10 mL). The organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography on silica gel (1–3% MeOH/CH_2Cl_2) to afford Boc-*m*-[G_1]-dend **13** (125 mg, 0.0449 mmol, 67%) as an off-white solid. mp (dec) 220 ºC ($CHCl_3$); ^{1}H NMR (400 MHz, 80 ºC, DMSO-d_6) δ 1.24 (s, 54 H), 1.55–1.70 (m, 12 H), 1.81–1.88 (m, 6 H), 1.96–2.05 (m, 6 H), 3.15–3.21 (m, 12 H), 4.28 (dd, *J* = 9.0 Hz, 4.7 Hz, 6 H), 7.26–7.33 (m, 12 H), 7.59–7.65 (m, 9 H), 7.80–7.82 (m, 6 H), 7.87–7.90 (dd, *J* = 7.7 Hz, *J* = 1.6 Hz, 3 H), 8.14–8.17 (m, 3 H), 8.48–8.49 (m, 3 H), 8.84 (s, 3 H), 8.90 (s, 6 H), 9.53 (s, 6 H), 10.68 (s, 3 H), 10.84 (s, 6 H), 11.00 (s, 3 H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 23.9, 28.4, 30.9, 47.0, 61.1, 79.3, 115.4, 121.0, 123.8, 125.0, 125.3, 125.7, 125.9, 126.2, 129.4, 130.4, 130.8, 131.4, 135.0, 136.0, 139.9, 150.1, 150.2, 162.2, 165.3, 167.0, 172.5; IR (KBr) 3455, 3279, 2973, 2361, 1680, 1592, 1513, 1402, 1305, 1156 cm^{-1}; MALDI-TOF MS calcd for $C_{147}H_{159}N_{27}O_{30}$ (M+Na) 2805.17. Found 2806.60.

***m*-[G_1]-dend (3).** To a solution of Boc-*m*-[G_1]-dend **13** (55 mg, 0.0197 mmol) in CH_2Cl_2 (2 mL) was added anisole (2 mL) at rt. The mixture was cooled to 0 ºC and TFA (2 mL) was added dropwise over 2 min. The reaction was stirred while warming to rt gradually over 12 h. The volatiles were removed in vacuo. To the residue was added diethyl ether (5 mL) and the solid precipitate was isolated by filtration. The precipitate was redissolved in a mixture of H_2O (2 mL) and CH_3CN (2 mL). To this mixture was added solid $NaHCO_3$ with stirring until pH ~8. The white solid precipitate was isolated by filteration and dried in vacuo over P_2O_5 to give *m*-[G_1]-dend **3** (42 mg, 0.0192 mmol, 98%) as a white solid. mp 260-263 ºC (CH_3CN); ^{1}H NMR (400 MHz, 80 ºC, DMSO-d_6) δ 1.74–1.80 (m, 12 H), 2.00–2.07 (m, 6 H), 2.21–2.30 (m, 6 H), 3.11–3.15 (m, 12 H), 4.37 (dd, *J* = 8.8 Hz, 4.1 Hz, 6 H), 7.32–7.36 (m, 12 H), 7.60–7.64 (m, 3 H), 7.68–7.78 (m, 12 H), 7.89 (d, *J* = 9.0 Hz, 3 H), 8.15 (d, *J* = 9.8 Hz, 3 H), 8.56 (s, 3 H), 8.89 (s, 9 H), 10.74 (s, 6 H), 10.78 (s, 3 H), 10.98 (s, 3 H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 24.0, 29.9, 46.3, 60.4, 115.6, 121.1, 123.8, 125.1, 125.8, 126.4, 126.5, 126.8, 129.3, 130.4, 131.1, 131.6, 135.1, 136.0, 140.0, 149.8, 150.7, 162.8, 165.3, 167.1; IR (KBr) 3247, 3070, 1682, 1591, 1519, 1454, 1304, 1203, 1134 cm^{-1}; MALDI-TOF MS calcd for $C_{117}H_{111}N_{27}O_{18}$ (M+H) 2182.86. Found 2183.07.

Boc-*o*-[G_1]-dend (14). To a solution of Boc-G1-ortho-

NH_2 (**12**) (464 mg, 0.53 mmol) in dry CH_2Cl_2 (2.7 mL) was added pyridine (1.4 mL). The reaction mixture was cooled to 0 ºC in an ice bath. To this mixture was added a solution of freshly prepared benzene-1,3,5-tricarbonyl trichloride (47 mg, 0.18 mmol) in CH_2Cl_2 (2.0 mL) dropwise over 2 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with cold 1 M HCl (20 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 × 20 mL). The organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography on silica gel (1–3% MeOH/CH_2Cl_2) to afford Boc-*o*-[G_1]-dend **14** (276 mg, 0.099 mmol, 55%) as an off-white solid. mp (dec) 235 ºC ($CHCl_3$); ^{1}H NMR (400 MHz, 80 ºC, DMSO-d_6) δ 1.18 (s, 54 H), 1.48–1.63 (m, 12 H), 1.75–1.82 (m, 6 H), 1.89–1.98 (m, 6 H), 3.08–3.12 (m, 12 H), 4.10 (dd, *J* = 8.7 Hz, 4.9 Hz, 6 H), 7.24–7.32 (m, 15 H), 7.53–7.59 (m, 9 H), 7.75–7.78 (m, 6 H), 7.92 (d, *J* = 8.7 Hz, 3 H), 8.2 (d, *J* = 8.7 Hz, 3 H), 8.70 (s, 3 H), 8.76 (s, 6 H), 9.50 (s, 6 H), 10.77 (s, 6 H), 11.05 (s, 3 H), 11.24 (s, 3 H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 23.8, 28.4, 30.9, 46.9, 61.1, 79.2, 115.5, 123.8, 124.6, 125.3, 125.6, 125.8, 126.1, 129.5, 129.6, 130.8, 131.3, 132.8, 136.4, 138.3, 149.9, 150.1, 154.0, 162.1, 164.4, 168.4, 172.5; IR (KBr) 3483, 3261, 2964, 1680, 1585, 1514, 1450, 1402, 1302, 1162 cm^{-1}; MALDI-TOF MS calcd for $C_{147}H_{159}N_{27}O_{30}$ (M+Na) 2805.16. Found 2805.67.

***o*-[G$_1$]-dend (4).** To a solution of Boc-*o*-[G_1]-dend **14** (24 mg, 0.0086 mmol) in CH_2Cl_2 (0.9 mL) was added anisole (0.9 mL) at rt. The mixture was cooled to 0 ºC and TFA (0.9 mL) was added dropwise over 2 min. The reaction was stirred while warming to rt gradually over 12 h. The volatiles were removed in vacuo. To the residue was added diethyl ether (2 mL) and the solid precipitate was isolated by filtration. The precipitate was redissolved in a mixture of H_2O (1 mL) and CH_3CN (1 mL). To this mixture was added solid $NaHCO_3$ with stirring until pH ~8. The white solid precipitate was isolated by filteration and dried in vacuo over P_2O_5 to give *o*-[G_1]-dend **4** (19 mg, 0.0085 mmol, 99%) as a white solid. mp 276–279 ºC (CH_3CN); ^{1}H NMR (400 MHz, 80 ºC, DMSO-d_6) δ 1.64–1.71 (m, 12 H), 1.91–2.00 (m, 6 H), 2.13–2.22 (m, 6 H), 3.05 (t, *J* = 7.1 Hz, 12 H), 4.35 (dd, *J* = 8.3 Hz, 6.9 Hz, 6 H), 7.28–7.33 (m, 12 H), 7.56 (dt, *J* = 8.1 Hz, *J* = 1.6 Hz, 3 H), 7.65–7.73 (m, 9 H), 7.96 (dd, *J* = 8.0 Hz, *J* = 1.4 Hz, 3 H), 8.20 (dd, *J* = 8.4 Hz, *J* = 1.0 Hz, 3 H), 8.71 (s, 3 H), 8.77 (s, 6 H), 10.70 (s, 6 H), 11.25 (brs, 6 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.1, 30.0, 46.3, 60.5, 115.8, 123.9, 124.7, 125.7, 126.2, 126.4, 126.7, 129.6, 131.0, 131.5, 132.8, 136.4, 138.2, 149.6, 150.5, 162.6, 164.4, 168.4, 168.7; IR (KBr) 3437, 2983, 2352, 1676, 1592, 1513, 1300, 1198 cm^{-1}; MALDI-TOF MS calcd for $C_{117}H_{111}N_{27}O_{18}$ (M+Na) 2204.8498. Found 2204.908.

Representative Procedure for Aldol Reaction between Cyclohexanone and 4-Nitrobenzaldehyde Catalyzed by m-*[G1]-dend (**3**):*

To a solution of *m*-[G_1]-dend **3** (9 mg, 0.0041 mmol) in anhydrous DMF (0.125 mL) were added AcOH (1.4 μL, 0.0248 mmol) and freshly distilled cyclohexanone (0.35 mL, 3.35 mmol). After stirring at rt for 15 min, water (22 μL, 1.24 mmol) and 4-nitrobenzaldehyde (19 mg, 0.124 mmol) were added. The resulting mixture was stirred at rt for 24 h. The reaction was treated with saturated aqueous ammonium chloride (1 mL). This mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20–40% EtOAc/pet ether) to give pure aldol products, 2-[hydroxy-(4-nitrophenyl)-methyl]-cyclohexanone (31 mg, 0.124 mmol, 100%), as a white solid. The diastereoselectivity was determined by ^{1}H NMR analysis to be 20:1 (*anti:syn*). The enantioselectivity was determined by chiral HPLC (Daicel Chiralpak IA, 20% *i*-PrOH/hexane, UV 254 nm, flow rate 1.0 mL/min). 96% ee for *anti* isomer (major), t_R 19.3 min, (minor) t_R 13.8 min. 43% ee for *syn* isomer (major), t_R 10.1 min, (minor) t_R 13.5 min.

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