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Efficiency and Fidelity in a Click Chemistry Route to Triazole Dendrimers via the Cu(I)-Catalyzed Ligation of Azides and Alkynes

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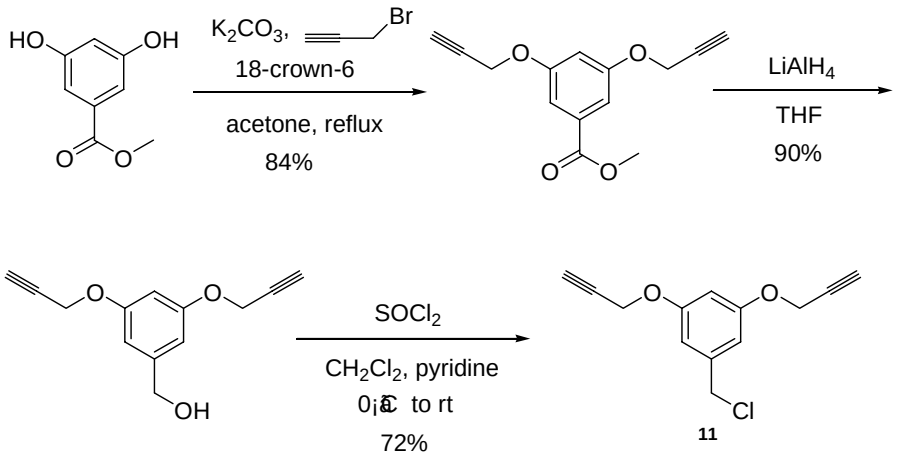
Experimental Section.

General Methods. Commercial reagents were obtained from Aldrich and were used with out further purification. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Analytical TLC was performed on commercial Merck Plates coated with silica gel GF254 (0.24 mm thick). Silica Gel for flash chromatography was Merck Kieselgel 60 (230-400 mesh, ASTM). NMR (^{1}H, ^{13}C) spectra were recorded either on a Bruker AMX-400, AMX-500 or AMX-600 MHz spectrometer. Coupling constants (*J*) are reported in hertz, and chemical shifts are reported in parts per million (δ) relative to $CHCl_3$ (7.26 ppm for ^{1}H and 77.2 ppm for ^{13}C) or DMSO (2.50 ppm for ^{1}H and 39.5 ppm for ^{13}C) or CD_3OD (3.31 ppm for ^{1}H and 49.0 ppm for ^{13}C) or acetone (2.05 ppm for ^{1}H and 29.9 ppm for ^{13}C) as internal reference. Preparation HPLC was performed on a Dynamax HPLC system using a ZORBAX SB-C18 column (21.2 mm i.d. × 25cm) with H_2O/CH_3CN as eluent, the flowing rate was 6.5ml/min. Gel Permeation Chromatography was performed in tetrahydrofuran (THF) on a Waters chromatograph equipped with four 5-μm Waters columns (300 mm × 7.7 mm) connected in series with increasing pore size (two mixed B, 10^3Å, 10^5Å). A Waters 410 differential refractometer and a 996 photodiode array detector were employed. The molecular weights of the polymers were calculated relative to linear polystyrene standards. The modulated differential scanning calorimetry (MDSC) measurements were performed with the TA Instruments DSC 2920 and a ramp rate of 4 degrees per minute. The thermal gravimetric analysis measurements were done with the TA Instruments Hi-Res TGA 2950, under nitrogen purge, and the ramp rate was 10 degrees per minute. 2-chloro- *N*,*N*-di(prop-2-ynyl)acetamide **12**;[1] azide **15**,[2] **16**,[3] **17**;[4] 1,3,5-tris(prop-2-ynyloxy)benzene **20**,[5] 1,1,1-tris(4-(prop-2-ynyloxy) phenyl)ethane **21**[6] were prepared according to the reported methods.

The nomenclature used for the dendritic framework is as follows: R-X-[G-n]-Y, where R describes the functional groups at periphery, Bn for benzyl , Boc for *tert*-butyl ethylcarbamate, *t*Bu for *tert*-butyl, MEE for (2-methoxyethoxy)ethane; X describes internal repeat units, B for 1, 3 dioxybenzene, F for formamide, S for

benzenesulfonamide; n is the number for generations; Y describes functional group at the focal point, either chloride, Cl, or azide, N_3.

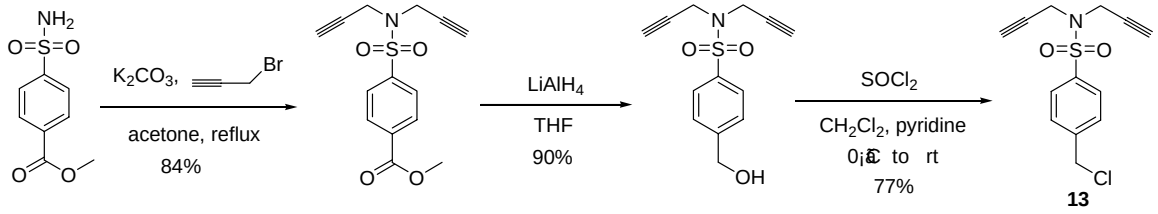
Syntheses of repeating units.



Methyl 3,5-Bis(propargyloxy)benzoate. To a stirred solution of methyl 3,5-dihydroxybenzoate (16.8 g, 100 mmol) and propargyl bromide (29.7 g, 220 mmol) in acetone (300 ml) were added potassium carbonate (15.1 g, 109 mmol) and 18-crown-6 (0.1 g, 0.4 mmol). The reaction mixture was heated at reflux under nitrogen for 24 hours, filtered and evaporated to dryness. The crude material was then crystallized in methanol to give the ester as pale yellow crystals (20.6 g, 84.4%). ^{1}H NMR (500MHz, $CDCl_3$): δ = 2.55 (t, J = 2.4 Hz, C≡C**H**, 2H), 3.92 (s, C**H**$_3$O, 3H), 4.73 (d, J = 2.4 Hz, C**H**$_2$C≡CH, 4H), 6.83 (s, *p*-Ar, 1H), 7.31 (s, *o*-Ar, 2H). ^{13}C NMR (125MHz, $CDCl_3$): δ = 52.76 (s, **C**H$_3$O, 1C), 56.51 (s, **C**H$_2$C≡CH, 1C), 76.38 (s, C≡**C**H, 1C), 78.34 (s, **C**≡CH, 1C), 107.91 (s, *p*-Ar, 1C), 109.27 (s, *o*-Ar, 2C), 132.54 (s, **C**COOCH$_3$, 1C), 158.90 (s, *m*-Ar, 2C), 166.86 (s, **C**OOCH$_3$, 1C).

3,5-Bis(propargyloxy)benzyl alcohol. To a stirred solution of the ester (20.6 g, 84.4 mmol) in anhydrous THF (170 ml) was added lithium aluminum hydride (3.99 g, 105 mmol) in small portions. Beckstrom's reagent (25 g) was then added to quench the remaining lithium aluminum hydride. The reaction mixture was filtered under vacuum, the solid was rinsed with dichloromethane and the filtrate dried with $MgSO_4$. After evaporation of the solvents, the alcohol was recovered as white crystals (16.4 g, 90.1%). ^{1}H NMR (500MHz, $CDCl_3$): δ = 2.46 (t, J = 2.4 Hz, C≡C**H**, 2H), 4.45 (s, C**H**$_2$OH, 2H), 4.61 (d, J = 2.4 Hz, C**H**$_2$C≡CH, 4H), 6.46 (s, *p*-Ar, 1H), 6.56 (s, *o*-Ar, 2H). ^{13}C NMR (500MHz, $CDCl_3$): δ = 56.30 (s, **C**H$_2$C≡CH, 1C), 65.50 (s, **C**H$_2$OH, 1C), 76.09 (s, C≡**C**H, 2C), 78.76 (s, **C**≡CH, 2C), 101.88 (s, *p*-Ar, 1C), 106.60 (s, *o*-Ar, 2C), 143.97 (s, **C**CH$_2$OH, 1C), 159.23 (s, *m*-Ar, 2C).

3,5-Bis(propargyloxy)benzyl chloride, 11. To a stirred solution of the alcohol (14.7 g, 68.0 mmol) in dichloromethane (200 ml) and pyridine (10.7 g, 136.0 mmol) was added and the mixture was placed on an ice bath. Thionyl chloride (12.1 g, 102 mmol) dissolved in dichloromethane (20 ml) was added dropwise to the reaction mixture and the ice bath was allowed to warm to room temperature. The reaction mixture was then allowed to stir under Ar for 24 h followed by quenching with water. The organic layer was allowed to separate and was washed with water (3 x 100 ml), dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash chromatography, loading with 1:1 dichloromethane:hexane and eluting with 2:1 dichloromethane:hexane to give the chloromethyl monomer, **1**, as a white solid; ^{1}H NMR (500MHz, $CDCl_3$) δ = 2.57 (t, 2H, ≡CH), 4.55 (s, 2H, CH_2Cl), 4.73 (d, 4H, CH_2O), 6.59 (t, 2H, ArH), and 6.80 (d, 1H, ArH).



4-(Chloromethyl)-N,N-di(prop-2-ynyl)benzenesulfonamide, **13**. The compound was prepared using a similar procedure as for **11**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (t, J = 2.4 Hz, C≡C**H**, 2H), 4.17 (d, J = 2.4 Hz, C**H**$_2$C≡CH, 4H), 4.61 (s, C**H**$_2$Cl, 2H), 7.52 (d, J= 6.4 Hz, Ar-H, 2H), 7.82 (d, J= 6.4 Hz, Ar-H, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.4 (s, **C**H$_2$C≡CH, 2C), 45.1 (s, **C**H$_2$Cl, 1C), 74.4 (s, C≡**C**H, 2C), 76.1 (s, **C**≡CH, 2C), 129.2 (s, Ar-C, 2C), 129.3 (s, Ar-C, 2C), 138.2 (s, **C**CH$_2$Cl, 1C), 142.9 (s, **C**SO$_2$, C).

Syntheses of monofunctional azides

1-Azido-2-(2-methoxyethoxy)ethane, 19. A solution of 1-bromo-2-(2-methoxyethoxy) ethane (12.4 g, 67.8 mmol) and sodium azide (13.2 g, 203 mmol) in water (150 ml) was stirred under reflux for 16 hours. The aqueous phase was extracted with dichloromethane (2 × 200 ml), dried with $MgSO_4$ and evaporated to dryness, to give 1**9** as a colorless oil in 87.3% yield. ^{1}H NMR (500MHz, $CDCl_3$): δ = 3.29 (s, C**H**$_3$O, 3H), 3.30 (t, J = 5.2 Hz, C**H**$_2$N$_3$, 2H), 3.44-3.48 (m, CH$_3$OC**H**$_2$, 2H), 3.53-3.60 (m, C**H**$_2$OC**H**$_2$, 4H). ^{13}C NMR (125MHz, $CDCl_3$): δ =50.89 (s, **C**H$_2$N$_3$, 1C), 59.27 (s, **C**H$_3$O, 1C), 70.29 (s, CH$_3$OCH$_2$**C**H$_2$, 1C), 70.84 (s, CH$_3$O**C**H$_2$CH$_2$, 1C), 72.21 (s, **C**H$_2$CH$_2$N$_3$, 1C).

Syntheses of cores

Diprop-2-ynyl piperazine-1,4-dicarboxylate, **22**. To a 4 ml CH_2Cl_2 solution of propargyl chloroformate (237 mg, 2 mmol) was added piperazine 86 mg at 0°C, followed

by dropwise addition of Et_3N. The reaction was then stirred at room temperature for 3 hrs. until LC-MS indicated the completion of the reaction. 5 ml 10% HCl was added, the separated organic phase was then washed with $NaHCO_3$ (sat.), brine, dried with Na_2SO_4. after evaporating the solvent, the crude product was purified by flash chromatography (hexane: ethyl acetate 3:1) and gave **22** as a white solid, yield 220 mg (88%). ^{1}H NMR (600 MHz, [D_6]Acetone): δ = 3.03 (t, J = 2.6 Hz, C≡C**H**, 2H), 3.48 (br, NC_2H_4N, 8H), 4.72 (d, J = 2.6 Hz, C**H**$_2$C≡CH, 4H).^{13}C NMR (150 MHz, [D_6]Acetone): δ = 44.3 (s, NC_2H_4N, 4C), 53.4 (s, **C**H_2C≡CH, 2C), 76.2 (s, CH_2**C**≡CH, 2C), 79.6 (s, C≡**C**H, 2C), 154.9 (s, CO, 2C). m.p. 101-102°C.

2,4,6-Tris(prop-2-ynyloxy)-1,3,5-triazine, **23**. Propargyl alcohol (10 ml) was added slowly to a suspension of cyanuric chloride (2.2 g, 12.1 mmol) in 15 ml THF at room temperature followed by K_2CO_3 (5.2 g, 36.3 mmol). Reaction heated to 60°C overnight. The reaction mixture was filtered. After evaporation of solvent, the residue was dissolved in 80 ml CH_2Cl_2, and washed with dilute citric acid (10%), saturated brine. Dried over $MgSO_4$, evaporated to give **2**3 as white solid in 90% yield. ^{1}H NMR (600 MHz, [D_6]Acetone): δ = 3.13 (t, J = 2.2 Hz, C≡C**H**, 3H), 5.10 (d, J = 2.2 Hz, C**H**$_2$C≡CH, 6H). ^{13}C NMR (150 MHz, [D_6]Acetone): δ = 53.4 (s, **C**H_2C≡CH, 3C), 77.3 (s, CH_2**C**≡CH, 3C), 78.4 (s, C≡**C**H, 3C), 173.5 (s, Ar-C, 3C). m.p. 69-70°C

A Representative Procedure A for the Cu(I) Catalyzed Triazole Ligation Reaction: 2-Chloro- *N,N*-di(prop-2-ynyl)acetamide **12** (300 mg, 1.765 mmol) was mixed with 470 mg (3.529 mmol, 2.00 eq.) of benzyl azide **14**. The mixture was mixed with 2 ml of 1:1

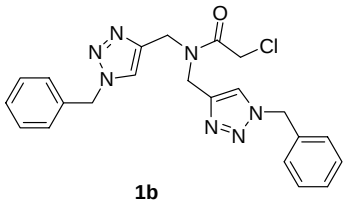
*t*BuOH/H_2O solution. Sodium ascorbate (35 mg, 0.177 mmol, 0.10 eq.) was added as a solid, followed by the addition of $CuSO_4$ (22 mg, 0.089 mmol, 0.05 eq.). The reaction was stirred overnight at room temperature. The white cloudy suspension was diluted with 10 ml H_2O and 1 ml concentrated NH_4OH, stirred for 10 minutes, and then filtered. The resulting filtrate, a white powder, was washed 3 times with 10 ml H_2O and dried to obtain the pure Bn-F-[G-1]-Cl **1b**. (737 mg, 96% yield).

A Representative Procedure B for the Cu(I)-Catalyzed Catalyzed Triazole Ligation Reaction: 300 mg (1.765 mmol) of **12** was mixed with 656 mg (3.529 mmol, 2.00 eq.) of Boc-protected azidoethylamine **16**. The mixture was mixed with 2 ml of 1:1 *t*BuOH/H_2O solution. Sodium ascorbate (35 mg, 0.177 mmol, 0.10 eq.) was added as a solid, followed by the addition of $CuSO_4$ (22 mg, 0.089 mmol, 0.05 eq.). The reaction was stirred overnight at room temperature. The light yellow mixture was diluted with 10 ml H_2O and 1 ml concentrated NH_4OH, stirred for 10 minutes and extracted 3 times with 30 ml portions of EtOAc. The organic layer was washed 2 times with saturated NaCl, dried over $MgSO_4$, and evaporated to yield pure product Boc-F-[G-1]-Cl, **1c** (898 mg, 94% yield).

A Representative Procedure for the Conversion of Dendritic Chlorides to Azides: 500 mg (1.36 mmol) of **1a** was dissolved in 4 ml acetone/water (4:1). NaN_3 (132 mg, 2.04 mmol, 1.5 eq.) was added, and the mixture was heated to 60°C for 1 hour. The mixture is cooled to room temperature, acetone evaporated, diluted with 10 ml H_2O, and extracted 3 times with EtOAc. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated. *t*Bu-F-[G-1]-N_3 **2a** was obtained as a white solid (490 mg, 96%).

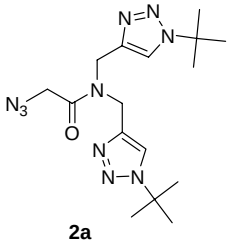
General Procedure for Non-aqueous Click Chemistry Catalyzed by $Cu(PPh_3)_3Br$. A solution of 3,5-bis(propargyloxy)benzyl chloride, **11**, (234 mg, 1.00 mmol), benzyl azide, **4**, (266 mg, 2.00 mmol), N,N-diisopropylethylamine (48 mg, 0.37 mmol) and $Cu(PPh_3)_3Br$ (55 mg, 0.12 mmol) in tetrahydrofuran (5 ml) was submitted to microwave irradiation at 140°C (nominal temperature) for 5 minutes. The crude product was purified by filtering through a silica plug eluting with a 9:1 mixture of dichloromethane and methanol, to give Bn-B-[G-1]-Cl (**1d**) as a colorless oil (477 mg, 95.5%). ^{1}H NMR (500MHz, $CDCl_3$): δ= 4.62 (s, C**H**$_2$Cl, 2H), 5.06 (s, C**H**$_2$O, 4H), 5.41 (s, C**H**$_2$N, 4H), 6.67 (s, Ar**H**, 3H), 7.21-7.37 (m, Ar**H**, 10H), and 8.23 (s, Ar**H**, 2H).

General Procedure for the Non-Aqueous Synthesis of Dendritic Azides. A mixture of the dendritic chloride **1d** (500 mg, 1.00 mmol) and sodium azide (325 mg, 5.0 mmol) was dissolved in DMSO (5 ml). The reaction was heated at 60°C for 24 h, poured into water (200 ml). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 ml), combined, washed with water (2 x 50 ml) dried over $MgSO_4$, and evaporated to dryness. Purification by filtration through a silica plug, eluting with 10% MeOH:EtOAc, gave the pure azidomethyl derivative **2d**. Yiled : 492 mg, 97.1%. ^{1}H NMR (500MHz, $CDCl_3$): δ = 4.36 (s, C**H**$_2$Cl, 2H), 5.03 (s, C**H**$_2$O, 4H), 5.44 (s, C**H**$_2$N, 4H), 6.63 (d, Ar**H**, 2H), 6.68 (t, Ar**H**, 1H), 7.22-7.35 (m, Ar**H**, 10H), and 8.21 (s, Ar**H**, 2H).



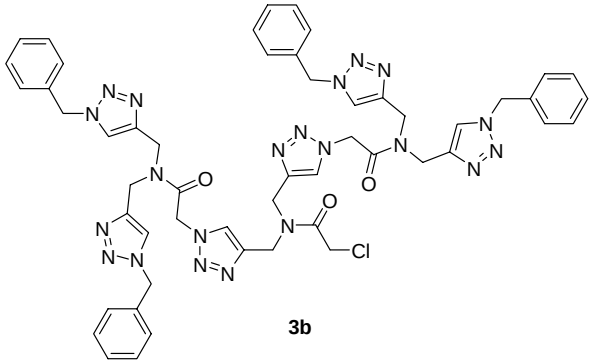
1b

Bn-F-[G-1]-Cl, **1b**: ^{1}H NMR (500MHz, $CDCl_3$): δ = 7.53 (s, 2H), 7.36 (m, 6H), 7.23 (m, 4H), 5.47 (s, 2H), 5.43 (s, 2H), 4.65 (s, 2H), 4.56 (s, 2H), 4.42 (s, 2H). ^{13}C NMR (125MHz, $CDCl_3$,): δ = 167.1, 134.4, 129.4, 129.1, 54.5, 43.1, 41.9. m.p. 111-112 °C.



2a

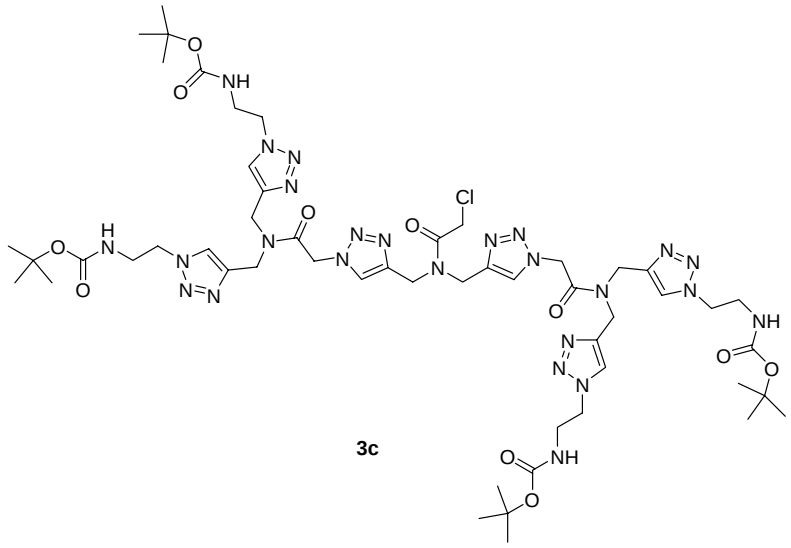
*t*Bu-F-[G-1]-N_3, **2a**: ^{1}H NMR (500MHz, $CDCl_3$): δ = 7.72 (s, 1H), 7.70 (s, 1H), 4.66 (s, 2H), 4.59 (s, 2H), 4.35 (s, 2H), 1.66 (s, 9H), 1.65 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$): δ = 163.8, 142.5, 121.9, 120.9, 60.4, 51.6, 43.1, 41.5, 30.6 ppm. Elemental anal Calcd for $C_{16}H_{26}N_{10}O$ (%): C, 51.32, H, 7.00, N, 37.41. Found: C, 51.21, H, 6.95, N, 36.50. m.p. 113-115°C.



3b

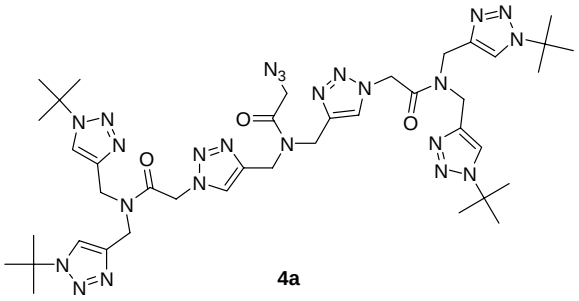
Bn-F-[G-2]-Cl, **3b**: ^{1}H NMR (500MHz, [D6]DMSO): δ = 8.24 (s, 1H), 8.08 (s, 1H), 8.02 (s, 1H), 7.91 (s, 1H), 7.35 (m, 20H), 5.70 (d, 4H), 5.60 (s, 4H), 5.54 (s, 4H), 4.67 (m, 8H), 4.55 (s, 2H), 4.51 (s, 4H) ^{13}C NMR (125MHz, [D6]DMSO): δ = 167.1, 144.1,

137.3, 137.2, 130.1, 129.5, 125.3, 125.2, 54.2, 54.1, 52.3, 44.0, 43.1, 42.6, 32.6. MALDI-TOF: 1076 (MNa^+), PDI: 1.01.



3c

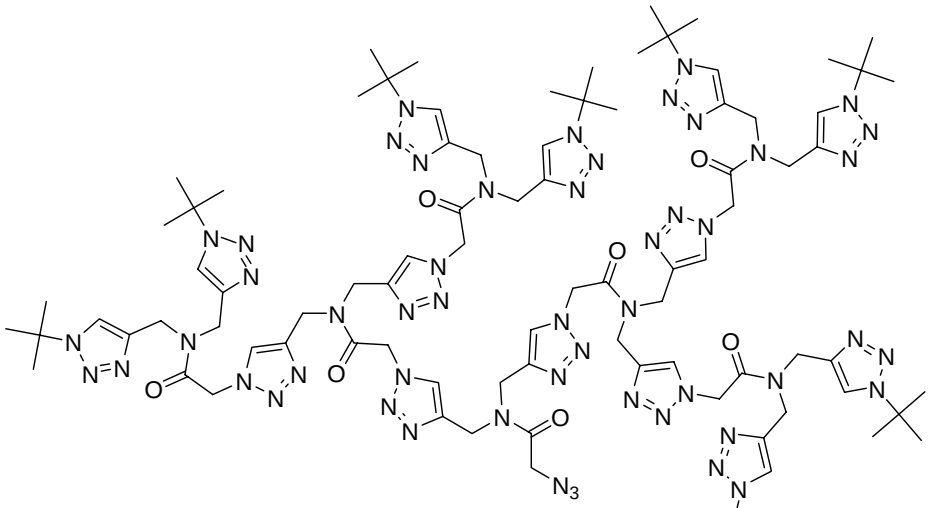
Boc-F-[G-2]-Cl, **3c**: ^{1}H NMR (500MHz, [D6]Acetone): δ = 8.04 (s, 1H), 8.02 (s, 1H), 7.82 (s, 1H), 7.80 (s, 1H), 7.77 (s, 2H), 6.25 (br, 4H), 5.75 (s, 4H), 4.75 (m, 8H), 4.62 (m, 6H), 4.48 (m, 8H), 3.55 (m, 8H), 1.37 (s, 36H). ^{13}C NMR (125MHz, [D6]Acetone): δ = 167.1, 166.9, 166.7, 156.8, 144.2, 143.9, 143.7, 126,2, 124.8, 124.7, 124.5, 79.3, 52.1, 50.7, 50.5, 43.5, 43.3, 42.5, 41.5, 28.7 ppm. MALDI-TOF: 1267 (MH^+), 1289 (MNa^+).



4a

*t*Bu-F-[G-2]-N_3, **4a**: ^{1}H NMR (500MHz, [D6]Acetone): δ = 8.16 (s, 1H), 8.14 (s, 1H), 7.89 (s, 1H), 7.86 (s, 1H), 7.80 (s, 1H), 7.78 (s, 1H), 5.77 (d, 4H), 4.80 (s, 2H), 4.77 (s, 2H), 4.74 (s, 2H), 4.67 (s, 2H), 4.60 (d, 4H), 4.41 (s, 2H), 1.68 (s, 9H), 1.67 (s, 9H), 1.63 (s, 18H). ^{13}C NMR (125MHz, [D6]Acetone): δ = 168.7, 166.8, 166.6, 144.2, 143.8,

143.7, 143.3, 126.2, 126.1, 121.4, 60.6, 60.1, 59.9, 52.1, 51.2, 42.6, 41.8, 41.5, 30.2 ppm. MALDI-FTMS: expect MH^+ 925.5353, found 925.5368.



6a

*t*Bu-F-[G-3]-N_3, **6a**: ^{1}H NMR (600MHz, [D6]DMSO): δ = 8.29 (d, 4H), 8.17 (d, 2H), 8.14 (s, 1H), 8.03 (d, 4H), 8. 00 (s, 1H), 7.96 (d, 2H), 5.76 (m, 12H), 4.77(s, 4H), 4.72 (d, 8H), 4.56 (t, 16H), 4.40(s, 2H), 1.61 (s, 36H), 1.57 (s, 36H). ^{13}C NMR (150MHz, [D6]Acetone): δ =168.2, 166.6, 166.4, 166.3, 166.2, 143.5, 143.4, 143.3, 143.1, 142.7, 125.8, 120.9, 59.5, 59.3, 51.6, 51.5, 50.6, 42.2, 41.9, 41.4, 40.8, 29.5 ppm, 29.1. MALDI-TOF: 2026 (MH^+), 2048 (MNa^+), PDI: 1.005.

Synthesis of dendrimer 7a: 160.2 mg (0.08 mmol) of *t*Bu-F-[G-3]-N_3 **6a** is mixed with 6.4 mg (0.026 mmol) of 2,4,6-tris-prop-2-ynyloxy-[1,3,5]triazine **23**. The mixture is diluted with 0.8 ml of 1:1 tBuOH:H_2O solution. Sodium ascorbate (3.1 mg, 0.016 mmol, 0.20 eq) is added as a solid, followed by the addition of $CuSO_4$ (2mg, 0.008 mmol, 0.10 eq). The reaction is stirred at room temperature and completed overnight as indicated by LC-MS. The reaction mixture is diluted with 5 ml H_2O and 1 ml concentrated

NH_4OH/citrate buffer, stirred for 2 minutes and extracted 3 times with 30 ml portions of $CHCl_3$. The organic layer is washed with brine, dried over $NaSO_4$, and evaporated to yield a while solid, which is then purified by prep-HPLC (pump flow gradient settings-solvent CH_3CN/H_2O; flowing rate: 6.5 ml/min, 0 min, 29% CH_3CN; 2 min, 58 % CH_3CN, 30 min 80% CH_3CN)to give pure dendrimer **7a** 150mg, 90% yield. ^1H NMR (600MHz, [D6]DMSO) δ = 8.26 (m, 16H), 8.20 (s, 3H), 8.15 (d, 6H), 8.00(m, 15H), 7.95 (d, 5H), 5.76 (m, 44H), 5.51(s,6H), 4.74 (m, 44H), 4.55 (m, 44H), 1.59 (dd, 108H), 1.54(dd, 108H). ^{13}C NMR (150 MHz, [D6]Acetone)167.3, 143.9, 143.6, 143.4, 143.1, 126.8, 122.2, 121.9, 119.3, 113.6, 60.7, 60.4, 52.4. 42.7, 41.4, 30.1. MALDI-TOF: calcd for $(C_{276}H_{393}N_{159}O_{24} + Na)^+$: 6345, found: 6345 ± 0.1%, PDI: 1.027.

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