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"Click" Chemistry-Mediated Phenylene-Cored Carborane Dendrimers‖

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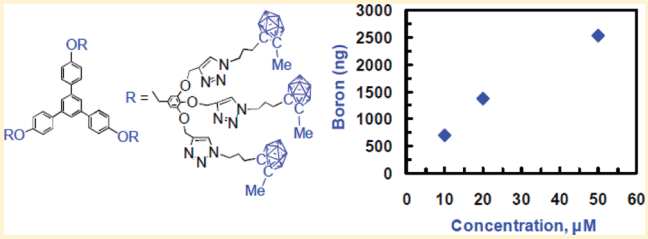
Supporting Information

ABSTRACT: Phenylene-cored small dendrimers containing three to nine peripheral *o*-carborane clusters were synthesized via Cu(I)-catalyzed Huisgen-type azide alkyne cycloaddition reactions. The resulting dendrimers have been characterized by IR and NMR spectroscopy and MALDI-TOF mass spectral analysis. The biological evaluation of branched dendrimer **16** containing nine carborane cages has been carried out using human liver cancer cells (SK-Hep1). Dendrimer **16** was accumulated in the SK-Hep1 cancer cells in a concentration-dependent manner. The highest boron accumulation up to 2540 ng of boron/5 × 10^5 cells was observed at a 50 μM concentration of **16** over a period of 20 h. The high accumulation of **16** into the tumor cell lines indicates that such dendritic boron drug delivery platforms could be possible for application in boron neutron capture therapy in cancer treatment.



INTRODUCTION

Dendrimers and dendritic macromolecules often find applications as drug delivery platforms.[1] Because of the dendrimer's unique branching architecture and high number of surface functional groups, it can carry large payloads of therapeutic molecules. Enhanced cellular uptake of dendrimer-based drug delivery systems has been observed.[2] Because of the leaky vasculature of tumor tissues, macromolecular and dendrimer-based drug delivery systems are preferentially transported to the tumor tissues and accumulate in them in a process known as the enhanced permeability and retention (EPR) effect.[3] Therefore, incorporation of carboranes into dendritic macromolecules could be a viable approach for the delivery of boron to the tumor tissues for successful treatment of cancer via boron neutron capture therapy (BNCT). It has been estimated that a concentration of 30 μg of ^{10}B per gram of tissue is necessary for effective BNCT; this is a relatively high concentration that can be achieved using dendritic molecules containing multiple carborane clusters.[4] Carboranes are relatively easy to functionalize, resistant to biodegradation, and boron-rich in nature.[5,6] Therefore, carboranes are useful in medicinal chemistry as a source of boron and as pharmacophores.[6] Dendritic structures containing multiple carborane clusters have been synthesized by employing various synthetic approaches.[4a,7] In an attempt to employ a new synthetic strategy for the synthesis of carborane-appended dendritic molecules in the present study, we have used a Cu(I)-catalyzed Huisgen-type azide−alkyne "click" cycloaddition reaction[8] for the syntheses of phenylene-cored carborane dendrimers[9] containing three to nine *o*-carborane clusters. The biological uptake of the branched dendrimer **16** that contains the highest boron content with nine *o*-carborane clusters has also been carried out using human hepatocellular carcinoma cells (SK-Hep1).

RESULTS AND DISCUSSION

Synthesis. When commercially available methyl-3,5-dihydroxybenzoate **1** was treated with propargyl bromide in the presence of K_2CO_3, bis(ether) **2** was obtained in quantitative yield. The bromide **4** was obtained in almost quantitative yield by reduction of **2** with $LiAlH_4$, followed by bromination with PBr_3 in CH_2Cl_2 at room temperature (see Scheme 1). The bromide **8** was obtained from methyl-3,4,5-trihydroxybenzoate, **5**, following the same sequence, that is, reacting **5** with propargyl bromide in the presence of K_2CO_3, and further reduction of ester **6** with $LiAlH_4$, followed by bromination with PBr_3 in CH_2Cl_2 at room temperature, as shown in Scheme 1.[10]

After the preparation of alkynyl dendrons, the central cores containing multiple peripheral alkyne moieties from 1,3,5-tris(4-hydroxyphenyl)benzene **9** were synthesized.[11] Whereas the carboranyl azide **13** was prepared according to the literature procedure,[11] the alkyne−azide "click" cycloaddition strategy was employed for the synthesis of carborane-appended dendritic macromolecules.[8] On the other hand, the alkynyl

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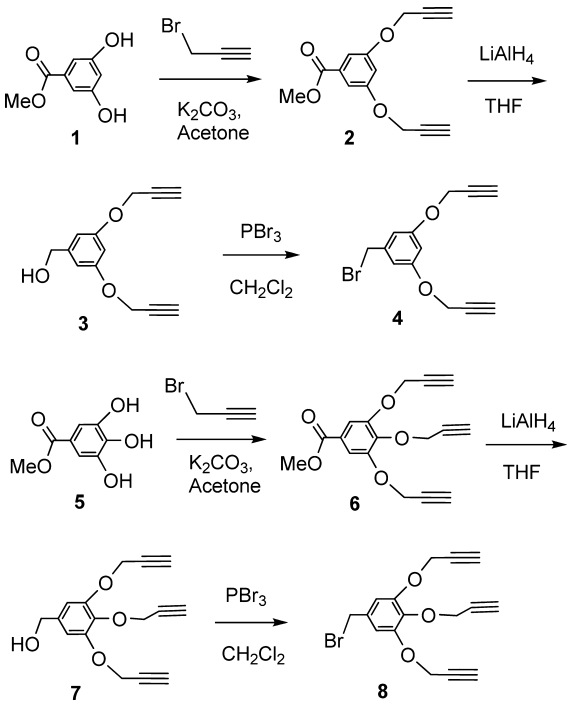
Scheme 1. Synthesis of Alkynyl Dendrons



core **10** was obtained from **9** by reacting with propargyl bromide and K_2CO_3 and was then reacted with carboranyl azide **13** under "click" reaction conditions, leading to **14** in 85% yield. Compound **14** contains three carborane cages appended to the central phenylene core, as shown in Scheme 2.

In a similar methodology, the alkynyl core **11** containing six alkynyl moieties in the periphery was obtained in 88% yield by the reaction between **9** and **4** in the presence of K_2CO_3. The dendrimer **15** was obtained via the "click" cycloaddition reaction between core **11** and carboranyl azide **13**, in 78% yield. As can be seen in Scheme 2, six carborane cages are appended to the central phenylene core. A further branched dendrimer species **16**, appended with nine carborane cages to the central phenylene core, was isolated in 76% yield following the same reaction procedure (see Scheme 2). Because of the presence of nine *o*-carborane clusters, **16** possesses the highest boron content in the series, which is up to 30% of the weight of the molecule. Therefore, the biological evaluation of **16** was warranted.

All compounds were characterized by ^{1}H, ^{13}C, and ^{11}B NMR spectra; IR spectra; and mass spectral analysis where possible. The IR spectra of compounds containing carborane clusters showed strong bands between 2580 and 2586 cm^{-1} corresponding to ν(B−H). The presence of carborane clusters was also evident from the ^{1}H, ^{13}C, and ^{11}B NMR spectra. Confirmatory mass spectral analyses of the compounds were also carried out, in addition to melting point measurements for all solid compounds. Finally, the mass spectral data of all compounds confirmed their identifications. The MALDI-TOF mass spectral data for the carborane-appended dendrimers **14**, **15**, and **16** showed prominent peaks at *m*/*z* 1192.13 (M^+, 100%), 2397.58 (M^+, 100%), and 3345.05 (M^++ 2Na), respectively (see the Supporting Information).

Biological Evaluation of Dendrimer 16. As shown in Figure 1, dendrimer **16** accumulated in the SK-Hep1 human hepatocellular carcinoma cells in a concentration-dependent manner over 20 h. At 10 μM, dendrimer **16** yielded 690 ± 59 ng of B per 5 × 10^5 cells, whereas at 20 and 50 μM, it yielded 1370 ± 244 and 2540 ± 142 ng of B per 5 × 10^5 cells, respectively. Further studies will be required to determine whether compound **16** is taken up into the cell or bound to the cell surface. The detailed description of the growth of the cell culture and preparation of the biodistribution assay and measurements are given in the Experimental Section.

CONCLUSIONS

The Cu(I)-catalyzed azide−alkyne cycloaddition reaction (CuAAC) has been found to be a facile approach for the synthesis of phenylene-cored small dendrimers containing three to nine carborane clusters at the periphery. All three carborane-appended dendrimers were synthesized from the single starting compound 1,3,5-tris(4-hydroxyphenyl)benzene **9** in very good yields. The biological evaluation of dendrimer **16** containing nine carborane cages has shown that the boron has been accumulated in the human liver cancer cells in a concentration-dependent manner. It was found that up to 2540 ng of boron per 5 × 10^5 cells was accumulated over a period of 20 h. The high accumulation of the macromolecular compound into the cancer cells indicates that the dendritic molecules could be the potential boron delivery platforms for BNCT applications.

EXPERIMENTAL SECTION

General Methods. All reactions were generally performed under argon in oven-dried flasks using Schlenk lines. Solvents and reagents were added by syringes. Solvents were dried using standard procedures. Reagents were used as purchased without further purification unless indicated otherwise. Products were all purified by column chromatography on silica gel (70−230 mesh), and yields refer to analytically pure samples. While the ^{1}H NMR spectra were recorded on a Fourier-Transform multinuclear NMR spectrometer at 500 and 300 MHz, the ^{13}C NMR spectra were recorded at 125 and 75 MHz. The chemical shifts are reported relative to tetramethylsilane (TMS) (^{1}H: δ = 0.00 ppm) and $CDCl_3$ (^{13}C: δ = 77.0 ppm). The integrals are in accordance with the assignments, the coupling constants (*J*'s) are all given in hertz, and all of the ^{13}C NMR spectra were proton-decoupled. The ^{11}B NMR spectra were recorded at 160.5 MHz, and the chemical shifts are relative to the BF_3·Et_2O standard. The infrared (IR) spectra of all compounds were recorded on an FT-IR spectrophotometer. Melting points of the solids were measured using a standard apparatus, and the data were uncorrected. Mass spectral analyses were carried out using ES and MALDI-TOF mass spectrometers.

Cell Culture. Human hepatocellular carcinoma cells (SK-Hep1) were chosen because of their well-characterized aggressive growth and accelerated nutrient uptake rates, reflective of highly malignant cancer,[12a] and the emerging interest in pursuing BNCT for hepatocellular carcinoma (HCC).[12b] SK-Hep1 were grown in Dulbecco's Modified Essential Medium (DMEM) supplemented with 2 mM L-glutamine and 10% (v/v) fetal bovine serum (FBS) and were maintained in a humidified atmosphere of 5% CO_2/95% air at 37 °C, as previously described.[12a] Cells were seeded into 12-well culture plates at a concentration of 4 × 10^4 cells per well and allowed to attach and grow to 90% confluence prior to initiation of experiments.

Biological Evaluation of Dendrimer 16. The carborane-appended dendrimer **16** was dissolved in dimethylsulfoxide (DMSO) as a 10 mM stock solution and added to the growth medium to final concentrations of 10, 20, and 50 μM. Control cells received vehicle (DMSO) alone (0.5% final [DMSO]). The medium was aspirated from the cells and replaced with medium containing the compound at 10, 20, and 50 μM, and cells were placed at 37 °C for 20 h. All assays were performed in triplicate for each time point and temperature. After each time period, the medium was aspirated and the cell monolayers were rinsed twice with 1 mL of phosphate-

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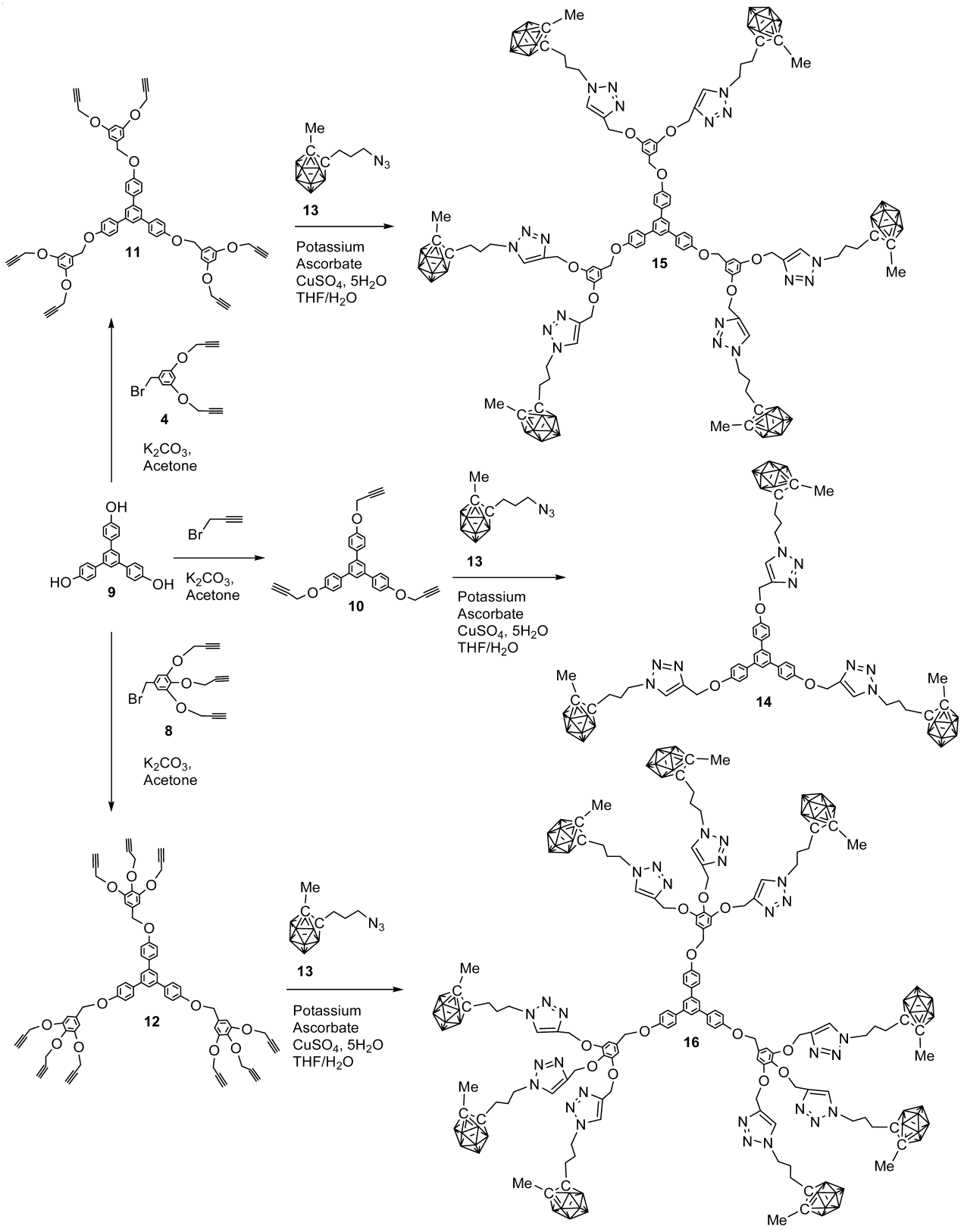
Scheme 2. Synthesis of Dendrimers Containing Three to Nine Carborane Clusters via "Click" Chemistry



buffered saline (PBS). The cells were scraped into 500 μL of PBS with a plastic spatula and triturated 10−15 times with a pipet to yield a single cell suspension. Cell pellets were obtained by centrifugation of the cell suspension at 500*g* for 2 min, followed by aspiration of the supernatant. Cell pellets were stored at −80 °C until assayed for boron content by ICP-MS. Quantitative measurements were performed on a PerkinElmer Sciex Elan 6000 inductively coupled plasma mass spectrometer. Results are reported as nanograms of boron per 5×10^5 cells.

Preparation and Analytical Data of Compounds 4 and 8. Methyl-3,5-dihydroxybenzoate **1** (10.0 g, 59.471 mmol) was dissolved in dry acetone (200 mL). Potassium carbonate (36.11 g, 261.67

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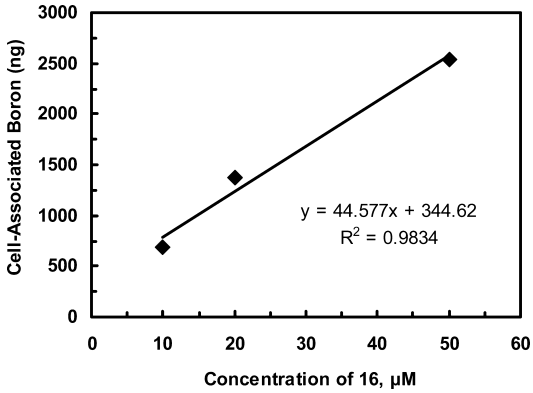

Figure 1. Accumulation of dendrimer **16** to SK-Hep1 human hepatocellular carcinoma cells. Cell pellets were assayed for boron content by inductively coupled plasma mass spectrometry (ICP-MS), as described in the Experimental Section. The values indicated on the *y* axis were the average of triplicate determinations for each concentration and are reported as nanograms of boron per 5×10^5 cells.

mmol) and propargyl bromide (80 wt % in toluene, 19.5 mL) were then added to it. The mixture was refluxed at 80 °C for 20 h, filtered through a silica pad, and was then concentrated. The organic layer was dried over $MgSO_4$ and evaporated. Compound **6** was synthesized by using a similar procedure from methyl-3,4,5-trihydroxybenzoate **5**. Both compounds **2** and **6** were synthesized in quantitative yields and used for further reaction without purification. $LiAlH_4$ (6.21 g, 163.76 mmol) was suspended in dry THF (200 mL) and cooled to 0 °C. A solution of **2** (10.0 g, 40.94 mmol) in 30 mL of dry THF was then added to it at 0 °C. The mixture was stirred at 0 °C for 1 h and then at room temperature for 5 h. $LiAlH_4$ was quenched with dropwise addition of water very carefully, and then the reaction mixture was extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated to get 9.0 g of pure product **3** in quantitative yield. Without purification, this product was used for the next reaction. To the solution of **3** (9.0 g, 41.62 mmol) in dichloromethane (150 mL) was added PBr_3 (4 mL, 41.62 mmol), and the reaction mixture was stirred at room temperature for 15 h. After the reaction was over, water was added to that reaction mixture and extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated to get 11.2 g of pure product **4**. Yield: 96%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.67 (d, 2H, J = 2.0 Hz), 6.58 (t, 1H, J = 2.0 Hz), 4.70 (d, 4H, J = 2.5 Hz), 4.44 (s, 2H), 2.57 (t, 2H, J = 2.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.7, 139.9, 108.7, 102.4, 78.1, 75.8, 56.0, 33.2. ES-MS (m/z): Calcd, 279.13; found, 279.0 (M^+, 100%). Compound **8** was synthesized from **5** by employing a procedure described elsewhere.[10]

General Procedure for Synthesis of Alkynyl Core. 1,3,5-Tris(4-hydroxyphenyl)benzene **9** was solubilized in acetone. To this solution, the alkynyl bromo compound and K_2CO_3 were added, and the reaction mixture was refluxed at 60−70 °C up to 24 h. The mixture was filtered through a cotton plug, and the solvent was evaporated and then purified by silica gel column chromatography.

10: 1,3,5-Tris(4-hydroxyphenyl)benzene **9** (140 mg, 0.395 mmol), acetone (20 mL), propargyl bromide (0.3 mL), and K_2CO_3 (327 mg, 2.37 mmol). Purification: Silicagel column chromatography using 20−30% EtOAc in hexane. Pure product: 176 mg. Yield: 95%. mp: 120−122 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (s, 3H), 7.66 (d, 6H, J = 8.0 Hz), 7.11 (d, 6H, J = 8.0 Hz), 4.78 (s, 6H), 2.58 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.2, 141.7, 134.6, 128.3, 124.0, 115.2, 78.5, 75.6, 55.9. IR (KBr): 3283, 2918, 2114, 1672, 1606, 1510, 1444, 1222, 1037, 921, 834 cm^{-1}. ES-MS (m/z): calcd, 468.5; found, 469.2 (M^+ + 1, 100%).

11: 1,3,5-Tris(4-hydroxyphenyl)benzene **9** (140 mg, 0.395 mmol), acetone (20 mL), bromide **4** (661 mg, 2.37 mmol), and K_2CO_3 (327 mg, 2.37 mmol). Purification: Silicagel column chromatography using 20−30% EtOAc in hexane. Pure product: 300 mg. Yield: 80%. Colorless solid. mp: 55−56 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (s, 3H), 7.63 (d, 6H, J = 8.65 Hz), 7.08 (d, 6H, J = 8.65 Hz), 6.76 (d, 6H, J = 1.75 Hz), 6.62 (d, 3H, J = 1.85 Hz), 5.10 (s, 6H), 4.71 (d, 12H, J = 2.20 Hz), 2.55 (t, 6H, J = 2.10 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.9, 158.3, 141.7, 139.6, 134.1, 128.4, 123.9, 115.2, 106.8, 101.7, 78.3, 75.7, 69.8, 55.9. IR (KBr): 3286, 2920, 2867, 2121, 1595, 1510, 1449, 1385, 1292, 1151, 1061, 818 cm^{-1}. MALDI-TOF-MS (m/z): calcd, 949.05; found, 948.87 (M^+, 100%).

12: 1,3,5-Tris(4-hydroxyphenyl)benzene **9** (300 mg, 0.8465 mmol), acetone (50 mL), bromide **8** (1.7 g, 5.07 mmol), and K_2CO_3 (700 mg, 5.07 mmol). Purification: Silicagel column chromatography using 50−60% EtOAc in hexane. Pure product: 840 mg. Yield: 89%. Sticky liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68 (s, 3H), 7.65 (d, 6H, J = 8.70 Hz), 7.10 (d, 6H, J = 8.75 Hz), 6.90 (s, 6H), 5.10 (s, 6H), 4.81−4.77 (m, 18H), 2.52−2.50 (m, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.3, 151.7, 141.8, 136.9, 134.1, 133.1, 128.3, 123.9, 115.2, 107.8, 79.1, 78.4, 75.9, 75.2, 69.9, 60.3, 57.1. IR (neat): 3286, 2926, 2868, 2121, 1606, 1509, 1444, 1386, 1230, 1180, 1110, 1005, 828 cm^{-1}. MALDI-TOF-MS (m/z): calcd, 1111.19; found, 1134.4 (M^+ + Na).

General Procedure for Synthesis of Click Dendrimer. The alkynyl core and the carboranyl azide **13** were dissolved in THF. $CuSO_4$, $5H_2O$, potassium ascorbate, and water were added to it. The reaction mixture was stirred at room temperature for 16 h. The mixture was then extracted with dichloromethane, and the organic layer was washed with aqueous ammonium chloride and water and dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography.

14: The alkynyl core **10** (50 mg, 0.106 mmol), carboranyl azide **13** (154 mg, 0.640 mmol), THF (3 mL), $CuSO_4$, $5H_2O$ (319.71 mg, 1.280 mmol), potassium ascorbate (548.63 mg, 2.561 mmol), and water (3 mL). Purification: silica gel column chromatography using 50−90% EtOAc in hexane. Pure product: 108 mg. Yield: 85%. mp > 230 °C (dec). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (s, 3H), 7.66 (s, 3H), 7.64 (d, 6H, J = 8.7 Hz), 7.10 (d, 6H, J = 8.7 Hz), 5.31 (s, 6H), 4.43 (s, 6H), 2.23 (s, 6H), 2.19 (s, 6H), 1.92 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.8, 144.6, 141.6, 134.3, 128.4, 123.9, 122.6, 115.1, 76.5, 75.0, 62.0, 49.2, 32.0, 29.9, 23.0. IR (KBr): 3140, 2944, 2580, 1607, 1510, 1467, 1232, 828 cm^{-1}. ^{11}B NMR (proton-decoupled): −4.0, −5.33, −9.50, −10.20. MALDI-TOF-MS (m/z): calcd, 1192.57; found, 1192.13 (M^+, 100%).

15: The alkynyl core **11** (70 mg, 0.073 mmol), carboranyl azide **13** (213 mg, 0.885 mmol), THF (4 mL), $CuSO_4$, $5H_2O$ (437 mg, 1.752 mmol), potassium ascorbate (750 mg, 3.504 mmol), and water (4 mL). Purification: silica gel column chromatography using 50−90% EtOAc in hexane. Pure product: 136 mg. Yield: 78%. Colorless solid. mp > 260 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68 (s, 3H), 7.65 (s, 3H), 7.63 (s, 9H), 7.07 (d, 6H, J = 8.50 Hz), 6.75 (s, 6H), 6.61 (s, 3H), 5.23 (s, 6H), 5.10 (s, 12H), 4.39 (s, 12H), 2.23−2.21 (m, 36H), 1.92 (s, 18H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.5, 158.3, 144.3, 141.7, 139.8, 133.9, 128.3, 123.7, 122.7, 115.2, 106.5, 101.4, 76.4, 75.0, 69.7, 61.9, 49.2, 32.0, 29.9, 23.0. ^{11}B NMR (proton-decoupled): −3.99, −5.61, −9.65, −10.38. IR (KBr): 2961, 2927, 2586, 2361, 2099, 1710, 1591, 1454, 1384, 1261, 1161, 1041, 803 cm^{-1}. MALDI-TOF-MS (m/z): calcd, 2397.12; found, 2397.58 (M^+, 100%).

16: The alkynyl core **12** (125 mg, 0.112 mmol), carboranyl azide **13** (489 mg, 2.030 mmol), THF (6 mL), $CuSO_4$, $5H_2O$ (1.01 g, 4.05 mmol), potassium ascorbate (1.73 g, 8.114 mmol), and water (6 mL). Purification: silica gel column chromatography using 20% methanol in ethyl acetate. Pure product: 280 mg. Yield: 76%. Colorless solid. mp > 230 °C. ^{1}H NMR (DMSO-d^6, 500 MHz): δ 8.26 (s, 3H), 8.14 (s, 6H), 7.82 (d, 6H, J = 8.50 Hz), 7.16 (d, 6H, J = 8.50 Hz), 7.0 (s, 9H), 5.19 (s, 6H), 4.44−4.37 (m, 18H), 4.0 (s, 18H), 2.51 (s, 18H), 2.36−2.29 (m, 18H), 1.98 (s, 27H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.6, 152.2, 144.1, 143.3, 141.5, 136.9, 133.3, 133.2, 128.6, 124.9, 115.7, 107.8, 78.7, 76.6, 69.8, 66.0, 62.6, 48.8, 31.5, 30.3, 22.8. ^{11}B NMR (proton-decoupled): −4.85, −6.23, −9.89, −10.92. IR (KBr): 3139, 2973, 2874, 2583, 1731, 1641, 1511, 1433, 1385, 1223, 1106, 1046,

827 cm^{-1}. MALDI-TOF-MS (m/z): calcd, 3299.6; found, 3345.05 (M^+ + 2Na).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving NMR spectra and MALDI-TOF spectra of compounds prepared in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

[∥]Dedicated to the memory of Professor F. Gordon A. Stone.

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