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“Click” Star-Shaped and Dendritic PEGylated Gold Nanoparticle-Carborane Assemblies

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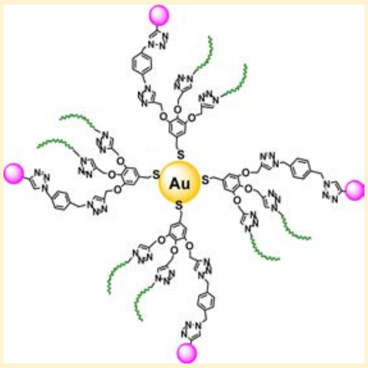
S *Supporting Information*

ABSTRACT: Carboranes that have a high boron content are key materials for boron neutron capture therapy (BNCT), while PEGylated gold nanoparticles (AuNPs) are also most useful in various aspects of nanomedicine including photothermotherapy, imaging and drug vectorization. Therefore, methods to assemble these key components have been investigated for the first time. Strategies and results are delineated in this article, and the nanomaterials have been characterized using transmission electron microscopy (TEM), dynamic light scattering (DLS), UV−vis., mass and multinuclear NMR data. A series of well-defined water-soluble bifunctional AuNPs containing carborane and polyethylene glycol (PEG) were synthesized through either two-step Cu(I)-catalyzed azide−alkyne cycloaddition CuAAC (“click”) reactions at the periphery of azido-terminated AuNPs in the presence of the efficient catalyst [$\mathrm{Cu^{I}tren(CH_2Ph)_6}$][Br] or simply by direct stabilization of AuNPs using a tris-carborane thiol dendron or a hybrid dendron containing both PEG and carborane.



■ INTRODUCTION

Carborane chemistry has been developed into nanomaterials during the past few decades because of the robustness and physicochemical properties of the carborane frameworks. Because of the structure of 12-vertex icosahedral $C_2B_{10}H_{12}$, this carborane possesses high boron content and stability to catabolism, can increase thermal and chemical stability of complexes, and provides the possibility of use as building block and template in material science,[1] nanomedicine,[2] and synthesis of highly stable dendrimers, polymers, or other supramolecules.[3] It has been demonstrated that the use of carborane can enhance hydrophobic interactions between pharmaceuticals and their receptors and increase the in vivo stability of pharmaceuticals. Gold nanoparticles (AuNPs) have been among the most extensively studied nanomaterials over a century because of their remarkable optical properties related to their plasmon absorption and are now heavily utilized in chemistry, biology, engineering, and medicine because of their unique optical, chemical, electrical, and catalytic properties.[4] AuNPs have attracted the interest of scientists especially in the areas of photothermal therapy, biosensing, imaging, and drug delivery.[5] Therefore, incorporation of carboranes into AuNPs could be a viable approach for the delivery of boron to the tumor tissues and cancer treatment through boron neutron capture therapy (BNCT). BNCT is a binary radiation therapy for the treatment of cancer that is based on the capture of thermal neutrons by ^{10}B nuclei which have a large capture cross section, and these ^{10}B nuclei can be selectively delivered to tumor cells.[6] Polyethylene glycol (PEG) has been extensively used as modifying agent in many biomedical products because of its nontoxicity, water-solubility, and the enhanced permeability and retention (EPR) effect. The PEGylated NPs can postpone or prevent the rapid clearance by the reticular-endothelium system (RES). Therefore, drugs carried by PEGylated AuNPs can have a prolonged circulation time in blood.[7] Thus, the PEGylated AuNPs have been widely utilized in materials science,[8] biological and pharmaceutical applications.[9] The AuNPs containing both carborane and PEG could be regarded as valuable nanomaterials with useful optical properties, increased water-solubility and biocompatibility, and further suitable for biomedical studies. The Huisgen-type Cu(I)-catalyzed azide−alkyne cycloaddition (CuAAC) reaction (“click” reaction) is the most efficient strategy to assemble a 1,2,3-triazole ring linking two molecular fragments together because of its atom economy, regioselectivity, wide substrate scope, and mild reaction conditions.[10] Moreover, the triazole group is completely biocompatible. The “click” modification of AuNPs has been a challenging topic of research in the past few years because of serious aggregation of AuNPs that induced low yield.[11] Recently, an efficient “click” catalyst [$\mathrm{Cu^{I}(CH_2Ph)_6tren}$][Br] (abbreviated $\mathrm{Cu^{I}}$-tren), has been reported, and only 7% of this

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catalyst is needed in toluene solution for the fabrication of sterically demanding "click" dendrimers.[12] Subsequently, this Cu^I-tren catalyst has also been successfully employed for the "click" functionalization of AuNPs. High yields were obtained using this functionalization method, and the aggregation was largely avoided because of the dendritic effect around the catalytically active metal center.[13]

With these tools in hands, it was desirable to investigate the possibility of synthesis, stability, and physicochemical behavior of assemblies between PEGylated AuNPs and carboranes using thiolate Au-ligands and "click" linkages. In this work, we have investigated the synthesis of bifunctional AuNPs containing both PEG and ortho-carborane units through "click" reactions between azido-terminated AuNPs and alkyne ligands in the presence of the Cu^I-tren catalyst. We have also examined the direct AuNP formation and stabilization using a tris-carborane thiol dendron or a hybrid thiol dendron containing one PEG branch and two carborane branches. The morphologies of the core size, hydrodynamic diameter, and polydispersity of the carborane-functionalized AuNPs have been determined by transmission electron microscopy (TEM) and dynamic light scattering (DLS), while the distribution of various functional groups on AuNPs have been verified by ^{1}H NMR, and the functional properties of AuNPs were further characterized by infrared (IR) spectroscopy.

■ RESULTS AND DISCUSSION

Synthesis of Azido-Terminated AuNPs. Dodecanethiolate-AuNPs (**AuNPs-1**) were synthesized through the typical Brust−Schiffrin "two-phases" method,[14] and the prefunctionalization of **AuNPs-1** was carried out by a classical ligand-substitution reaction. Briefly, **AuNPs-1** was dissolved in CH_2Cl_2 solution containing certain amount of undecanethiol, stirred under N_2 at 25 °C for a few days, during which time the ligand-replacement occurred on the surface of the AuNPs (Scheme 1). Three azido-terminated AuNPs (**AuNPs-2a**, **AuNPs-2b**, **AuNPs-2c**) with different dodecanethiolate:azidoundecanethiolate ligand ratio were obtained under different ligand-substitution conditions (Table 1): **AuNPs-2b** that contains 33% azido ligands on the surface was obtained with 1:1 ratio of azidoundecanethiol to dodecanethiolate ligands within 2 days. When the reaction time was prolonged to 5 days, **AuNPs-2a** containing 50% azido ligands was obtained under the same ligand ratio. With the purpose of introducing a higher % of azido groups, the ligand-exchange reaction was repeated 3 times with a ligand ratio of 2: 1, and the reaction time was 3 days for each time. This procedure yielded **AuNPs-2c** with 80% azido ligands in 80% yield, which was a little bit lower than the yield of the single substitution to obtain **AuNPs-2a** (90%) and **AuNP-2b** (>95%), because of increase of aggregation in the process of extended multiple-step ligand-substitution reaction.

Table 1. Ligand-Substitution Reaction of Azido-Terminated AuNPs-2a, AuNPs-2b, and AuNPs-2c

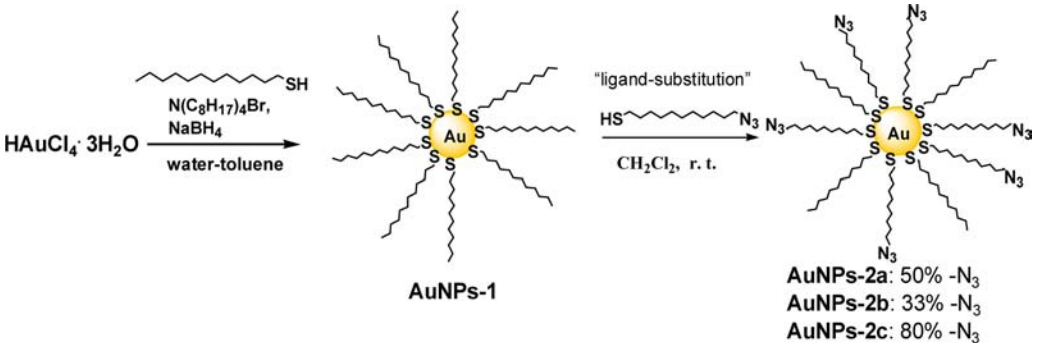
azido-AuNPs	percentage (-N_3)	reaction time (day)	feed ratio[a] (azido/alkane)	yield (%)
AuNPs-2a	50%	5	1: 1	90
AuNPs-2b	33%	2	1: 1	95
AuNPs-2c	80%	3 + 3 + 3	2: 1[b]	80

[a] Ligand ratio of azidoundecanethiol to dodecanethiolate ligand bound to AuNPs. [b] The feed ratio was 2: 1 in each time.

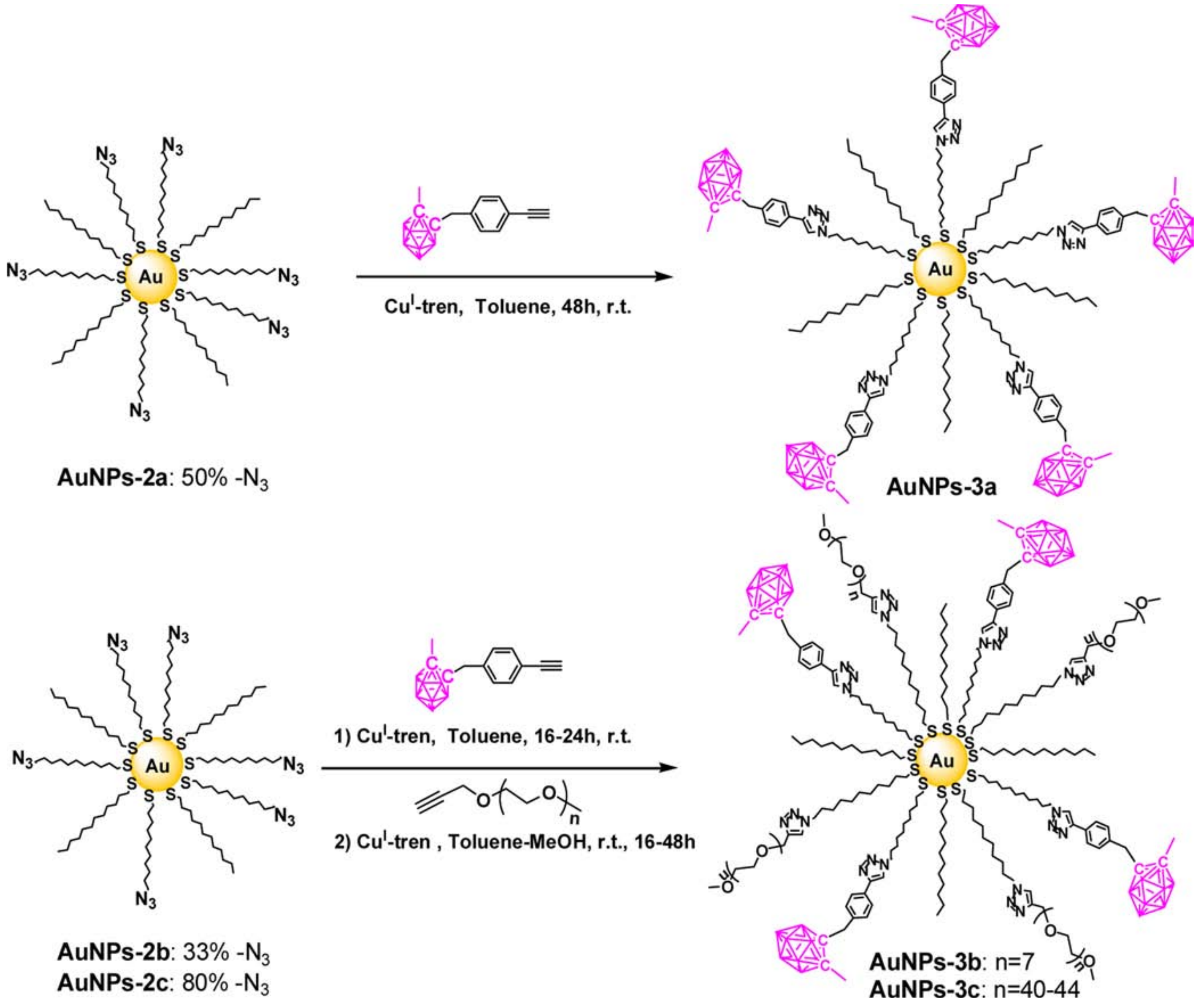
The presence of azido group in the AuNPs has been confirmed by ^{1}H NMR (Supporting Information, Figure S1) and IR (Supporting Information, Figure S3) spectra. The spectra also indicated the percentage of azido-functional group on AuNPs, obtained through ligand substitution, depending upon both the reaction time and the feed ratio of the two different ligands.

"Click" Functionalization of AuNPs with Carborane and (or) PEG. The carborane-functionalized **AuNP-3a** was first obtained through a "click" reaction in the presence of the homogeneous $[Cu^I(CH_2Ph)_6tren][Br]$ catalyst (10%) in toluene solution, while an excess carborane alkyne *per* azido group (2: 1) was employed. The reaction was monitored by IR spectra until the ν_{N3} band had disappeared. The excess carborane and catalyst were removed by washing the AuNPs with ethanol and diethyl ether successively. **AuNP-3a** containing 50% carborane groups was obtained in 40% yield after removal of a precipitate of Au black by filtration. Subsequent stepwise "click" reactions were carried out for the synthesis of bifunctional AuNPs containing both PEG and carborane. In this method, azido-terminated AuNPs were reacted with carborane-alkyne and PEG (M_w 350 or 2000)-alkyne successively in the presence of 10% Cu^I-tren catalyst (Scheme 2). When **AuNPs-2b**, containing 33% azido ligands, were used as starting material, **AuNP-3b** was obtained with 17% carborane and 17% PEG350 ligands involving 4:1:1 molar ratio of dodecanethiolate ligands, carborane, and PEG350, respectively (see Supporting Information, Figure S7). The yield of **AuNP-3b** was increased up to 65% with the decrease in functional group, when compared to that of **AuNP-3a**. With the purpose of obtaining water-soluble carborane-AuNPs, PEG2000-alkyne and

Scheme 1. Synthesis of AuNPs-1 by the Brust−Schiffrin Method, and the Ligand-Exchange Synthesis of Azido-Terminated AuNPs



Scheme 2. Schematic Illustration of the “Click” Functionalization of AuNPs



AuNPs-2c containing a large percentage of azido groups were employed. Ultimately, water-soluble **AuNPs-3c** was obtained with the surface capped by 17% carborane, 66% PEG ligands, and 17% dodecanethiolate ligands. The molar ratio of dodecanethiolate-ligands: carborane: PEG350 on the surface of AuNPs-**3c** was 1: 1: 4, as confirmed by ^{1}H NMR spectra (Supporting Information, Figure S10). In this case, the hydrophilic PEG ligand properties led to improved water solubility and biocompatibility of **AuNPs-3c**. Another advantage of introducing a large percentage of PEG2000 was that the “click” reaction did not decrease the yield significantly, despite PEG being a longer chain and present in high proportion. This attributed to the flexibility of PEG in solution. The coating of PEG2000 onto the Au surface isolated the AuNPs from each other, which inhibited the AuNPs aggregation.

The UV−vis spectrum of **AuNPs-3c**, in Figure 1, exhibits a plasmon band at 524 nm, while its TEM image indicates the average core diameter of 4.75 nm. The hydrodynamic diameter of **AuNPs-3c** in aqueous solution, provided by DLS measurement, is 10.2 nm. The complete disappearance of the ν_{N3} band at 2090.9 cm^{-1} in the IR spectrum was evident after the second set of “click” reactions, when compared to the strong ν_{N3} peak of **AuNP-2c** (Figure 2). IR spectrum of **AuNPs-3c** also shows clearly the σ_{B-H} stretching vibration at 2580.84 cm^{-1}. The core size determined using TEM images for **AuNPs-3a**, **AuNPs-3b**, and **AuNPs-3c** are similar to those recorded before the “click” reaction (Supporting Information), which demonstrated that the “click” reactions with AuNPs have no adverse effects on the polydispersity, despite the reaction yields being decreased because of aggregation. The DLS measurement showed the hydrodynamic diameters of **AuNPs-3a** (15.6 nm) and **AuNPs-3b** (15.4 nm), but the hydrodynamic diameter of **AuNP-3c** was much smaller (10.2 nm), presumably because of the effect of suppressing long linear PEG2000 branches during assembly among individual AuNPs. The DLS size-distribution histograms of **AuNPs-3a**, **AuNPs-3b**, and **AuNPs-3c** displayed narrow polydispersity of the “clicked” AuNPs, as TEM indicated.

Direct Synthesis of Bifunctional AuNPs. The tris-carborane thioacetate dendron **3**, a precursor for dendritic AuNPs, was synthesized by “click” reaction between the tris-alkyne dendron **1** and carborane-azide **2** in the presence of copper sulfate and sodium ascorbate (Scheme 3a). The hybrid thioacetate dendron **4**, containing one carborane branch and two PEG branches, was synthesized by “click” reaction between

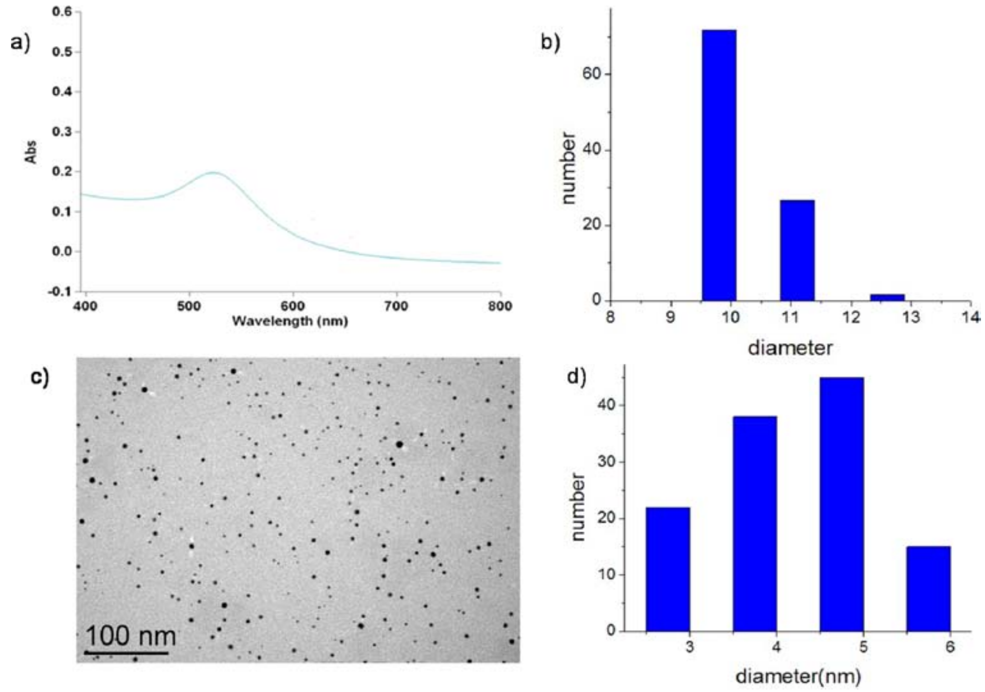


Figure 1. (a) UV–visible spectrum, (b) DLS size-distribution histogram (measured in water solution), (c) TEM image, and (d) the core size-distribution histogram of **AuNPs-3c**.

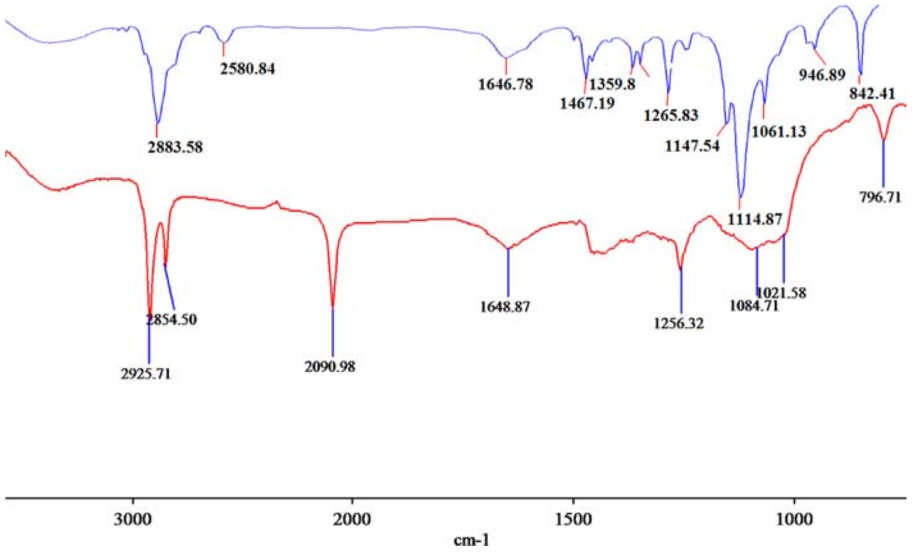
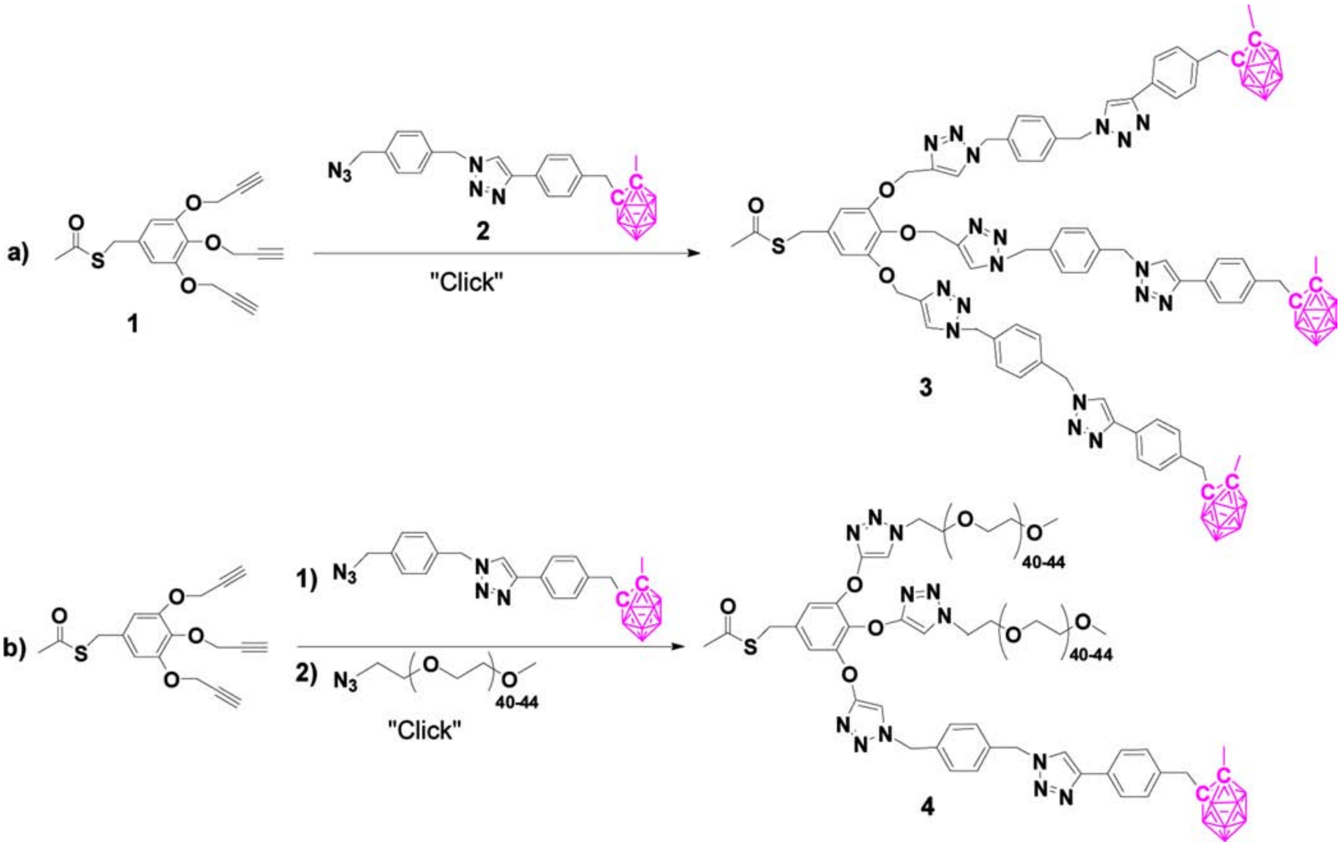


Figure 2. IR spectrum of **AuNPs-3c** (top, blue curve) compared to that of **AuNP-2c** (bottom, red curve). It shows the complete disappearance of the ν_{N3} band at 2090.9 cm^{-1} after "click" reactions, and the appearance of the σ_{B-H} stretching vibration at 2580.8 cm^{-1}.

the dendron **1** and only 1 equiv of compound **2** and then further "click" reaction with 2 equiv of PEG2000-azide (Scheme 3b). Interestingly, the direct synthesis does not undergo any aggregation, contrary to the multistep synthesis. With the direct-synthetic approach, the tris-carborane thiol dendron **5** was obtained first from dendron **3**, in situ, and the **AuNPs-4a** stabilized by bifunctional PEG550-SH mixed-ligands were subsequently synthesized through a simple one-step reduction procedure (Scheme 4a).

The direct synthesis involved 1: 1: 1 molar ratio of tris-carborane thiol dendron **5**, PEG550 thiol ligand, and $HAuCl_4$ $3H_2O$, respectively. After purification, **AuNPs-4a** was shown to contain 20% dendron **5** and 80% PEG550 thiolate ligands at the periphery and, consequently, the ratio of carborane group to PEG ligand was found to be 3: 4 (Supporting Information, Figure S26). An increase in the number of carborane moieties was accomplished by utilizing the tris-carborane dendron **5** (Scheme 4a). With the purpose of precisely controlling the ratio of two functional groups (herein, the PEG/carborane ratio), the hybrid tris-dendron **6**, obtained from dendron **4** in situ, was used for direct AuNP synthesis. The water-soluble **AuNPs-4b** capped with dendron **6** was synthesized in methanol solution through a simple reduction of Au(III) by $NaBH_4$ (Scheme 4b). The ratio of carborane to PEG in **AuNPs-4b** was exactly the same as with dendron **4**, revealing that the invaluable advantage of this strategy is the control of relative amounts of two functional groups. The AuNPs that were obtained by this reaction essentially preserve the properties of

Scheme 3. “Click” Syntheses of Carborane-Containing Dendrons[a]



[a]Copper sulphate and sodium ascorbate were employed stoichiometrially in each case.

the dendron. The TEM images of **AuNPs-4a** and **AuNPs-4b** are presented in Figure 3 showing the average core diameter of 3.43 and 7.59 nm, respectively. The size-distribution histograms showed that **AuNPs-4a** and **AuNPs-4b** are quite monodisperse.

The average core diameter of **AuNPs-4b** is larger (7.59 nm, Figure 3b) than those of other AuNPs, described above, which presumably results from slower thiol-gold interactions due to dendronic bulk inhibition around the thiol group. The hydrodynamic diameters of **AuNPs-4a** and **AuNPs-4b** were also measured in aqueous solution by DLS analysis. The results indicate that the hydrodynamic diameters of **AuNPs-4a** and **AuNPs-4b** are 19 and 14.5 nm, respectively.

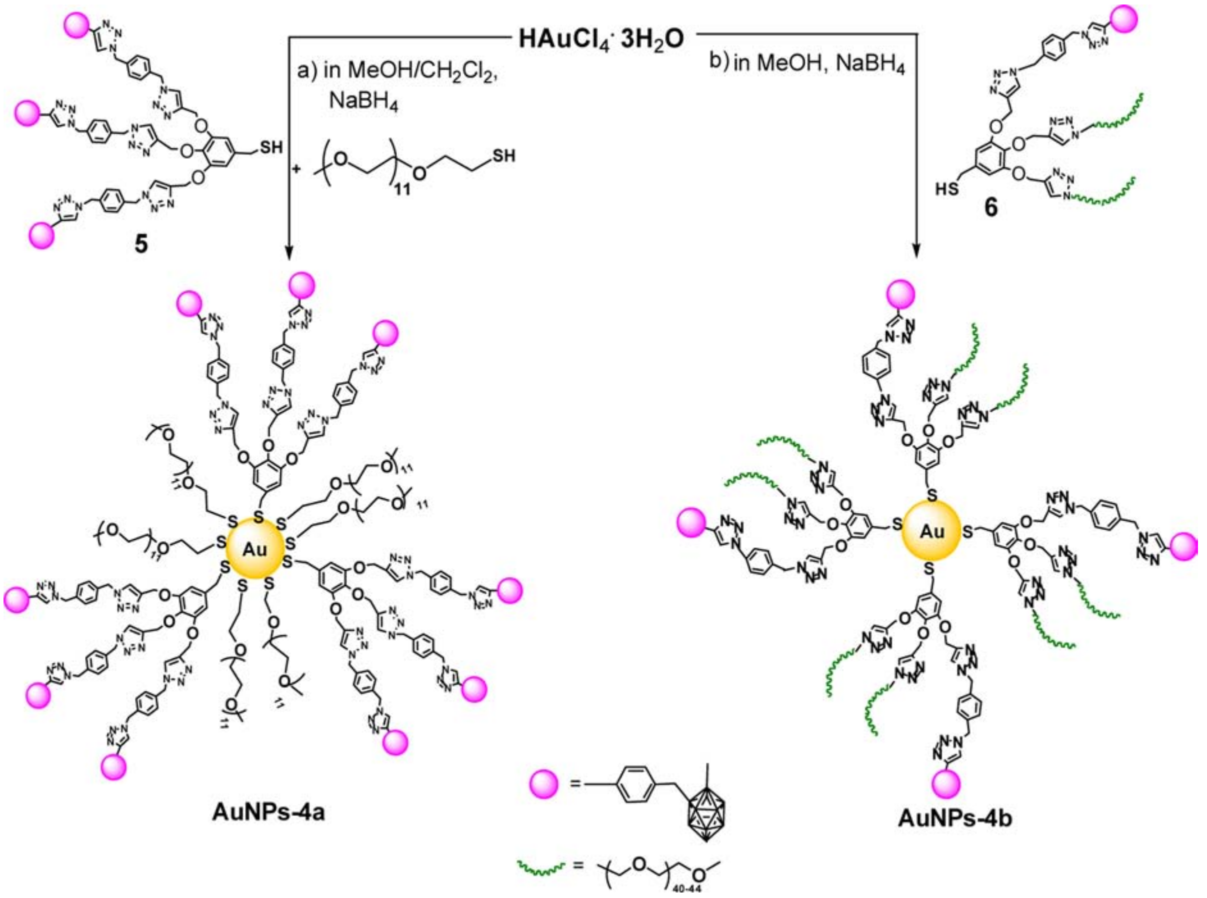
The FT-IR spectra of dendron **4** and **AuNPs-4b** are shown in Figure 4. The characteristic band due to the strong stretching mode of vibration of the C−O−C bond ($\sigma_{\text{C−O−C}}$) in the PEG chain at 1105 ± 10 cm^{-1} is the dominating feature in both spectra. The secondary strong and broad absorption around 2580 ± 10 cm^{-1} is due to $\sigma_{\text{B−H}}$ stretching vibration,[15] that indicates the existence of the carborane cluster structure. The comparison of the FT-IR spectra of dendron **4** and **AuNP-4b** indicates a subsequent bonding of the carborane dendron to the AuNPs with a weak $\sigma_{\text{B−H}}$ vibration as a result of shielding of the carborane absorptions by nearby AuNPs. A similar characteristic $\sigma_{\text{B−H}}$ signal was also observed in the FT-IR spectra of other carborane-containing molecules (Supporting Information).

According to the core size determined by TEM and the ligand ratio estimated by ^{1}H NMR, the amounts of carborane units and of PEG ligand *per* AuNP are calculated using Leff’s method based on both theoretical and experimental data.[16] As shown in Table 2, each AuNP carries more than 50 carborane units, and particularly, **AuNPs-4b** with more than 220 carborane units at the periphery could potentially find applications in BNCT for cancer treatment.

■ CONCLUSION

The present study showed two feasible approaches to synthesize the AuNPs-carborane assemblies. The two-step “click” modification of azido-terminated AuNPs in the presence of the $[\text{Cu}^{\text{I}}(\text{CH}_2\text{Ph})_6\text{tren}][\text{Br}]$ catalyst gives bifunctional AuNPs in good yield, and the core size remains unchanged during the “click” reaction. The ratio of carborane to PEG functional ligands can be controlled by the feed ratio. Water-soluble AuNPs were obtained when a large percentage of long chain PEG (M_w 2000) was employed. With this method, bifunctional AuNPs can be obtained with a narrow polydispersity. In the direct synthesis method, the mono- or bi- functional thiol dendron was introduced onto the surface of AuNPs through a simple reduction reaction. This direct synthesis method would be of great interest for multifunctionalization of AuNPs, because the prefunctionalization of a dendron can be efficiently achieved to avoid multistep AuNP synthesis. Remarkably, the hybrid dendron-stabilized AuNPs have an invariable ratio of two functional groups, and this ratio is thus exactly the same as that of the dendron. Furthermore, no aggregation of AuNPs occurred in this method. We conclude that the direct synthesis method would facilitate the procedure of AuNP functionalization. Thus, a series of well-designed bifunctional

Scheme 4. Schematic Illustration of Direct Synthesis of (a) AuNPs-4a and (b) AuNPs-4b



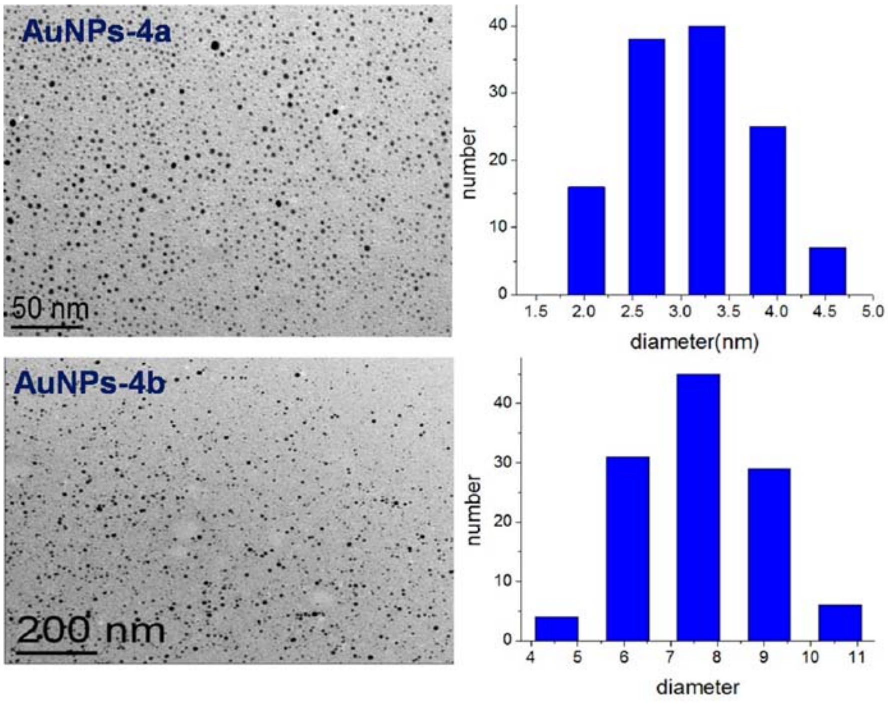


Figure 3. TEM images and diameter histogram distribution of **AuNPs-4a** and **AuNPs-4b**, respectively.

AuNPs containing carborane and PEG ligands with core sizes in the range of 3.42 to 7.59 nm were synthesized and fully characterized. The bifunctional AuNPs, in particular the water-soluble AuNPs such as **AuNPs-3c**, **AuNPs-4a**, and **AuNPs-4b** could provide a biocompatible platform in therapeutical BNCT investigation or some other applications.

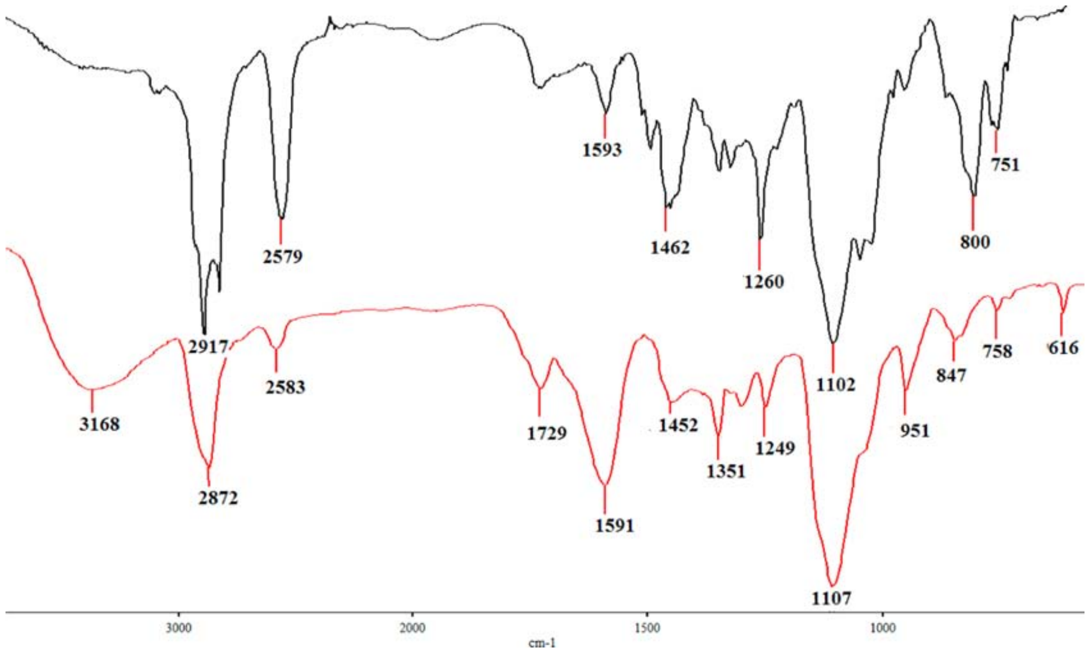


Figure 4. FT-IR spectra of dendron **4** (upper, in blue curve) and **AuNP-4b** (bottom, red curve).

Table 2. Core Size, Ligand Ratio, and Calculated Number of Carborane or PEG Ligands of Carborane-AuNPs

AuNPs	core diameter (nm)	ligand ratio[a]	number of carborane[b]	number of PEG[c]
AuNP-3a	3.42	1:1:0	86	0
AuNPs-3b	5.18	4:1:1	65	65
AuNPs-3c	4.75	1:1:4	55	222
AuNPs-4a	3.43	0:3:4	74	99
AuNPs-4b	7.59	0:1:2	282	565

[a] Molar ratio of dodecanethiolate: carborane: PEG. [b] Calculated amount of carborane per AuNP. [c] Calculated amount of PEG per AuNP.

■ EXPERIMENAL SECTION

General Information. All chemicals and solvents were used as received. ^{1}H NMR spectra were recorded at 25 °C with a Bruker AC200, 300, or 400 MHz spectrometer. The ^{13}C NMR spectra were obtained in the pulsed FT mode at 50, 75, or 100 MHz with a Bruker AC 200, 300, or 400 MHz spectrometer. All the chemical shifts are reported in parts per million (δ, ppm) with reference to Me_4Si (TMS) for the ^{1}H and ^{13}C NMR spectra. The mass spectra were recorded using an Applied Biosystems Voyager-DE STR-MALDI-TOF spectrometer. The DLS measurements were made using a MalvernZetasizer 3000 HAS instrument at 25 °C at an angle of 90°. UV−visible absorption (UV−vis) spectra were measured with a Perkin-Elmer Lambda 19 UV−visible spectrometer. The infrared (IR) spectra were measured with an ATI Mattson Genesis series FT-IR spectrophotometer. The elemental analyses were performed by the Center of Microanalyses of the CNRS at Lyon Villeurbanne, France.

Synthesis of Dodecanethiolate-AuNPs (AuNP-1). Dodecanethiolate-AuNPs (**AuNP-1**) were synthesized through the typical Brust−Schiffrin method.[14] Briefly, an aqueous solution of hydrogen tetrachloroaurate (15 mL, 106 mg, 0.27 mmol) was mixed with the toluene solution of tetraoctylammoniumbromide (20 mL, 600 mg, 1.09 mmol). The two-phase mixture was vigorously stirred until the hydrogen tetrachloroaurate was totally transferred into the organic layer, followed by the addition of dodecanethiol (28 mg, 0.14 mmol), then the mixture was further stirred for 20 min. A freshly prepared solution of sodium borohydride (11 mL, 131 mg, 4.8 mmol) was quickly added with vigorous stirring, and the mixture immediately became dark. After further stirring for 2 h, the organic phase was separated and dried over sodium sulfate, then concentrated to 5 mL under vacuum. The crude product was precipitated in 150 mL of ethanol and then washed again with ethanol, yield: 90%. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.55 (2H, HS-CH_2), 1.26 (20H, -CH_2CH_2-), 0.87 (3H, -CH_3).

Ligand-Substitution Synthesis of Azido-Terminated AuNPs-2a, AuNPs-2b, and AuNPs-2c. **AuNPs-1** (80 mg) and azidoundecanethiol (50 mg) were mixed in CH_2Cl_2 solution, and the solution was stirred for 2 days under N_2 at room temperature. After removal of solvent by rotary evaporator, the obtained **AuNPs-2b** were then washed with ethanol to remove the excess thiols (yield: 95%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ_{ppm} = 3.24 (2H, CH_2-N_3), 1.58 (2H, HS-CH_2) 1.26 (20H, -CH_2CH_2-), 0.87 (3H, -CH_3). Upon continuing the reaction during 5 more days, after the same treatment, **AuNPs-2a** were obtained with yield 90%. ^{1}H NMR ($CDCl_3$, 200 MHz): δ_{ppm} = 3.24 (2H, CH_2-N_3), 1.55 (2H, HS-CH_2) 1.27 (20H, -CH_2CH_2-), 0.88 (3H, -CH_3). Through a repeated ligand-substitution process (3 times) with prolonged reaction time (3 days) in each period, **AuNPs-2c** were obtained in 80% yield. ^{1}HNMR ($CDCl_3$, 200 MHz): δ_{ppm} = 3.24 (2H, CH_2-N_3), 1.58 (2H, HS-CH_2), 1.28 (20H, -CH_2CH_2-), 0.88 (3H, -CH_3). UV−vis: SPB at 518 nm. TEM: average diameter: 4.43 nm. IR: ν_{N3} 2090 cm^{-1}.

"Click" Synthesis of Carborane-AuNPs, AuNP-3a. Azido-terminated **AuNPs-2a** (50 mg, 0.022 mmol azido-ligand) and 1-Me-9-benzyl-*o*-carborane containing an ethynyl substituent of the benzene ring[3] (carborane alkyne) (12 mg, 0.044 mmol) were dissolved in 20 mL of toluene; then the solution was degassed and flushed with N_2. The "click" catalyst [Cu(I)(hexabenzyl)tren)]Br (Cu^I-tren) (0.1 equiv, 0.4 mg) was added, and the solution was allowed stir 2 days at 30 °C under N_2. After removal of toluene under vacuum, **AuNPs-3a** were washed with ethanol and diethyl ether to remove the excess carborane alkyne and the catalyst, respectively (yield: 40%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ_{ppm} = 7.46 (3H, *C*H in Ar, and *C*H in triazole), 7.15 (2H, *C*H in Ar), 3.45 (4H, CH_2-carborane and CH_2-triazole), 1.59−1.25 (20H, -CH_2CH_2-), 0.89 (3H, -CH_2CH_3). UV−vis: SPB at 522 nm. IR: disappearance of ν_{N3} band at 2090 cm^{-1}. TEM: average core-diameter: 3.42 nm. DLS analysis: average diameter = 15.6 nm.

"Click" Synthesis of Both Carborane and PEG350 Functionalized AuNP-3b. **AuNPs-2b** (40 mg, 0.012 mmol azido-ligand) and the carborane alkyne (0.006 mmol, 0.5 equiv per N_3 branch) were dissolved in 15 mL of toluene, then the solution was flushed with N_2. Cu^I-tren (0.001 mmol, 0.1 equiv) was added, the solution was then stirred at 30 °C under N_2. The reaction was finished in 1 day as monitored by FT-IR, which was indicated by the disappearance of the typical $\sigma_{C\equiv C}$ band at 2120 cm^{-1}. Then the propargylated PEG monomethyl ether (M_w = 388 g/mol, 0.006 mmol, 0.5 equiv.) was injected and the second "click" reaction was carried out in situ. The second reaction was finished in 24 h. After removal of toluene under vacuum, **AuNPs-3b** was washed with methanol and diethyl ether to remove the excess carborane, PEG, and the catalyst (yield 65%). ^1H NMR ($CDCl_3$, 300 MHz), δ_{ppm} = 7.36−7.24 (5H, H_{Ar}), 3.69 (28H, -CH_2CH_2O-), 3.61 (3H, -OCH_3), 3.51 (2H, CH_2-triazole), 3.41 (2H, CH_2-carborane), 2.73 (2H, -CH_2SH), 2.20 (3H, carborane-CH_3), 1.30 (22H, -$CH_2CH_2CH_2$-), 0.91 (3H, -CH_2CH_3). UV−vis: SPB at 530 nm. IR: disappearance of both the $\sigma_{C\equiv C}$ band at 2121 cm^{-1}, and the ν_{N3} band at 2090 cm^{-1}. TEM: average core diameter = 5.18 nm. DLS: average diameter = 15.4 nm.

"Click" Synthesis of Both Carborane and PEG2000 Functionalized AuNP-3c. **AuNPs-2c** (40 mg, 0.029 mmol azido-ligand) and the carborane alkyne (0.0058 mmol, 0.2 equiv. per N_3 branch) were dissolved in 15 mL of toluene, then the solution was degassed and flushed with N_2. After addition of Cu^I-tren (0.0029 mmol, 0.1 equiv.), the solution was stirred at 30 °C under N_2. The reaction was finished in 1 day as the typical $\sigma_{C\equiv C}$ band at 2100 cm^{-1} disappeared. Then a toluene solution (2 mL) of propargylated PEG monomethyl ether (PEG2000) (M_w 2038 g/mol, 0.023 mmol, 0.8 equiv.) was injected, and the second "click" reaction was carried out in situ. The second reaction was confirmed to be finished in 36 h, as monitored by IR. After removal of toluene in vacuum, **AuNPs-3c** were obtained after washing with methanol and diethyl ether to remove the excess carborane, PEG, and catalyst (yield 60%). ^1H NMR ($CDCl_3$, 300 MHz): δ_{ppm} = 7.88 (1H, CH in trizaole), 7.86 (1H, CH in triazole), 7.55−7.46 (4H, CH_{Ar}), 4.67 (2H, -OCH_2CH_2-triazole), 3.64 (176H, -CH_2CH_2O-), 3.51 (2H, CH_2-triazole), 3.41 (2H, CH_2-carborane), 3.36 (3H, -OCH_3), 2.62 (2H, -CH_2SH), 2.16 (3H, carborane-CH_3), 1.24 (22H, -$CH_2CH_2CH_2$-), 0.88 (3H, -CH_2CH_3). UV−vis: SPB at 524 nm. IR: σ_{B-H} stretching vibration at 2580 cm^{-1}; disappearance of both the σ_{alkyne} band at 2120 cm^{-1}, and the ν_{N3} band at 2090 cm^{-1}. TEM: average core diameter = 4.75 nm. DLS: average diameter = 10.2 nm.

Synthesis of Carborane-Azide 2. Carborane alkyne (0.8 mmol, 216.8 mg) and 1,4-bis-(azidomethyl)benzene (8 mmol, 1.5 g) were dissolved in 15 mL of tetrahydrofuran (THF). $CuSO_4$ $5H_2O$ (8 mmol, 200 mg) aqueous solution was then added, followed by the dropwise addition of a freshly prepared aqueous solution of sodium ascorbate (16 mmol, 316 mg) to obtain a 1: 1 THF/water ratio. The solution was stirred overnight at room temperature under N_2 atmosphere. After removal of THF under vacuum, CH_2Cl_2 was added to dissolve the product, and the organic solution was washed 3 three times with water to remove the catalyst. After drying with anhydrous Na_2SO_4, the solvent was removed under vacuum. Purification by silica gel chromatography (petroleum ether/CH_2Cl_2 1: 1) provided the pure product as white crystals (yield 92%). ^1H NMR ($CDCl_3$, 300 MHz): δ_{ppm} = 7.81−7.80 (2H, CH_{Ar}), 7.71 (1H, $CH_{triazole}$), 7.33: (4H, CH_{Ar}), 7.25−7.24 (2H, CH_{Ar}), 5.59 (2H, CH_2-triazole), 4.36 (2H, CH_2-N_3), 3.47 (2H, CH_2-carborane), 2.16 (3H, carborane-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_{ppm} = 147.60, 136.21, 134.94, 134.78, 130.86, 130.34, 128.91, 128.49, 125.86, 119.97, 75.04, 54.27, 53.85, 40.95, 23.69. ^{11}B NMR ($CDCl_3$, 96 MHz): δ_{ppm} = −4.19, −5.80, −10.53 (typical for *o*-carborane). MS (ESI, $M+Na^+$): calcd. for 484.3 *m/z*, found in 484.3 *m/z*. IR: ν_{N3} band at 2098 cm^{-1}, σ_{B-H} at 2583.1 cm^{-1}. Anal. Calcd. for $C_{20}H_{28}B_{10}N_6$: C 52.18, H 6.13, N 18.25; found: C 51.62, H 5.99, N 18.07.

Synthesis of the Tris-Alkyne Thioactetate Dendron 1. A dimethylformamide (DMF) solution of 5-(bromomethyl)-3,4,5-tris-(prop-2-yn-1-yloxy)benzene[17] (3 mmol, 996 mg) and potassium thiolacetate (4 mmol, 343 mg) was stirred at room temperature for 20 h under N_2 atmosphere. Then water was added to quench the reaction, and the product was extracted with CH_2Cl_2. The organic phase was washed 3 times with water, and then dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation (yield 95%). ^1H NMR ($CDCl_3$, 300 MHz): δ_{ppm} = 6.09 (2H, CH_{Ar}), 4.74 (4H, CH_2-C≡CH), 4.70 (2H, CH_2-C≡CH), 4.07 (2H, CH_2S-), 2.51 (2H, HC≡C−), 2.45 (1H, HC≡C−), 2.36 (3H, CH_3-CO). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_{ppm} = 194.9, 151.55, 136.45, 133.80, 109.25, 79.23, 78.42, 75.94, 75.26, 60.34, 57.09, 33.65, 30.34. MS (ESI, $M+Na^+$): calcd. for 351.3 *m/z*, found in 351.1 *m/z*. IR: $\sigma_{C\equiv C}$ band at 2121 cm^{-1}. Anal. Calcd. For $C_{18}H_{16}O_4S$: C 65.84, H 4.91, S 9.76; found: C 65.04, H 4.98, S 9.65.

Synthesis of the Tris-Carborane Thioacetate Dendron 3. The dendron **1** (0.32 mmol, 106 mg) and carborane-azide **2** (0.96 mmol, 444 mg) were dissolved in 10 mL of THF. $CuSO_4$ $5H_2O$ (0.96 mmol, 240 mg) in aqueous solution was added, followed by the dropwise addition of a freshly prepared aqueous solution of sodium ascorbate (1.92 mmol, 380 mg) to obtain a 1: 1 THF/water ratio. The solution was stirred overnight at room temperature under N_2. After removal of THF under vacuum, CH_2Cl_2 and 5 mL of a concentrated (30%) aqueous ammonia solution were added. The mixture was stirred during 30 min to remove the Cu ions trapped inside the dendron as $[Cu(NH_3)_2(H_2O)_2]^{2+}$, and the organic layer was washed with water. After drying with anhydrous Na_2SO_4, the solvent was removed under vacuum (yield 92%). ^1H NMR ($CDCl_3$, 300 MHz): δ_{ppm} = 7.8−7.7 (12H, $CH_{triazole}$ and CH_{Ar}), 7.19−7.17 (12H, CH_{Ar}), 6.53 (2H, CH_{Ar} in the focal point), 5.52−5.28 (12H, Ar-CH_2-triazole), 5.01 (6H, -CH_2-O-), 3.92 (2H, CH_2-S-), 3.42 (6H, CH_2-carborane), 2.28 (3H, CH_3-CO), 2.12 (9H, CH_3-carborane). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_{ppm} = 195.36, 152.19, 147.77, 144.32, 136.81, 135.77, 135.56, 135.50, 135.42, 135.14, 134.22, 131.07, 130.43, 129.00, 128.90, 128.85, 128.78, 128.70, 126.03, 123.77, 120.58, 120.37, 120.17, 108.82, 75.22, 66.38, 63.24, 54.04, 54.39, 41.12, 33.72, 30.62, 23.90. ^{11}B NMR ($CDCl_3$, 96 MHz): δ_{ppm} = −6.38, −10.54 (typical for *o*-carborane). MS (MALDI-TOF, $M+Na^+$): calcd. for 1733.1 *m/z*, found in 1732.7 *m/z*. IR: disappearance of ν_{N3} band at 2098 cm^{-1}, σ_{B-H} at 2583 cm^{-1}. Anal. Calcd. for $C_{78}H_{100}B_{30}N_{18}O_4S+H_2O$: C 54.21, H 5.95, N 14.59, S 1.86; found: C 54.00, H 5.98, N 14.24, S 2.14.

Synthesis of the Hybrid Dendron 4. The dendron **1** (0.65 mmol, 212 mg) and carborane-azide **2** (0.65 mmol, 300 mg) were dissolved in 30 mL of THF, and $CuSO_4$ $5H_2O$ (0.65 mmol, 162 mg) in 2 mL aqueous solution was added, followed by the dropwise addition of a freshly prepared aqueous solution of sodium ascorbate (1.3 mmol, 257 mg) to obtain a 1:1 THF/water ratio. This solution was stirred overnight under N_2 at room temperature. After removal of THF under vacuum, 20 mL of CH_2Cl_2 and 5 mL of a concentrated (30%) aqueous ammonia solution were added. The mixture was stirred 30 min to remove the Cu ions trapped inside the dendron as $[Cu(NH_3)_2(H_2O)_2]^{2+}$. The organic layer was isolated and washed with water. After drying with anhydrous Na_2SO_4, the solvent was removed under vacuum. The monocarborane dendron was obtained as a mixture of carborane in the *m*- branch (major) or in the *p*- branch. (yield 87%). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.8−7.7 (4H, $CH_{triazole}$ and CH_{Ar}), 7.3−7.21 (6H, CH_{Ar}), 6.72−6.65 (2H, CH_{Ar} in the focal point), 5.6−5.4 (4H, Ar-CH_2-triazole), 5.33 (2H, -CH_2-O-), 4.77−4.76 (2H, -CH_2-O-CCH), 4.74−4.73 (2H, -CH_2-O-CCH), 4.10 (2H, CH_2-S-), 3.42 (2H, CH_2-carborane), 2.55 (1H, HCC−), 2.49 (1H, HCC−), 2.38 (3H, CH_3-CO), 2.20 (3H, CH_3-carborane). MS (ESI, $M+Na^+$): calcd. for 812.4 *m/z*, found in 812.4 *m/z*. IR spectroscopy: σ_{C-O-C} band at 1107 cm^{-1}, and $\sigma_{C\equiv C}$ band at 2121 cm^{-1}. Subsequently, the monocarborane dendron (0.24 mmol, 190 mg) and PEG-alkyne monomethylether (0.48 mmol, 975 mg) were dissolved in 10 mL of THF, an aqueous solution of $CuSO_4$ $5H_2O$ (0.48 mmol, 120 mg, 5 mL) was then added. After degassing and refilling with N_2, the aqueous solution of sodium ascorbate (0.96 mmol, 190 mg, 5 mL) was dropwise added into the reaction solution. After stirring overnight under N_2 at room temporature, the solvent was evaporated with a rotary evaporator, and 30 mL of CH_2Cl_2 and 10 mL of a concentrated (30%) aqueous ammonia solution were added. The mixture was stirred until the organic layer became colorless to remove the Cu ions trapped inside the dendron. The organic layer was then isolated and washed with water. After drying with anhydrous Na_2SO_4, the solvent was removed under vacuum. ^1H NMR ($CDCl_3$, 300 MHz): δ_{ppm} = 7.72−7.69 (6H, $CH_{triazole}$ and CH_{Ar}), 7.27−7.16 (6H, CH_{Ar}), 6.72−6.65 (2H, CH_{Ar} in the focal point), 5.54−5.48 (6H, Ar-CH_2-triazole), 3.61−3.50 (176H, -CH_2CH_2O-), 3.42 (2H, CH_2-carborane), 3.34 (3H, CH_3-CO), 2.12 (3H, CH_3-carborane). ^{13}C NMR

($CDCl_3$, 75 MHz): δ_{ppm} = 152.23, 151.57, 147.46, 144.37, 135.54, 134.93, 130.92, 130.45, 129.73, 128.89, 128.71, 125.88, 124.55, 120.56, 109.28, 95.57, 87.32, 87.10, 78.95, 76.47, 75.78, 75.18, 72.69, 72.02, 71.43, 70.65, 70.40, 69.45, 62.36, 61.66, 59.07, 53.77, 50.31, 42.89, 40.95, 30.47, 23.78. ^{11}B NMR ($CDCl_3$, 96 MHz): δ_{ppm} = −6.05, −10.50 ppm. IR spectroscopy: disappearance of ν_{N3} band at 2098 cm^{-1}, σ_{B-H} at 2579 cm^{-1}. MS (MALDI, M+Ag^+) of dendron **4**: Calcd. at 4888.8 *m/z*, found at 4888.5 *m/z*. Anal. Calcd. for $C_{216}H_{402}B_{10}N_{12}O_{92}S$ +$2H_2O$: C 53.87, H 8.50, N 3.49, S 0.67; found: C 53.23, H 8.45, N 2.80, S 0.65.

Synthesis of AuNPs-4a Stabilized by Mixed Ligands. *Synthesis of the Tris-Carborane Thiol Dendron **5** and Me-PEG550-SH.* The dendron **3** (128 mg, 0.075 mmol) was dissolved in 2 mL of CH_2Cl_2, and mixed with Me-PEG550-thioacetate (41.85 mg, 0.075 mmol), and the obtained solution was refluxed in 10 mL of methanol for 3 h under N_2 in the presence of 0.5 mL of concentrated (37%) HCl solution. Then the mixture was cooled down to room temperature, and the obtained thiol dendron **6** and Me-PEG550-SH were used for the next step without any purification.

*Synthesis of Tris-Carborane Thiolate-Dendron **5** and **AuNPs-4a** Stabilized by Mixed Me-PEG550-SH Ligands.* $HAuCl_4$ $3H_2O$ (30 mg, 0.075 mmol) was added to the mixture of Me-PEG550-SH (39 mg, 0.075 mmol) and dendron **5** (125 mg, 0.075 mmol) in a solution of 10% CH_2Cl_2/methanol, then an aqueous solution (5 mL) of freshly prepared $NaBH_4$ (0.75 mmol, 28 mg) was added dropwise with vigorous stirring. After further stirring for 2 h, the organic solvent was removed by evaporation under vacuum, then **AuNPs-4a** was dissolved in water. The free ligands were removed by dialysis in a large volume of distilled water (3 × 4 h). ^1H NMR ($CDCl_3$, 300 MHz): δ_{ppm} = 7.75−7.69 (6H, CH_{triazole}), 7.2−7.13 (24H, CH_{Ar}), 5.55−5.45 (12H, triazole-CH_2-Ar), 5.05−4.93 (6H, -CH_2O-), 3.60 (44H, -CH_2CH_2O-), 3.35(3H, -OCH_3), 2.14 (9H, CH_3-carborane). UV−vis: SPB at 522 nm. IR: $\sigma_{C=C}$ at 1645 cm^{-1}, σ_{C-O-C} band at 1110 cm^{-1}, σ_{B-H} at 2580 cm^{-1}. TEM: average diameter of the core = 3.4 nm. DLS analysis (in aqueous solution): average hydrodynamic diameter = 19 nm.

Synthesis of AuNPs-4b. *Synthesis of the Hybrid Thiol Dendron **6** from Dendron **4**.* Dendron **4** (283 mg, 0.063 mmol) was dissolved in 2 mL of CH_2Cl_2; then the solution was refluxed in 10 mL of methanol for 3 h under N_2 in the presence of 0.3 mL of concentrated (37%) HCl solution. The solution was cooled down to room temperature; then the obtained solution containing the thiol dendron **6** was used for the next step without any purification.

*Synthesis of **AuNPs-4b** Capped with Dendron **6**.* $HAuCl_4$ $3H_2O$ (16.5 mg, 0.042 mmol) was added into the thiol dendron **6** (0.075 mmol) in solution of 20% CH_2Cl_2/methanol; then a freshly prepared $NaBH_4$ (0.21 mmol, 8.3 mg) aqueous solution (3 mL) was slowly added with vigorous stirring. After further stirring for 1 h, the organic solvent was removed by evaporation. **AuNPs-4b** was then dissolved in 10 mL of water, and the free ligands was removed by dialysis in 800 mL of distilled water for 4 h. The dialysis process was repeated two more times. ^1H NMR ($CDCl_3$, 300 MHz): δ_{ppm} = 7.79−7.76 (6H, CH_{triazole} and CH_{Ar}), 7.059 (6H, CH_{Ar}), 6.53 (2H, CH_{Ar} in the core arene), 5.40 (6H, Ar-CH_2-triazole), 3.50 (176H, -CH_2CH_2O-), 3.42 (2H, CH_2-carborane), 3.23 (3H, CH_3-CO). UV−visible spectroscopy: plasmon band at 522.4 nm. TEM image: average core diameter = 7.6 nm. DLS analysis (in aqueous solution): average hydrodynamic diameter = 14.5 nm. IR spectroscopy: σ_{C-O-C} band at 1107 cm^{-1}, σ_{B-H} at 2583 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterizations and data of ligands and AuNPs. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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