

Click Chemistry

A Highly Active and Magnetically Recoverable Tris(triazolyl)-Cu^I Catalyst for Alkyne–Azide Cycloaddition ReactionsDong Wang,^[a] Laetitia Etienne,^[b] María Echeverría,^[c] Sergio Moya,^[c] and Didier Astruc*^[a]

Abstract: Nanoparticle-supported tris(triazolyl)-CuBr, with a diameter of approximately 25 nm measured by TEM spectroscopy, has been easily prepared, and its catalytic activity was evaluated in the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction. In initial experiments, 0.5 mol% loading successfully promoted the CuAAC reaction between benzyl azide and phenylacetylene, in water at room temperature (25 °C). During this process, the iron oxide nanoparticle-supported tris(triazolyl)-CuBr displayed good monodispersity, excellent recoverability, and outstanding reusability. Indeed, it was simply collected and separated from the reaction medium by using an external magnet, then used for an-

other five catalytic cycles without significant loss of catalytic activity. Inductively coupled plasma (ICP) analysis for the first cycle revealed that the amount of copper leached from the catalyst into the reaction medium is negligible (1.5 ppm). The substrate scope has been examined, and it was found that the procedure can be successfully extended to various organic azides and alkynes and can also be applied to the one-pot synthesis of triazoles, through a cascade reaction involving benzyl bromides, alkynes, and sodium azide. In addition, the catalyst was shown to be an efficient CuAAC catalyst for the synthesis of allyl- and TEG-ended (TEG = triethylene glycol) 27-branch dendrimers.

Introduction

The copper-catalyzed 1,3-dipolar cycloaddition reaction between alkynes and azides (CuAAC), yielding 1,4-disubstituted 1,2,3-triazoles,^[1] is undoubtedly the most representative example of a “click” reaction^[2] to date. The CuAAC reaction demonstrates excellent atom economy, exclusive regioselectivity, a high tolerance to a range of functional groups, and the use of mild reaction conditions. In addition, 1,2,3-triazoles possess many interesting properties, such as antibacterial,^[3] antiallergic,^[4] anti-HIV,^[5] and antineoplastic^[6] activity. 1,2,3-triazoles also have the potential for coordinating to metal centers, which can be useful for sensing and in further catalytic reactions.^[7] Therefore, the CuAAC reaction has been extensively applied in organic synthesis, biology, and materials science^[8] since its discovery by the groups of Sharpless^[1a] and Meldal^[1b] in 2002.

However, the majority of reported CuAAC systems, in particular the systems that use homogeneous catalysts, have been susceptible to contamination by the cytotoxic Cu^I ion, which

restricts the application of such systems in electronics and biomedicine. To overcome this drawback, a wide range of strategies have been investigated. Chromatographic purification of the crude product, washing the crude product with ethylenediaminetetraacetic acid (EDTA) or ammonia, and performing CuAAC reactions under continuous flow conditions (quadratureTM, thiourea resin, or activated charcoal as the metal scavenger) are all acceptable methods, but they are scavenger-, energy-, and time-consuming procedures. The development of an astute copper-free click strategy has been proposed, but this strategy has only been used for the CuAAC reactions of cyclooctyne reagents.^[9] The heterogenization of click-chemistry catalysts appears to be a logical solution; the use of heterogeneous catalysts could result in easy removal, recovery, and reusability of the copper catalyst; thereby, minimizing copper contamination of the reaction products. Until now, several supports have been employed for immobilization of copper species, such as polymers,^[10] zeolites,^[11] activated carbon,^[12] alumina,^[11a,13] resin,^[14] carbon nanotubes,^[15] and silica.^[16]

In a related context, functionalized magnetic nanoparticles have emerged as viable alternatives.^[17] Magnetic nanosized catalysts can easily be separated from reaction mixtures by using an external magnet. They display better stability and reusability, more efficient catalytic activity, lower preparation costs, and lower toxicities in comparison with other materials that are used as supported heterogeneous catalysts. These properties are due to their insoluble, paramagnetic, and nanosized nature.^[18] In addition, the size, shape, morphology, and dispersity of magnetic nanosized catalysts are controllable. Therefore it is possible to design different magnetic nanocatalysts for specific catalytic applications.^[19]

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Among the various copper sources for CuAAC reactions, including Cu^{II} salt/reductant mixtures, Cu^{I} salts, copper nanoparticles, Cu^{I} complexes, and Cu^0 /oxidant mixtures, Cu^{I} complexes represent the most efficient copper source in terms of product yield and catalyst turn-over numbers (TONs). The use of Cu^{I} -ligand complexes was shown to both accelerate the catalytic process, in comparison with the ligand-free Cu^{I} species, and stabilize Cu^{I} intermediates. Moreover, it is relatively straightforward to graft Cu^{I} complexes onto a support in hybrid material assemblies. Indeed, nitrogen-based ligands and N-heterocyclic carbenes (**1a–e**, Figure 1) were found to be excellent ligands

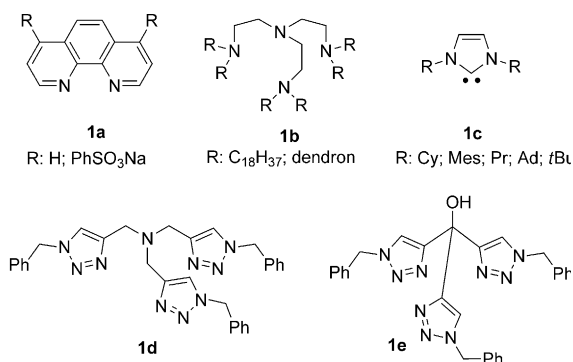


Figure 1. A selection of ligands currently used in CuAAC reactions. Cy = cyclohexyl; Mes = mesityl; Pr = *n*-propyl; Ad = adamantyl.

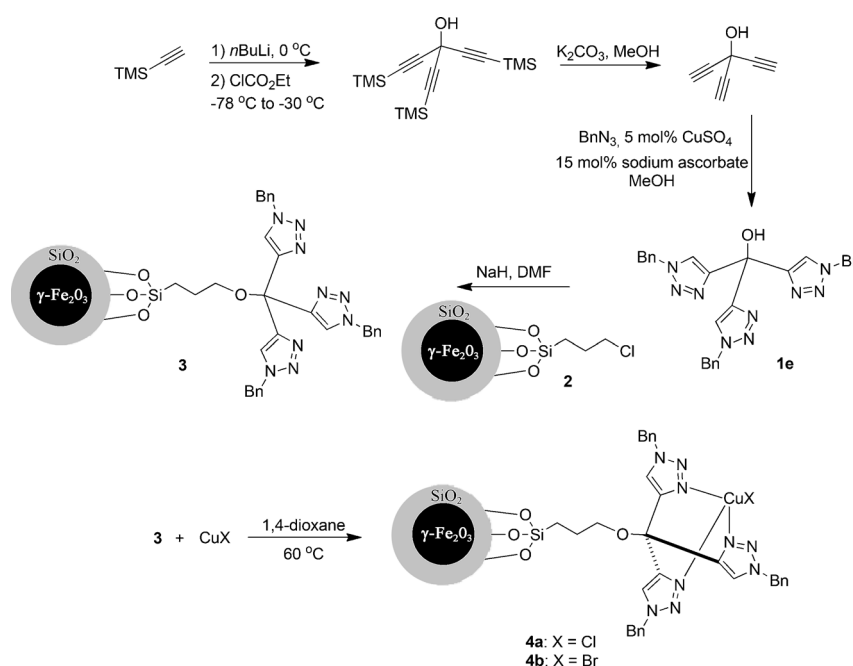
for CuAAC reactions.^[20] Fokin et al. designed polytriazoles **1d** that showed outstanding activity for click reactions with various substrates.^[21a,b] Subsequently, Pericàs et al. prepared tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol ligand, **1e**, and $\text{CuCl}\cdot\mathbf{1e}$, which efficiently catalyzed CuAAC reactions in water, or under neat conditions, in a short reaction time with a low catalyst loading. In addition, the hydroxyl group of **1e** proved to be a very promising anchoring point for immobilization, allowing the assembly of heterogeneous CuAAC catalysts.^[21c] Our group synthesized Cu^{I} complexes with (hexabenzyl)tren **1b**, and dendritic analogues with 18- or 54-branch termini that are powerful catalysts for click reactions. The catalytically active metallodendrimers provided a rare positive dendritic effect that was also mechanistically very useful.^[22] Herein, we present the synthesis of a magnetic $\text{Cu}^{\text{I}}\cdot\mathbf{1e}$ complex, in which **1e** was not only used as the chelating framework for the Cu^{I} salt, but also as a linker to SiO_2 -coated $\gamma\text{-Fe}_2\text{O}_3$ nanoparticles. Both the catalytic activity

and the reusability of the catalyst, for CuAAC reactions, have been investigated.

Results and Discussion

Synthesis of magnetic iron oxide nanoparticle-supported tris(triazolyl)- Cu^{I} complexes

The primary step for the synthesis of the iron oxide nanoparticle-supported tris(triazolyl)- Cu^{I} complexes was the synthesis of tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol, **1e** (Scheme 1). The CuAAC reactions were conducted, in the presence of copper sulfate and sodium ascorbate (a catalytic system developed by Sharpless et al.),^[1a] between three equivalents of benzyl azide and a tris(alkynyl)carbinol intermediate. This intermediate was readily prepared by the addition of trimethylsilylacetylide to ethyl chloroformate, followed by removal of the trimethylsilyl (TMS) groups. The 3-chloropropyltriethoxysilane-functionalized magnetic nanoparticles, **2**, were obtained through immobilization of 3-chloropropyltriethoxysilane on the surface of robust $\text{SiO}_2/\gamma\text{-Fe}_2\text{O}_3$ ^[23] by means of heterogenization with the Si–OH binding sites of $\text{SiO}_2/\gamma\text{-Fe}_2\text{O}_3$ in toluene heated at reflux. Magnetic nanoparticle-supported tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol, **3**, was prepared by alkylation of **2** with **1e**.^[14b] The loading of **3** was calculated by determination of the nitrogen content (C, H, N elemental analysis), the result indicated that the content was approximately 0.068 mmol g^{-1} . Finally, complexation of **3** with CuCl or CuBr (1.1 equivalents) resulted in the assembly of magnetic nanoparticle-supported tris(triazolyl)- CuCl , **4a**, or tris(triazolyl)- CuBr , **4b**, respectively. Transmission electron microscopy (TEM) images showed that the diameter of **4b** was approximately 25 nm (Figure 2a).



Scheme 1. Synthesis of $\text{CuX}\cdot\mathbf{1e}/\text{SiO}_2/\gamma\text{-Fe}_2\text{O}_3$ (**4**). Bn = benzyl.

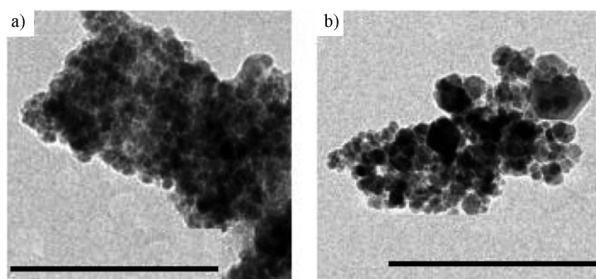


Figure 2. a) TEM image of CuBr-1 e/SiO₂/γ-Fe₂O₃ (**4b**) before the CuAAC reactions; b) TEM image of **4b** after eight reaction cycles. Scale bars = 200 nm.

Optimization of the conditions for alkyne–azide cycloadditions catalyzed by **4**

The catalytic applications of magnetically recyclable catalyst **4** in the cycloaddition reaction between benzyl azide and phenylacetylene, yielding the corresponding 1,4-disubstituted 1,2,3-triazoles, was investigated under various conditions (Table 1). In these preliminary experiments, CuAAC reactions

Table 1. Screening of solvents and catalysts for CuAAC. ^[a]				
Entry	Cat. ([mol %])	Solvent Ratio ([mL]:[mL])	Time [h]	Yield [%] ^[b]
1	4a (0.17)	MeOH/H ₂ O (1:1)	4	28
2	4a (0.2)	MeOH/H ₂ O (1:1)	24	61
3	4a (0.5)	MeOH/H ₂ O (1:1)	68	98
4	4a (1)	MeOH/H ₂ O (1:1)	24	91
5	4a (1)	EtOH/H ₂ O (1:1)	24	90
6	4a (1)	H ₂ O (1)	24	90
7	4b (0.5)	H ₂ O (1)	12	89
8	4b (0.5)	H ₂ O (1)	20	97

[a] The reaction was carried out with phenylacetylene (1 mmol) and benzyl azide (1.05 mmol) in the presence catalysts **4a** or **4b**, in the stated solvent at room temperature, under a nitrogen atmosphere. [b] Isolated yields after column chromatography.

were conducted in a mixture of MeOH and H₂O (1:1), with various loadings of **4a**, under a nitrogen atmosphere at room temperature. Increasing yields of 1,2,3-triazoles were obtained with increasing catalyst loading, in the range 0.17–1.0 mol%. The reactions proceeded in excellent yields (91 %) in the presence of 1 mol% **4a** (entry 4), and replacing the mixed solvent MeOH/H₂O by H₂O alone or by EtOH/H₂O did not affect the catalytic efficiency. Catalyst **4b** was then evaluated in CuAAC reactions and demonstrated superior catalytic activity compared with that of **4a** (0.5 mol% **4b** provided 1,2,3-triazoles with 97 % yield, in water, within 20 h at room temperature) Considering our goal of an economic and environmentally friendly reaction, these aqueous conditions are clearly favorable. Moreover, the excellent catalytic performances of **4a** and **4b** benefited from the good monodispersity of the SiO₂-coated iron oxide nanoparticles in water.

Investigation of the reusability of **4b** in the CuAAC reaction between benzyl azide and phenylacetylene

The reusability of the highly active magnetic nanoparticle-supported Cu^I complex, **4b**, was tested by using the model reaction between benzyl azide and phenylacetylene, with 0.5 mol% [Cu] in water at room temperature, under a nitrogen atmosphere. Catalyst **4b** showed excellent magnetic properties and monodispersity. After completion of the first reaction, the catalyst was collected by using an external magnet, successively washed with CH₂Cl₂ and methanol, and dried under vacuum for 2 h. A new reaction was then performed with fresh reactants under the same conditions. The results are summarized in Table 2; **4b** could be reused six times without significant

Table 2. Reusability test for catalyst 4b in the cycloaddition reaction between phenylacetylene and benzyl azides. ^[a]		
Run	Yield [%] ^[b]	Yield [%] ^[c]
1	97	96
2	95	93
3	94	72
4	92	39
5	92	–
6	92	–
7	84	–
8	67 ^[d]	–

[a] The reaction was carried out with phenylacetylene (1 mmol) and benzyl azide (1.05 mmol) in the presence of **4b** (74 mg, 0.005 mmol copper), at room temperature in water for 20 h. [b] Isolated yields after column chromatography. The reaction was carried out in nitrogen-purged H₂O (for 10 min) under a nitrogen atmosphere. [c] Isolated yields after column chromatography. The reaction was carried out in air. [d] The reaction time was 45 h.

loss of its catalytic activity, a decrease in the yield of the reaction only being observed after six cycles. The TEM image revealed that the morphology and size of **4b** changed over time, and a particle aggregation problem emerged after eight reaction cycles (Figure 2b). In addition, the leaching of copper species from the initial catalyst into the reaction media, a key issue for evaluating heterogeneous catalysts for CuAAC reactions, was investigated. After the first cycle, inductively coupled plasma (ICP) analysis revealed that 0.04 % of copper species was released from the initial catalyst into the reaction media, and the amount of residual copper species in the crude reaction product was approximately 1.5 ppm, compared with 5–15 ppm for other catalysts in the literature.^[7,8] Thus, copper species leaching into the crude product was not completely eliminated, but appeared to be negligible.^[17c] As anticipated, the tris(triazolyl) fragment proved to be a stable chelating framework for the adsorption of the Cu^I salt, and a good linker for the SiO₂-coated γ-Fe₂O₃ nanoparticles through straightforward C–O bond formation. Magnetic catalyst **4b** also performed well in the presence of air, but became deactivated after the second run, probably caused by aerobic oxidation of the Cu^I species into a Cu^{II} species.

We then questioned whether CuBr did not coordinate with the tris(triazolyl) ligand to form a copper complex, but was simply caged in the iron oxide nanoparticles. In order to answer this point, a control experiment was performed by mixing SiO₂-coated γ -Fe₂O₃, without the tris(triazolyl) ligand, with CuBr (three equivalents according to the amount of CuBr used in synthesis of **4b**).^[14b] The obtained mixture was used for promoting the cycloaddition reaction of benzyl azide with phenylacetylene. To achieve a clear comparison, the amount of the mixture corresponded to the weight of **4b** at the same scale. The results showed that a 54% yield was obtained in the first run, and only 18% in the second run. Therefore, it is reasonable to infer that the iron oxide supported tris(triazolyl)-CuBr complex is the actual catalytic species.

Investigation of the substrate scope for CuAAC reactions catalyzed by **4b**

Encouraged by the efficiency of the reaction protocol described above, the scope of the reaction was examined with magnetic catalyst **4b** (0.5 mol% [Cu]), in water under a nitrogen atmosphere, at room temperature. Firstly, various terminal alkynes were investigated in reactions with benzyl azide. For each substrate, the reusability of **4b** was examined for the first three runs. As shown in Figure 3, on carrying out the CuAAC reaction between benzyl azide and phenylacetylene on a 0.25 mmol scale, the desired 1,4-disubstituted 1,2,3-triazole, **5a**, was produced in 96% yield with 100% selectivity (the selectivity was determined by using ¹H NMR spectroscopy), and a slight decrease in the yield was observed from runs one to three (down to 92%). Electron-donating (CH₃O, NH₂) and electron-withdrawing (CHO) groups on the alkynes were tolerated, and no direct correlation could be drawn between the electronic nature of the terminal alkynes and the outcome of the reaction. Heteroatom-containing alkynes, 2-ethynylpyridine and 3-ethynylpyridine, were suitable cycloaddition partners,

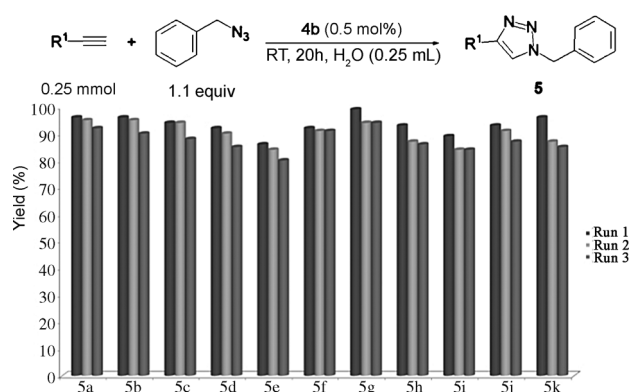


Figure 3. Substrate scope of terminal alkynes in the presence of catalyst **4b**. The bar graph shows the yield of isolated products. **5a**: R¹ = C₆H₅ (yield of the first three runs: 96, 95, and 92%); **5b**: R¹ = 4-CHOC₆H₄ (96, 95, and 90%); **5c**: R¹ = 4-CH₃OC₆H₄ (94, 94, and 88%); **5d**: R¹ = 4-NH₂C₆H₄ (92, 90, and 85%); **5e**: R¹ = pyridine-2-yl (86, 84, and 80%); **5f**: R¹ = pyridine-3-yl (92, 91, and 91%); **5g**: R¹ = C₄H₉ (99, 94, and 94%); **5h**: R¹ = C₅H₁₁ (93, 87, and 86%); **5i**: R¹ = HOC(CH₃)₂ (89, 84, and 84%); **5j**: R¹ = HOC(C₆H₅)₂ (93, 91, and 87%); **5k**: R¹ = ferrocenyl (96, 87, and 85%).

and the corresponding 1,2,3-triazoles, **5e** and **5f**, were obtained in 86 and 92% yields, respectively. The somewhat lower yield of the former reaction is probably attributable to the relatively bulky structure. Aliphatic alkynes containing linear chains were also suitable substrates, producing 1,4-disubstituted 1,2,3-triazoles **5g** and **5h** in excellent yields (99 and 93%, respectively). It was found that longer-chain aliphatic terminal alkynes resulted in the lowest yields. The products **5i** and **5j** were separated with high conversions when aliphatic terminal alkynes with hydroxyl groups were employed in CuAAC reaction. This procedure has been successfully extended to include ferrocenylacetylene as a substrate, the yield of the obtained product, **5k**, being 96%. The reusability of **4b** was also verified with all substrates, as shown in Figure 3.

The substrate scope of organic azides was then further investigated (Figure 4). The results indicated that benzyl, alkyl, and aryl azides could be successfully employed to assemble 1,2,3-triazoles through the CuAAC reaction with phenylacetylene. The yields decreased steadily upon increasing the alkyl-chain length of the organic azides (**6a–6c**). When phenyl azide was used, **4b** smoothly promoted the formation of 1,2,3-triazole **6d** with a 92% yield. However, organic azides with electron-donating (CH₃) or electron-withdrawing (I) substituents resulted in lower yields. For each substrate, **4b** was recovered and reused three times with good catalytic activity.

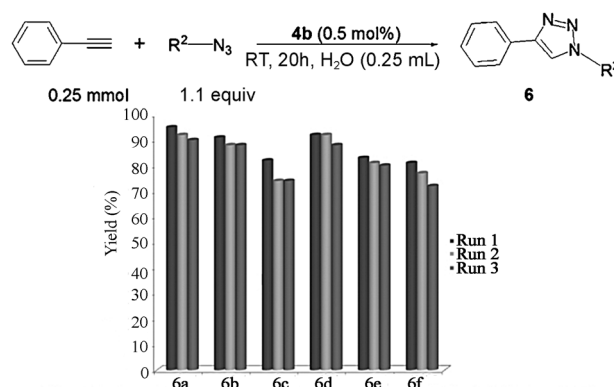


Figure 4. Substrate scope of organic azides in the presence of catalyst **4b**. The bar graph shows the yield of isolated products. **6a**: R² = C₆H₁₃ (yield of the first three runs: 95, 92, and 90%); **6b**: R² = C₆H₁₇ (91, 88, and 88%); **6c**: R² = C₁₈H₃₇ (82, 74, and 74%); **6d**: R² = C₆H₅ (92, 92, and 88%); **6e**: R² = 4-CH₃OC₆H₄ (83, 81, and 80%); **6f**: R² = 4-IC₆H₄ (81, 77, and 72%).

Cascade-reaction strategies display significant advantages over classical stepwise methods and have frequently been used as a powerful method in organic synthesis. Cascade reactions offer rapid and convergent construction of molecules from commercially available starting materials, without the isolation and purification of any intermediates, resulting in saving time, cost, and energy. In this context, taking into account the interest in avoiding storage and manipulation of organic azides, which can be hazardous, a three-component one-pot process was investigated by testing an azido reaction/1,3-dipolar cycloaddition of alkynes, sodium azide, and benzyl bromides (Figure 5). This process performed smoothly with

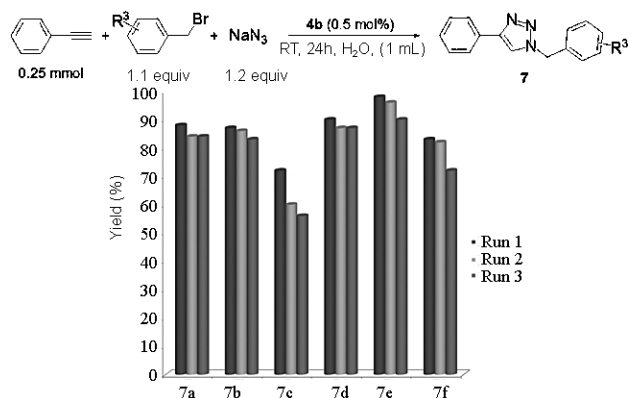


Figure 5. One-pot azide formation and subsequent CuAAC reaction mediated by **4b**. **7a**: $R^3 = 4\text{-Br}$ (yield of the first three runs: 88, 84, and 84%); **7b**: $R^3 = 3\text{-I}$ (87, 86, and 83%); **7c**: $R^3 = 4\text{-CN}$ (72, 60, and 56%); **7d**: $R^3 = 4\text{-NO}_2$ (90, 87, and 87%); **7e**: $R^3 = 3\text{-CH}_3$ (98, 96, and 90%); **7f**: $R^3 = 1\text{-CH}_2\text{-4-C}_6\text{H}_5\text{-1H-[1,2,3]triazole}$ (83, 82, and 72%).

0.5 mol% **4b**, without other additives, in water for 24 h at room temperature. Both electron-donating (3- CH_3) and electron-withdrawing (4-Br, 3-I, and 4- NO_2) substituents on benzylbromide showed good reactivity with sodium azide and phenylacetylene, producing the corresponding 1,2,3-triazoles in excellent yields. When 4-cyano benzylbromide was involved in the reaction, a lower yield (72%) was obtained, attributable to the coordination behavior of 4-cyano benzylbromide with the active copper center, resulting in deactivation of the catalyst. The double-azido CuAAC reaction of 1,2-dibromomethylbenzene proceeded well in the presence of 1 mol% **4b**, yielding product **7f**, which contains two triazole fragments, in 83% yield, and only a trace amount of the single triazole product. The reusability of **4b** was also investigated in the cascade-reaction strategy. Thus, it was shown that **4b** could be recovered and reused three times with only a slight decrease in the yield of the reaction. We also attempted the same tandem reactions, but with a linear-chain alkyl bromide (1-bromooctane), sodium azide, and phenylacetylene. Unfortunately, only a trace of desired product was obtained, probably because of the poor reactivity of 1-bromooctane with sodium azide in water at room temperature. Also, no triazole was produced when an aryl bromide (phenyl bromide) was employed, owing to the inability of phenyl bromide to undergo $\text{S}_\text{N}2$ reactions.

Encouraged by the efficiency of the reaction protocol described above, **4b** was probed as a CuAAC catalyst for the synthesis of 27-branch dendrimers by 1→3 connectivity between dendritic nona-azide polymer **8** and two propargylated phenol dendrons (**9a** and **9b**). In a previous report,^[8e,24] it was indicated that these reactions reached completion only in the presence of a quantitative amount of the catalyst developed by Sharpless et al. We found that 8 mol% of **4b** per branch successfully catalyzed the quantitative synthesis of 27-allyl and 27-TEG dendrimers (**10a** and **10b**, respectively) over 26 h or two days, respectively (Scheme 2). Moreover, after the first cycle of the synthesis of **10a**, **4b** was recharged and completed another synthesis of **10a**, within approximately three days, under ambient conditions.

Conclusion

The syntheses of iron oxide nanoparticle-supported tris(triazolyl)- Cu^{I} complexes, **4**, has been shown to be straightforward and convenient. The CuBr version of the magnetic nanoparticle catalyst, **4b**, showed, with low loading (0.5 mol%), good catalytic activity, recoverability, and reusability in CuAAC reactions. The catalyst was easily separated from the reaction medium by using an external magnet and showed good catalytic activity for six cycles. The amount of leaching copper species from the initial catalyst into the reaction media, determined by inductively coupled plasma (ICP) analysis, is negligible. This system has a broad substrate scope, and 25 1,4-disubstituted 1,2,3-triazoles were synthesized in good to excellent yields, including 27-allyl and 27-TEG dendrimers. For each small molecular substrate, **4b** was reused three times with either the same catalytic efficiency or only a slight decrease in yield. The outstanding performance of **4b** benefited from the excellent inherent properties of iron oxide nanoparticles and the powerful chelating nature of the tris(triazolyl) ligand with Cu^{I} centers. The above-mentioned results show that the reported procedure is easy-to-operate, economical, and environmentally friendly, as well as being in accordance with the principles of click chemistry and green chemistry. Magnetic catalyst **4b** could potentially be applied to CuAAC reactions for the synthesis of macromolecules, biomolecules, and nanoparticles.

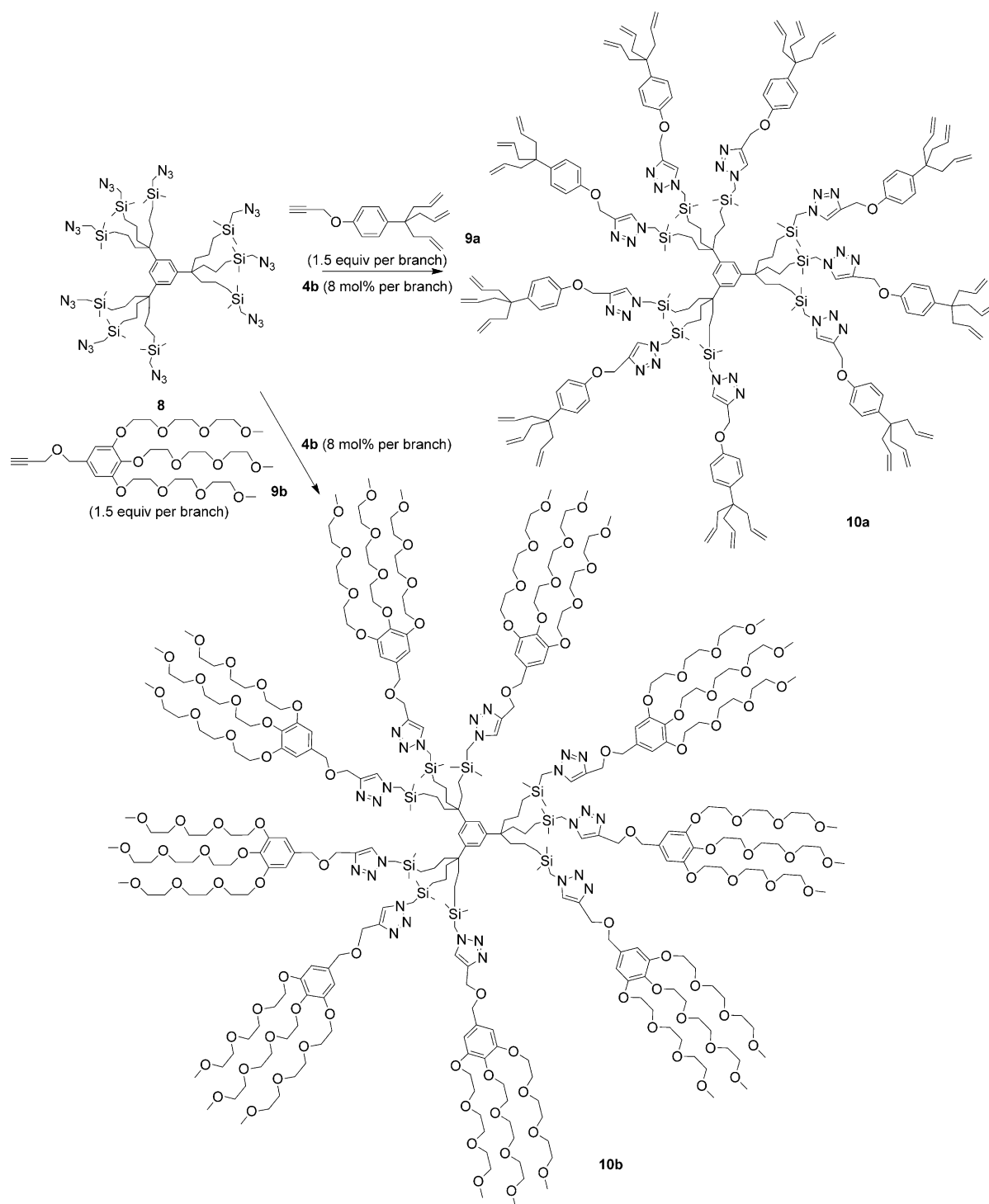
Experimental Section

General

All reactions were performed under nitrogen by using standard Schlenk techniques, unless otherwise noted. DMF was freshly distilled from calcium hydroxide, 1,4-dioxane was dried over Na foil, and distilled from sodium benzophenone under nitrogen immediately prior to use. CuBr was purified by stirring in glacial acetic acid overnight, followed by filtration, washing with ethanol and then drying under vacuum; it was stored under nitrogen and in the dark. All commercially available reagents were used as received, unless indicated otherwise. Flash column chromatography was performed using silica gel (300–400 mesh). ^1H NMR spectra were recorded by using a 300 MHz spectrometer, and ^{13}C NMR spectra were recorded at 75 MHz by using a 300 MHz spectrometer. Elemental analyses were performed by the Center of Microanalyses of the CNRS at Lyon Villeurbanne, France. The infrared spectra were recorded on an ATI Mattson Genesis series FTIR spectrophotometer. The inductively coupled plasma optical emission spectroscopy (ICP-OES) analyses were carried out using a Varian ICP-OES 720ES apparatus. Room temperature throughout the paper is 23–25 °C.

Synthesis of tris(triazolyl)methanol (**1e**)^[21c]

A solution of trimethylsilylacetylene (2.3 mL, 16.6 mmol) in anhydrous THF (20 mL) was cooled to -78°C . Then, 2.5 M *n*BuLi in hexane (6.1 mL, 15.2 mmol) was added dropwise, and the solution was stirred for 4 h. Ethyl chloroformate (442 μL , 4.61 mmol) was added, and the reaction was stirred overnight while warming to -30°C . The reaction was quenched with saturated NH_4Cl solution, diluted with water, and extracted with Et_2O (3×30 mL). The com-



Scheme 2. Synthesis of dendrimers **10a** and **10b** through CuAAC reactions catalyzed by **4b**.

binded organic phase was dried over Na_2SO_4 , and the solvent was removed under reduced pressure. The crude product was further purified by silica-gel chromatography (petroleum ether/ethyl acetate as eluent) to yield tris(trimethylsilylethynyl)methanol in 67% yield (1.0 g). $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta = 2.82$ (s, 1H), 0.18 ppm (s, 27H).^[21c] In a round-bottomed flask, the obtained tris(trimethylsilylethynyl)methanol in methanol (10 mL) was stirred in the presence of K_2CO_3 (4.20 g, 37.5 mmol) at room temperature overnight. The solution was filtered to remove excess K_2CO_3 and added to a solu-

tion of benzyl azide (1.25 g, 9.40 mmol) in methanol (10 mL). $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (38.9 mg, 0.156 mmol) and sodium ascorbate (93.0 mg, 0.468 mmol) were added, and the mixture was stirred for 14 h at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and washed with saturated Na_2CO_3 solution (5×30 mL). The organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification was performed by flash column chromatography, with petroleum ether/ethyl acetate as eluent, and

product **1e** was obtained in 37% yield (0.58 g). ¹H NMR (300 MHz, CDCl₃): δ = 7.64 (s, 3H), 7.24–7.38 (m, 15H), 5.47 (s, 6H), 5.04 ppm (s, 1H).^[21c]

Synthesis of iron oxide nanoparticle-supported tris(triazolyl)methanol ligand (**3**)^[14b]

A solution of **1e** (252 mg, 0.5 mmol) in DMF (2 mL) was added dropwise into a suspension of NaH (15 mg) in anhydrous DMF (2 mL) at 0 °C. After stirring for 45 min at room temperature, the suspension became a clear solution and was cooled to 0 °C and the added through a syringe to a sonicated DMF solution of **2** (400 mg). The reaction mixture was allowed to warm to room temperature, and dried at 80 °C for 96 h. After this time the reaction mixture was cooled down to room temperature, and the magnetic solid was separated by using an external magnet and then successively washed with DMF (20 mL), THF (20 mL), MeOH (20 mL), and Et₂O (20 mL). The resulting magnetic nanoparticles were dried in a vacuum at 45 °C overnight. The amount of tris(triazolyl) ligand in the functionalized magnetic nanoparticles, **3**, was 0.068 mmol g⁻¹, which was calculated from the results of elemental nitrogen analysis (found: N 0.8582%).

Synthesis of iron oxide nanoparticle-supported tris(triazolyl)methanol catalyst (**4**)

In a round-bottomed flask, a mixture of CuX (0.15 mmol, X = Br or Cl) and iron oxide nanoparticle-supported tris(triazolyl)methoxy ligand **3** (2 g) in anhydrous 1,4-dioxane (40 mL) was sonicated for approximately 15 min and stirred at 45 °C overnight. The iron oxide nanoparticle-supported tris(triazolyl)methanol–CuX catalysts **4** were successively washed with 1,4-dioxane (20 mL), toluene (20 mL), and Et₂O (20 mL), then dried at 45 °C overnight under vacuum and stored before use.

General procedures for the **4b**-catalyzed cycloaddition of alkynes and organic azides

A dried Schlenk tube equipped with a magnetic stirring bar was charged, under a nitrogen atmosphere, with alkyne (0.25 mmol), organic azide (0.275 mmol), catalyst **4b** (18.4 mg), and nitrogen-purged H₂O (0.25 mL). The mixture was stirred at room temperature for 20 h, and CH₂Cl₂ (5 mL) was added. The catalyst was collected by using a magnet and washed with CH₂Cl₂ (3 × 5 mL) and MeOH (5 mL), then dried at room temperature under vacuum. During the above-mentioned treatment for the reaction, the catalyst was always kept under a nitrogen atmosphere. The combined organic phase was dried over Na₂SO₄ and filtered, the filtrate was removed under reduced pressure in order to obtain the crude product, which was further purified by silica-gel chromatography (petroleum ether/ethyl acetate as eluent) to yield the corresponding 1,4-disubstituted 1,2,3-triazole. The recovered catalyst was then used for the next reaction cycle.

General procedures for one-pot azide formation and subsequent CuAAC reaction catalyzed by **4b**

Alkyne (0.25 mmol), benzyl bromide (0.275 mmol), sodium azide (0.3 mmol), nitrogen purged H₂O (1 mL), and **4b** (18.4 mg) were added to a flask with a stirrer bar, and the mixture was stirred for 24 h at room temperature under nitrogen. CH₂Cl₂ (5 mL) was added to the mixture, and the catalyst was collected by using a magnet and washed with CH₂Cl₂ (3 × 5 mL) and MeOH (5 mL), then dried at room temperature under vacuum. The combined or-

ganic phase was dried over Na₂SO₄ and filtered, the filtrate was removed under reduced pressure in order to obtain the crude product, which was further purified by silica-gel chromatography (petroleum ether/ethyl acetate as eluent) to yield the corresponding 1,4-disubstituted 1,2,3-triazole. The recovered catalyst was then used for the next reaction cycle.

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