Double-Hydrophilic Block Copolymer Nanoreactor for the Synthesis of Copper Nanoparticles and for Application in Click Chemistry

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RESEARCH ARTICLE

Ultrasound (US), a nonconventional energy source, has become a very popular and useful technology in organic chemistry. Several examples of US-assisted reaction have indicated that high yields and short reaction times are reasonable, and applications of this energy transfer process on click reactions have been published. Stable, water-soluble copper nanoparticles (Cu NPs) were synthesized using a double-hydrophilic block copolymer as a template. The prepared Cu NPs were effective as catalysts for the [3+2] cycloaddition of azides with terminal alkynes to provide products in good yields and with high regioselectivity. An environment-friendly process of synthesizing regioselective triazoles was developed from a variety of azides with terminal alkynes, in which the water-soluble Cu NPs were utilized, under 10 min sonication. The Cu NPs can be reused three times under the present reaction conditions, without any loss of catalytic activity. Block copolymer nanoreactors were shown to be promising in creating a number of water-soluble catalytic metal NPs for a wide variety of organic transformations.

1. INTRODUCTION

The synthesis of well-defined nanoparticles (NPs) is of special interest in nanoscience, particularly for their catalytic applications due to the interesting properties associated with their nanoscale dimension. As metal and metal oxide NPs are very stable both physically and chemically, they have been frequently used as catalysts.[1,2] In addition, their distinct characteristics as NPs with large surface areas make them applicable to a wide range of fields. Among the many metal oxide NPs in existence, copper oxide (Cu_2O, CuO) are well-known *p*-type semiconductor materials with potential applications in the area of solar-energy conversion and catalysis. For example, Tarascon et al. recently used copper oxide NPs as an anode for lithium ion cells,[3] while Izaki et al. employed them with ZnO for solar-cell plates, demonstrating their potential in electrochemical applications.[4] Moreover, copper oxide NPs are nontoxic, environment-friendly, and highly stable, and as such, recyclable.

To date, a number of methods of preparing Cu_2O NPs with different particle sizes morphologies, and properties have been described, including controlled thermal decomposition, chemical reduction with the proper surfactant, electrochemical reduction, microemulsion, and the use of reverse micelles in a supercritical solvent. In all of these methods, control over the particle size and morphology is achieved through the use of either templating materials or a capping reagent during NP growth. Block copolymers have received much attention of late as attractive templates or scaffolds for engineering inorganic nanostructured materials to control the sizes and spatial locations of NPs.[5–7]

Click chemistry is a highly efficient cycloaddition method that became a highly popular synthesis method since its introduction in 2001 by Sharpless.[8,9] The Azide-alkyne Huisgen method, involving Cu(I)-catalyzed cycloaddition between terminal acetylenes and azides at room temperature, is one of the most efficient reactions within the click chemistry philosophy.[10] The reaction proceeds in variable solvents in the presence of catalysts to yield stable triazoles with possible applications in pharmaceuticals, DNA modification, and organic synthesis.[11]

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The commonly used catalysts in click reaction are Cu and ruthenium. The Cu catalyst generates 1,4-regioisomer as a product, while the ruthenium catalyst generates 1,5-regioisomer (Eq. (1)).
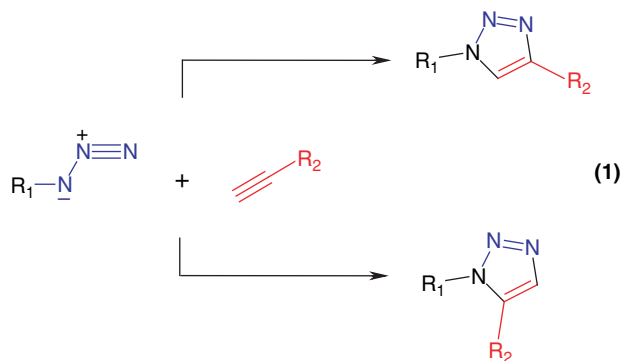
Ultrasound (US), a nonconventional energy source, has become a very popular and useful technology in organic chemistry.[12] Several examples of US-assisted reaction have indicated that high yields and short reaction times are reasonable, and applications of this energy transfer process on click reactions have been published.[13]

The analysis of environmental substances has become an increasingly important issue due to the problems associated with global environmental pollution. Performing click chemistry in aqueous media is still challenging, however, due to the absence of a stable and active catalyst that is water-soluble.[14] Aqueous click chemistry has the economic, environmental, and processing benefits of both homogeneous aqueous catalysis and aqueous two-phase catalysis. Water clearly stands out as the solvent of choice, with its fast reaction rate, high yield, selectivity, cheapness, "green" solvent nature, and environmental acceptability. In this context, double-hydrophilic block copolymers (DHBCs) were employed in the growth control of inorganic phases, such as mineralization with unusual structural specialty and complexity in an aqueous solution.[8] These DHBCs consist of one active ionizable block and one neutral block. The introduced metal ions interact with the ionizable block in solution, thus inducing micelle formation, which promotes the stabilization of the colloidal micelle in water. Once the formation of micelle is induced, it acts as a nanoreactor to control the NP growth within the micellar core. The DHBC method can provide an easy solution-phase synthesis approach without harsh conditions, and can create a potentially biocompatible shell around the NPs to improve the solubility and compatibility of the prepared particles. In this study, poly(acrylic acid)-*b*-poly(ethylene oxide) (PAA-*b*-PEO) DHBC was used to prepare sterically stabilized Cu NPs with controllable sizes.

2. EXPERIMENTAL PROCEDURE

2.1. General Remarks

Reagents were purchased from Aldrich Chemical Co. and Strem Chemical Co. and used as received. The reaction products were analyzed via ^{1}H-NMR spectroscopy, with spectra obtained on a Varian Mercury Plus (300 MHz). The chemical-shift values were recorded as parts per million relative to tetramethylsilane as an internal standard, unless otherwise indicated, and as coupling constants in Hertz. The reaction products were assigned by comparison with the literature value of known compounds. The water-soluble Cu NPs were characterized by TEM (JEOL 2100 operated at 200 kV). Samples were prepared by placing a few drops of the corresponding colloidal solution on carbon-coated Cu grids (Ted Pellar, Inc). The X-ray powder diffraction (XRD) patterns were recorded on a D8 Discover (12 kW) diffractometer. The Cu NPs were characterized using an X-ray photoelectron spectroscope (XPS) (Thermo Fisher, K-alpha) and a UV/Vis spectroscope (VARIAN, Cary 5000), and the Cu-loading amounts were measured via inductively coupled plasma optical-emission spectrometry (ICP-OES).

2.2. General Procedure for the [3+2] Cycloaddition of Azides with Terminal Alkynes

0.4 ml water-soluble Cu NPs (20 mM, 1 mol%), benzyl azide (0.1 mL, 0.80 mmol), phenylacetylene (0.13 mL, 1.18 mmol), and 4.5 mL H_2O were placed in a 10 mL-pressure Schlenk tube, followed by sonication for 10 min at 100 °C, with 50% amplitude, using a Fisher Scientific Sonic Dismembrator 500 (Pittsburgh, PA, USA). After 10 min, the water-soluble Cu NPs were recovered via centrifugation, and the clean solution was analyzed at 300 MHz NMR.

2.3. Water-Soluble Cu NPs

The Cu NPs were prepared according to the following protocols. First, double-hydrophilic block copolymer PEO(3500)-*b*-PAA(7500) (Polymer Source Inc, Canada) (21.15 mg, 0.20 mmol carboxylic-acid groups) and copper chloride dihydrate (17.8 mg, 0.10 mmol) in 5.0 mL water were separately prepared and mixed under vigorous stirring. 1.0 M NaOH (0.10 mL, 0.10 mmol) was added to this solution mixture, and blue precipitation was obtained. Subsequently, 10.0 M hydrazine (0.10 mL, 1.0 mmol) was added dropwise to the resulting suspensions under vigorous stirring. As soon as hydrazine was added, the solution turned orange. After 20 min of vigorous stirring, the reaction mixture kept still for 10 min, after which the solution color changed to brownish red. The solution mixture was centrifuged to remove the large aggregates of particles therein (1500 rpm, 15 min), then the recovered supernatant was used as a catalyst for click chemistry.

3. RESULTS AND DISCUSSION

3.1. Catalyst Characterization

According to the optimized protocol presented, the prepared Cu NPs exhibit a red homogeneous aqueous suspension. As surface plasmon resonance (SPR) is a well-known phenomenon in many transition metal NPs, the absorption peak at around 570 nm supports the nanoscale dimension of Cu NPs.[16] This value also matches that of the previously reported SPR of Cu NPs.

The transmission electron microscopy (TEM) image further shows the spherical shape of the Cu NPs with an average diameter of ca. 6 nm at a relatively narrow size distribution (Fig. 2). In addition, the highly crystalline nature of the Cu NPs was demonstrated via high-resolution TEM measurement with a 2.09 Å lattice spacing, which corresponds to the primary reflection of the (111) peak in Cu NPs. Energy-dispersive spectrometer (EDS) measurement, however, indicated the presence of a small amount of oxygen as well as elemental Cu in the prepared Cu NPs, which may indicate the oxidized layer of Cu on the surfaces of the particles. As such, the Cu NPs were investigated via XRD. It was observed that there were two main peaks ($\theta = 43.2°$ and $50.3°$) assigned to the reflections of the (111) and (200) planes in the Cu phase, together with a small peak that corresponds to the (111) plane in the CuO phase (Fig. 3). There were also some peaks associated with the residual NaCl formed during the NaOH treatment.

In addition, X-ray photoelectron spectroscopy (XPS) further revealed the presence of a copper oxide layer after the deconvolution of the obtained peaks (Fig. 3(b)). The Cu2p$_{3/2}$ peak of elemental Cu was found at 932.4 eV, whereas Cu^{2+} had one main peak at 933.5 eV and shakeup satellite peaks (characteristics of materials with a d^9 configuration in the ground state, such as Cu^{2+}) at higher bonding energies.[17] Taken together, it is postulated that the prepared Cu NPs in fact had core–shell-type structures consisting of a Cu core with a thin shell of copper oxide. The suppression of the oxidation of metallic Cu was
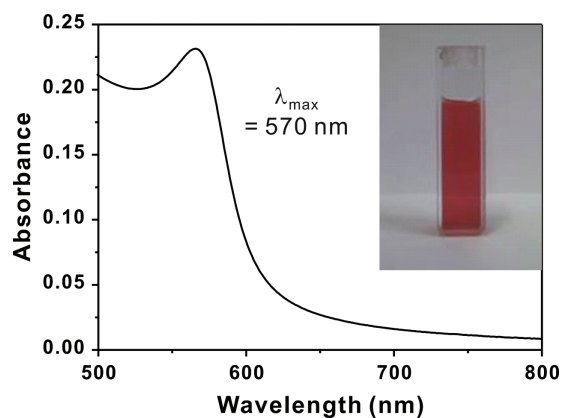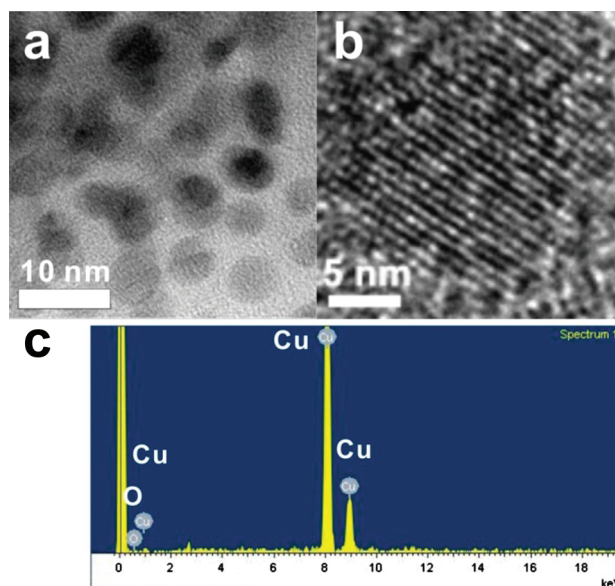

Fig. 2. (a, b) TEM images of the prepared Cu NPs. (c) The corresponding EDS pattern.

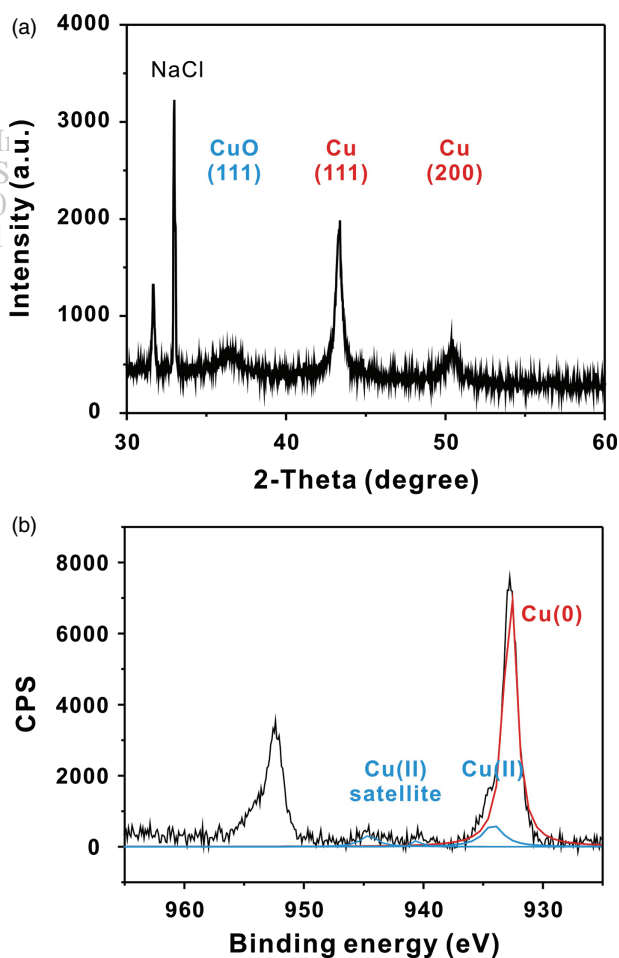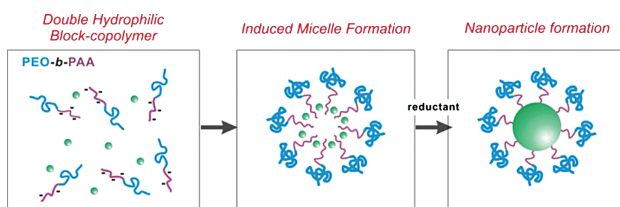**Fig. 3.** (a) XRD and (b) high-resolution Cu2p3/2 XPS spectra of the prepared Cu NPs. The deconvoluted peaks represent the coexistence of Cu and copper oxide.


Fig. 1. UV/vis spectrum of the prepared Cu NPs. (Inset) Photo image of the Cu NPs.

Scheme 1. Synthetic procedure of water-soluble copper nanoparticles.

Table I. Optimization of the click reaction catalyzed by water-soluble Cu NPs.

Entry	Cat (mol %)	Temp (°C)	Time (h)	conv (%)[a]
1	1 mol% CuO-poly	25	3	3[b]
2	1 mol% CuO-poly	50	10 min	17
3	1 mol% CuO-poly	100	5 min	37
4	1 mol% CuO-poly	100	10 min	>99
5	1 mol% CuO-poly	100	10 min	27[c]
6	0.5 mol% CuO-poly	100	10 min	38
7	Recovered # 4	100	10 min	99
8	Recovered # 7	100	10 min	100

[a]Determined by ^{1}H-NMR. Yields are based on the amount of benzyl azide used. [b]Traditional stirring. [c]Conventional thermal heating at 100 °C.

probably due to the presence of a strongly coordinating double-hydrophilic block copolymer in preventing excess oxidation to pure copper oxide.

The original sizes and structures of the CuO NPs were preserved during catalytic transformation. The absolute amount of Cu that was used for click chemistry was determined via inductively coupled plasma optical-emission spectroscopy (ICP-OES). The CuO NPs within a DHBC shell showed excellent catalytic activity towards a wide range of azides and acetylenes.

3.2. Reaction Test
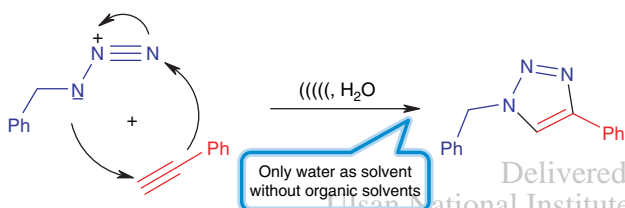
As shown in Table I, the reactions of benzyl azide and phenylacetylene were studied in the presence of Cu NPs in water. The cycloaddition reaction of benzyl azide (0.1 mL, 0.80 mmol) and phenylacetylene (0.13 mL, 1.18 mmol) with water-soluble Cu NPs in H_2O (4.5 mL), off the shelf, afforded 1,4-disubstituted 1,2,3-triazoles as a single regioisomer. This CuO nanostructure catalyzed a reaction sequence that regiospecifically united the azides and terminal acetylenes to give only 1,4-disubstituted 1,2,3-triazoles. The reaction was carried out at 25–100 °C, using benzyl azide and phenylacetylene as the benchmark substrates. The best results were obtained when H_2O was used as the solvent, in which 10 min sonication was executed with 50% amplitude, at 100 °C. It was observed that the application of US irradiation significantly increased the reaction rates and yields (5–10 min) compared with the traditional stirring (Table I, entries 1 and 5).

When the water-soluble Cu NPs (1 mol%) were used, 1-benzyl-4-phenyl-1*H*-1,2,3-triazole was obtained in over 99% conversion within 10 min (Table I, entry 4). In general, it was found that increasing the reaction temperature and time were effective means of increasing the conversion (Table I, entries 2 and 3). When the catalyst of the water-soluble Cu NPs (0.5 mol%) was used, a 38% yield was achieved under the same conditions (Table I, entry 6). Remarkably, the water-soluble Cu NPs were separated via centrifugation after the reaction, and were reused three

times without any catalytic activity loss, under the same reaction conditions. These results confirm that the catalytic system presented herein satisfies the conditions for heterogeneous catalysts (easy separation, recyclability, and persistence).

The use of a variety of azides and terminal alkynes in this reaction was also studied, and the results are shown in Table II. In some cases, the electron-donating or electron-withdrawing groups on the benzyl azides greatly affected the reactivity. The electron-withdrawing groups disfavored the reaction with the lower obtained yields. Within these groups, nitrogen dioxide exhibited the largest effect (Table II, entries 2 and 3).

As an example, the reaction of the phenyl group was directly linked to the reactive azide, and the p-methoxy group gave the expected 1-(4-methoxyphenyl)-4-phenyl-1*H*-1,2,3-triazole as a single regioisomer with 100% conversion (Table II, entry 4). In some cases, the steric and electronic effects greatly affected the reactivity. The sterically bulky and electron-withdrawing groups disfavored the reaction, with lower obtained yields. When the phenyl group was directly linked to the reactive azide, its analogue with a Ph-O, p-Cl group gave the expected 1-(4-phenoxyphenyl)-4-phenyl-1*H*-1,2,3-triazole, 1,4-diphenyl-1*H*-1,2,3-triazole, and 1-(4-Chlorophenyl)-4-phenyl-1*H*-1,2,3-triazole as lower obtained yields (Table II, entries 6 and 7). In a second series of experiments, various terminal alkynes bearing different groups were submitted to benzyl azide. Hydroxy-substituted alkynes such as propargyl alcohol, and 2-methyl-3-butyn-2-ol, also gave the expected adducts of (1-benzyltriazol-4-yl)methanol, and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol as single regioisomers in good to high yields (Table II, entries 9 and 10). The reaction with aliphatic alkynes, such as 1-octyne, gave high yields (Table II, entry 11). Acetylenes conjugated with an ester group, such as phenyl propargyl ether, reacted without incident with the benzyl azide. The corresponding triazoles 1-benzyl-4-(phenoxymethyl)-1*H*-1,2,3-triazole were obtained in high yields (Table II, entry 12).

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Table II. US-promoted $[3+2]$ cycloaddition of various azides with terminal alkynes in the presence of water-soluble Cu NPsa.

Entry	Azide	Alkyne	Product	Conv. (%)
1				100
2				100
3				87
4				100
5				89
6				68
7				26
8				59
9				>99
10				100
11				56
12				>99

4. CONCLUSIONS

Stable, water-soluble copper nanoparticles (Cu NPs) were synthesized using a double-hydrophilic block copolymer as a template. The prepared Cu NPs were effective as catalysts for the $[3+2]$ cycloaddition of azides with terminal alkynes to provide products in good yields and with high regioselectivity. An environment-friendly process of

synthesizing regioselective triazoles was developed from a variety of azides with terminal alkynes, in which the water-soluble Cu NPs were utilized, under 10 min sonication. Water-soluble Cu NPs were shown to be useful reagents for a wide variety of organic transformations.

References and Notes

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18. Characterization of new compound (Table II, entry 5): ¹H-NMR (CDCl₃, 300 MHz): $\delta = 8.18$ (s, 1H), 7.91 (*d*, $J = 7.2$ Hz, 2H), $7.49 - 7.30$ (m, 6H), 6.98 (*d*, $J = 8.4$ Hz, 1H), 3.89 (s, 3H). ¹³C-NMR (CDCl₃, 75 MHz): $\delta = 160.7$, 148.4, 138.1, 130.6, 130.3, 128.9, 128.5, 125.9, 117.8, 114.7, 112.4, 106.4, 55.7. HRMS for $C_{15}H_{13}N_3O_1$: cacld. 251.1059; found 223.1007 ($C_{15}H_{13}N_1O_1$).