CuO hollow nanostructures catalyze [3 + 2] cycloaddition of azides with terminal alkynes†

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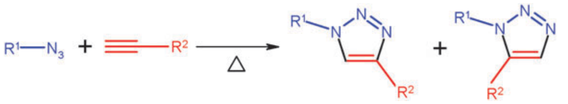
CuO hollow nanostructures have been used for the catalytic [3 + 2] cycloaddition of azides with terminal alkynes to provide the products in good yields with high regioselectivity.

As metal oxide nanoparticles are very stable both physically and chemically, they have recently been used frequently as metal catalysts.[1] In addition, their distinct qualities as nanoparticles, such as large surface area, makes them applicable to a wide range of fields. Among the metal oxide nanoparticles, copper oxides (Cu_2O, CuO) are p-type semiconductor materials with a low band gap energy. Recently, Tarascon's group used copper oxide (Cu_2O, CuO) nanoparticles as an anode for lithium ion cells,[2] while Izaki's group employed them with ZnO, a n-type semiconductor material, for solar cell plates, demonstrating their highly useful electrochemical characteristics.[3] In addition, copper oxide (Cu_2O, CuO) nanoparticles have sufficient space to adsorb harmful gases, as proven by the application of copper oxide as a gas sensor by Yadong's group.[4] In addition, Cu(II) nanoparticles are non-toxic, environmentally friendly, and highly stable, and as such, are recyclable. The research presented within intends to use Cu(II) nanoparticles for click chemistry.

Click chemistry is a chemical philosophy introduced in 2001 by Sharpless, and is important in understanding the behavior of low-weight molecules.[5] Click chemistry has had a very big impact on organic synthesis, drug discovery, and biological applications.[6] The desired triazole-forming cycloaddition may need high temperatures and, usually results in a mixture of the 1,4 and 1,5 regioisomers (eqn (1)).



(1)

In general, as a catalyst, a Cu(I) salt is directly used, or Cu(II) after reduction.[7] Recently, reactions capitalizing upon the advantages of Cu(I) or Cu(II) nanoparticles have been reported.[8] There is a case where, from Cu nanoclusters of Cu(0), Cu(I) is generated *in situ* and Cu/Cu-oxide nanoparticles are used. In particular, the example of using air protected mixed Cu/Cu-oxide, reported by the Ponti group, revealed that it produced very good results—87 to 95% yield—for three kinds of azide and ten kinds of internal and terminal alkynes.[8c] In addition, heterogeneous systems such as copper-in-charcoal, alumina-supported copper nanoparticles, and Cu(I)-modified zeolites have been reported.[9] Accordingly, this communication shows the best results of click reactions using well-designed, uniform, hollow-structured CuO nanoparticles. Various types of Cu nanoparticles are tested and help in reviewing the efficiency of the reaction in terms of the shape of the CuO nanoparticles and understanding the behavior of the catalysts.

In the present study, an approach for gram-scale synthesis of uniform Cu_2O nanocubes by a one-pot polyol process was used (see ESI†)[10] The CuO hollow nanostructures were prepared by adding aqueous ammonia solutions to Cu_2O nanocube colloidal solutions. Such hollow morphologies were achieved mainly through a sequential dissolution–precipitation process under precise control by changing the pH of the reaction mixture in air. Increasing the pH of the solution led to formation of hollow cubes, hollow spheres and urchin-like particles (ESI†).

Research studies testing the effectiveness of the catalysts have used benzyl azide and phenylacetylene as the benchmark substrates. The cycloaddition reaction of benzyl azide (1 mmol) and phenylacetylene (1.5 mmol) with the prepared CuO nanostructures (4 mg, 5 mol%) in H_2O/*t*-BuOH (1.6 mL/0.8 mL) afforded 1,4-disubstituted 1,2,3-triazoles as a single regioisomer. The CuO nanostructures catalyzed the reaction sequence which regiospecifically combines azides and terminal acetylenes to give only 1,4-disubstituted 1,2,3-triazoles.

As shown in Table 1, in order to determine the solvent system most suitable for the catalyst, several experiments were conducted. Considering the hygroscopic properties of THF, dioxane and toluene, it is expected that the reaction conditions will be affected by the amount of water present (entries 1–4, Table 1). Both *t*-BuOH[11] and water as solvents gave high yields under mild conditions (entries 5 and 6) though best results were obtained with a solvent mixture of *t*-BuOH and H_2O (2 : 1) (entry 4), which indicates that solubility and hygroscopic properties are all important factors.

In the case of using commercially available CuO, less than 1% yield was found under the same conditions and upon extending the reaction for 24 h, only a yield of 35% was achieved. In addition, under optimum reaction conditions, no reaction occurred without catalyst (entries 7–9, Table 1). Next, in order to examine the characteristics of the catalyst according to the various nanostructure morphologies, three different types of CuO(II) nanostructures were tested.

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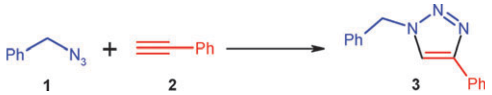
† Electronic supplementary information (ESI) available: I: Experimental. II: Characterization: ^1H and ^{13}C NMR spectra. III: Figures. IV: ^1H and ^{13}C NMR spectra of products. See DOI: 10.1039/b917781g

Table 1 Optimization of click reaction catalyzed by various CuO(II) nanostructures



Entry	Catalyst (5 mol%)	T/°C	t/h	Solvent	Conv.[a] (%)
1	CuO urchins	60	12	THF–H_2O (24 : 1)	4
2	CuO urchins	100	12	Dioxane/H_2O (24 : 1)	61
3	CuO urchins	110	12	Toluene/H_2O (24 : 1)	93
4	CuO urchins	25	3	H_2O/*t*-BuOH (2 : 1)	96
5	CuO urchins	25	3	H_2O	90
6	CuO urchins	25	3	*t*-BuOH	71
7	Commercial CuO[b]	25	24	H_2O/*t*-BuOH (2 : 1)	35
8	Commercial CuO[b]	25	3	H_2O/*t*-BuOH (2 : 1)	<1
9	—	25	3	H_2O/*t*-BuOH (2 : 1)	0
10	CuO urchins	25	3	H_2O/*t*-BuOH (2 : 1)	93[c]
11	CuO hollow spheres	25	3	H_2O/*t*-BuOH (2 : 1)	100[c]
12	CuO hollow cubes	25	3	H_2O/*t*-BuOH (2 : 1)	94[c]
13[d]	CuO hollow spheres	25	0.5	H_2O/*t*-BuOH (2 : 1)	98

[a] Determined by ^1H NMR spectra. [b] Purchased from Aldrich (nanopowder, cat No. 544868). [c] Conversion based upon an average of two runs. [d] In the presence of 1.0 eq. Et_3N.

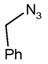
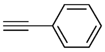
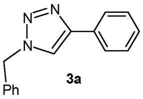
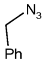
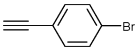
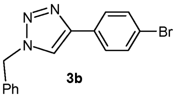
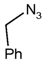
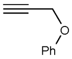
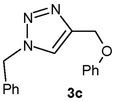
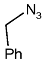
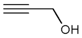
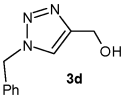
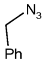
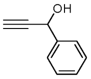
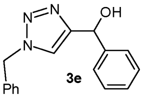
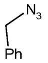
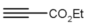
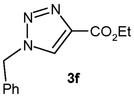
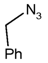
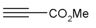
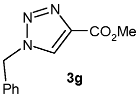
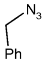
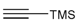
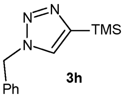
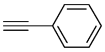
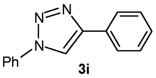
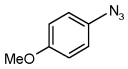
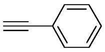
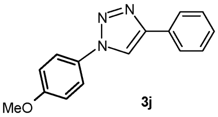
In general, the effect of catalytic performance can be viewed according to the shape of nanoparticles in terms of: (1) surface area; (2) the atoms on corners and edges; (3) exposed crystal faces.[12] The activity trend is: CuO hollow spheres > CuO hollow cubes > CuO urchins. In the case of the CuO(II) nanostructures used herein, it is suggested that this is simply a simple surface area effect, rather than an increase in reactivity at certain defect sites (entries 10–12, Table 1). The active surface areas and the crystallite sizes in the different CuO nanostructures would be main factors to decide their catalytic activities. The CuO nanostructures with different shapes were obtained by controlling the dissolution and precipitation rates of Cu_2O nanocubes under basic condition. The single crystalline domain sizes of the CuO nanostructures were measured to be 2 nm for hollow cubes, 4 nm for hollow spheres, and > 20 nm for urchin-like particles, respectively. The fast precipitation of CuO hollow cubes compared to urchin-like particles leads to smaller crystallite sizes (~2 nm), maintaining the original cube frame in the hollow particles. The slow CuO growth and precipitation rates of urchin-like particles lead to the largest single crystalline domains (> 20 nm). Generally, the smaller the size of the particles the higher is the active surface area leading to enhanced activity in catalysis. However, CuO hollow spheres showed slightly better activity than that of hollow cubes in Table 1. The lower activity of hollow cubes with smallest crystalline domains than that of hollow spheres can explained by their effective surface areas. The BET (Brunauer–Emmett–Teller) surface areas of CuO nanostructures measured by nitrogen sorption experiments are 79 $m^2\ g^{-1}$ for hollow cubes, 113 $m^2\ g^{-1}$ for hollow spheres, and 81 $m^2\ g^{-1}$ for urchin-like particles, respectively, and it is quite reasonable that the catalytic activities are also dependent on the active surface areas of the catalysts. When Et_3N (1.0 eq.) was added, the reaction was faster and was complete within 30 min (entry 13, Table 1).

Furthermore, good results were achieved using various terminal alkynes (Table 2). Acetylenes conjugated with an ester group such as phenyl propargyl ether reacted readily with benzyl azide. The corresponding triazoles 1-benzyl-4-(phenoxymethyl)-1*H*-1,2,3-triazole were obtained in high yields (entry 3). Hydroxy-substituted alkynes such as propargyl alcohol and 1-phenyl-2-propyn-1-ol also gave the expected adducts (1-benzyltriazol-4-yl)methanol and (1-benzyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanol as single regioisomers in good to high yields (entries 4 and 5). The reaction with alkynes containing electron-withdrawing substituents such as ethyl propiolate and methyl propiolate gave distinctly high yields (entries 6 and 7) while reactions with aliphatic alkynes such as ethynyltrimethylsilane was relatively sluggish (entry 8). In a second series of experiments, various azides bearing different groups were reacted with phenylacetylene. When the phenyl group is directly linked to the reactive azide, Phenyl azide or its analogue with a *para*-methoxy group gave the expected triazoles **3i** and **3j** as single regioisomers. A single regioisomer was always produced whatever the substitution and yields of isolated products remained excellent.

Additionally, any changes in the shape of the catalyst after the reaction was examined. As shown in Fig. 1 (and ESI†), the structure of CuO hollow spheres remained unchanged after the reaction, showing recyclability of the catalyst. After the reaction, the CuO hollow spheres was separated through centrifugation and used in click reactions with phenylacetylene at least three times without loss of catalytic activity. However, for more recycling, the collected quantity of the catalyst decreased (the quantity of the first use was 4.0 mg), and thus the yields were lowered. In order to compensate for this, current work in this lab is focused on immobilizing CuO hollow nanostructures on a support material such as charcoal for use as an improved heterogeneous catalyst.

In summary, oxidation of Cu_2O nanocubes has been controlled to yield CuO hollow cubes, hollow spheres or urchin-like particles, through a sequential dissolution–precipitation process. Various types of CuO nanoparticles have been used for the catalytic [3 + 2] cycloaddition of azides with terminal alkynes to provide products in good yields with high regioselectivity. Reaction conditions were substantially improved in

Table 2 [3 + 2] Cycloaddition of aides with terminal alkynes in the presence of CuO hollow spheres

Entry	Azide	Alkyne	Product	Conv (%)[a]
1			 3a	100
2			 3b	42
3			 3c	100
4			 3d	100
5			 3e	62
6			 3f	100
7			 3g	100
8			 3h	45
9			 3i	100
10			 3j	100

[a] Determined by ^{1}H-NMR. Yields are based on the amount of azide used.

comparison with previous catalytic systems and commercially available micro-size CuO. In addition, reactions were accelerated with stoichiometric Et_3N. Efforts are ongoing to explore the scope and limitations of the heterogeneous version of CuO hollow catalysis of the click reaction.

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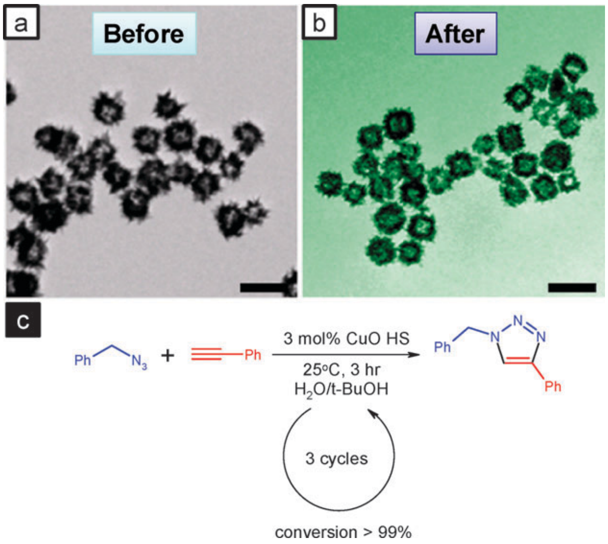

Fig. 1 TEM images of CuO hollow spheres before (a) and after use (b). The scale bars represent 200 nm. Recycling of click reactions catalyzed by CuO hollow spheres (c).

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