Copper nitride nanoparticles supported on a superparamagnetic mesoporous microsphere for toxic-free click chemistry[†]

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Copper nitride nanoparticles supported on a mesoporous superparamagnetic silica microsphere exhibit superior activity toward the Huisgen cycloaddition of azides and alkynes. The nitride catalyst offers significant advantages over homogeneous Cu catalysts.

Click chemistry represents a group of organic reactions that proceed rapidly under ambient conditions and give high yields with great selectivity.¹ The Huisgen 1,3-dipolar cycloaddition (HDC) of azides and alkynes catalyzed homogeneously by soluble copper complex has emerged as the most common click reaction;^{2,3} it is a powerful tool for covalently linking functionalized molecules.⁴ A major drawback of the catalyst is that it contains the cytotoxic Cu^I ion, which precludes its use in living systems and in reactions of industrial interest.⁵ In order to make the HDC reaction applicable to biomolecules, it is required to develop insoluble solid catalysts. Here we report a newly discovered copper nitride (Cu_3N) nanoparticle (NP) supported on a superparamagnetic silica microsphere, which exhibits superior activity toward the HDC reaction. In contrast to the Cu^I complexes,³ the heterogeneous Cu₃N catalyst is a solid and it is easily separated by applying a magnet; this raises the prospect of toxic-free click chemistry. The nitride catalyst can be applied to living and environmentally benign systems.

The typical procedure for carrying out the HDC reaction in solution has involved the use of stable Cu^{I} complexes such as CuI and CuSO₄/Na-ascorbate.³ Highly efficient reactions can also be heterogeneously catalysed by Cu and CuO particles on various supports as well as immobilized Cu complexes.⁶ It has been reported that Cu metal alone is able to catalyze this HDC reaction in solution; the reaction proceeds slowly.⁷ Careful examination of the Cu surface by various means, however, revealed that the reaction is catalyzed by the Cu^I species

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Fig. 1 Reaction scheme for the synthesis of a $Cu_3N/Fe_3N@SiO_2$ silica microsphere. Dark blue spheres and green ovals represent Fe_3N and Cu_3N nanoparticles embedded within mesoporous shells of a silical sphere, respectively.

formed in the native oxide layer on the Cu surface.⁸ This suggests that Cu-based oxides can promote the HDC reaction. In this regard, we have screened a number of materials containing Cu as potential heterogeneous catalysts and have singled out Cu₃N nitride as a promising candidate largely because the formal oxidation state of Cu in Cu₃N is +1, and also because its physical properties are quite similar to those of ionic solids. In addition, Cu₃N adopts the anti-ReO₃ structure with an open cubic framework of Cu₆N octahedra, which is suitable for interaction with guest organic molecules.⁹ Remarkably, a preliminary study with the supported Cu₃N nitride showed a high catalytic activity toward the HDC reaction, and hence it can be considered as a new heterogeneous solid catalyst that is free of cytotoxicity.

Our approach to the synthesis of Cu₃N NPs supported on superparamagnetic mesoporous silica microspheres is illustrated in Fig. 1, which is based on our previous work concerning the fabrication of the core/shell CoFe₂O₄@SiO₂ microsphere.¹⁰ Using two immiscible solvents iron precursors were incorporated into core/shell mesoporous silica microspheres, which were subject to annealing at 700 °C in NH₃. Iron nitride phases containing Fe₃N as a major component were formed within the mesoporous shells in the silica, which are denoted as Fe₃N@SiO₂. A Cu source was then infiltrated into the Fe₃N@SiO₂ microsphere, and this was followed by annealing at 250 °C in NH₃. This led to the formation of Cu₃N NPs within the shells. A crucial step for embedding nitride NPs within the mesoporous shells was the infiltration of Fe and Cu sources into the shells, thereby enabling nitride phases to grow exclusively within the pores. Hereafter we denote the resulting black microsphere with an average diameter of approximately 500 nm as Cu₃N/Fe₃N@SiO₂.

Transmission electron microscopy (TEM) images of $Cu_3N/Fe_3N@SiO_2$ show the core/shell structure, which has a shell thickness of approximately 100 nm surrounding the dense silica core (Fig. 2a and b). The surface morphology of

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Fig. 2 High resolution TEM images of $Cu_3N/Fe_3N@SiO_2$ with low and high magnifications (a and b). Elemental distribution maps of (c) Fe and (d) Cu present in $Cu_3N/Fe_3N@SiO_2$.

the silica template was sustained during the growth of Fe_3N and Cu_3N phases, suggesting that both nitride phases are successfully incorporated into pores in the shells without destruction of the parent core/shell shape. The scanning TEM was employed to observe the distribution of Cu and Fe atoms on a $Cu_3N/Fe_3N@SiO_2$ microsphere. Both elements are uniformly distributed over the silica surface (Fig. 2c and d), thus implying that agglomeration of Cu_3N and Fe_3N NPs is less likely to occur on the silica surface.

The formation of Cu₃N phase is evident from the XRD data of Cu₃N/Fe₃N@SiO₂ given in Fig. 3a. The first three strong reflections can index in a cubic cell (space group: *Pm3m*) of Cu₃N with a lattice parameter of 3.829 Å. The cell size is slightly larger than that obtained from bulk Cu₃N powders.¹¹ In addition to the peaks ascribed to the Cu₃N phase, several broad peaks originating from iron nitrides appeared in the XRD data (Fig. 3b). The average sizes of the Cu₃N and Fe₃N particles calculated by the Scherrer equation are 22.4 and 20.5 nm, respectively. The field-dependent magnetization



Fig. 3 XRD patterns of (a) $Cu_3N/Fe_3N@SiO_2$ and (b) $Fe_3N@SiO_2$. Calculated XRD patterns of Fe_3N and Cu_3N below the experimental data are obtained on the basis of crystallographic data. The inset is a unit cell structure of Cu_3N in which the Cu atoms occupy the edge centres of the unit cell and the N atoms are located at the cube corners.

data of $Cu_3N/Fe_3N@SiO_2$ collected at 10 and 300 K (see Fig. S1 in the ESI†) show that coercivity values are negligibly small, revealing the presence of superparamagnetic state.

Curve-fitting results of X-ray photoelectron spectroscopy (XPS) data of Cu₃N/Fe₃N@SiO₂ microspheres and Cu₃N powders show that the Cu $2p_{3/2}$ peak near 933 eV is composed of two peaks at 933 and 935 eV (see Fig. S2 in the ESI[†]). The former peak, shifted by approximately 0.7 eV to higher binding energy relative to that of Cu metal, indicates the presence of the Cu(I) species in Cu₃N.¹² The latter peak is ascribed to the Cu(II) ion present in the native CuO layer on the surface. Interestingly, a couple of satellite peaks around 942 eV associated with CuO can be distinctively observed in the spectra of bulk Cu₃N while they are buried among the background peaks for Cu₃N/Fe₃N@SiO₂. Although a purely ionic model might not be appropriate to describe the bonding nature of Cu₃N, the XPS results imply that Cu₃N is composed of Cu⁺¹ and N³⁻ ions. Bond valence calculations, where bond valence sums for Cu_3N are +0.90 at the Cu site and -2.69 at the N site, also support the XPS data.¹¹ It is thus evident that Cu₃N has an ionic character although a covalent nature should be included to accurately describe the chemical bonding in Cu₃N.

We conducted preliminary experiments on the HDC of benzyl azide (1) with phenylacetylene (2) to yield the expected triazole 3 with the Cu₃N/Fe₃N@SiO₂ catalyst. A wide range of amines and solvents were screened to optimize reaction conditions (see Tables S1 and S2 in the ESI[†]). All reactions proceeded rapidly in the presence of tertiary amines with good yields and high selectivity. In contrast, a similar reaction in the absence of amine yielded a small amount of 3, suggesting that amine promotes the HDC reaction as is the case for soluble CuI catalysts.¹³ Several organic solvents were tested in the presence of triethylamine. Among them, CH₃CN emerged as the most reliable solvent for the HDC reaction, and it was used in subsequent reactions. To confirm whether Cu₃N in Cu₃N/Fe₃N@SiO₂ plays a major role in accelerating the formation of triazole, the same experiment was conducted with bulk Cu₃N. Complete conversion was observed within 3 h; this clearly indicates that Cu₃N is the only active component in Cu₃N/Fe₃N@SiO₂ for the HDC reaction.

For general application, the HDC reaction was performed in the presence of $Cu_3N/Fe_3N@SiO_2$ with five alkynes and three azides, which led to triazoles in high yields (Table 1). The reusability of the $Cu_3N/Fe_3N@SiO_2$ catalyst was examined, where the reaction of **1** with **2** in the presence of the recycled catalyst was repeated up to 5 times. The recycled catalysts, separated by a magnet, showed activities toward the HDC reaction that were virtually identical to those of the virgin catalyst, indicating that leaching of Cu_3N in the catalyst is less likely to occur during the reaction process.

The essential element for the activity of the catalyst is believed to be the Cu^{I} species in $Cu_{3}N$. It should be noted that the solid $Cu_{3}N$ particle provides the active surface containing Cu^{I} species, which promotes the HDC reaction. The mechanism for the click reaction driven by the catalyst might be analogous to that of the well-known HDC reaction catalyzed by soluble Cu^{I} complexes although there are clear **Table 1** Synthesis of various 1,2,3-triazoles by $Cu_3N/Fe_3N@SiO_2$ catalyst^{*a*}

$\begin{array}{c} \hline R^{1} - N_{3} + = - \hline R^{2} \end{array} \xrightarrow[CU_{3}N/Fe_{3}N@SIO_{2}]{CH_{3}CN} \\ \hline CH_{3}CN \\ RT, shaking \end{array} \xrightarrow[N=N]{R^{1}} \hline N_{N=N} \\ \hline R^{2} \end{array}$			
	N ₃	$\rightarrow 0^{\circ}$ N ₃	HO
—=	12 h, 81	12 h, 82	12 h, 76
∩ H M	24 h, 89	4 d, 79	5 d, 72
NH NH	5 d, 79	14 d, 82	5 d, 89
O ₂ N N H	2 d, 89	4 d, 60	24 h, 84
N. N	24 h, 91	24 h, 90	24 h, 82

^{*a*} All reactions were conducted with 1.0 mmol of alkyne and 1.1 mmol of azide in 4 mL of acetonitrile using $Cu_3N/Fe_3N@SiO_2$ (20 mg) and 0.3 equiv. of Et₃N. The numbers in Table 1 imply 'time, yield (%)'.

distinctions between individual reaction steps associated with heterogeneous Cu₃N NPs and homogeneous Cu^I complexes.¹⁴

In conclusion, we have found that Cu_3N exhibits superior catalytic activity toward the HDC reaction. This click reaction catalyzed heterogeneously by Cu_3N possesses kinetics comparable to that of the reaction catalyzed homogeneously by soluble Cu^I complexes. Since Cu_3N is not cytotoxic, the nitride catalyst for the HDC reaction offers significant advantages over soluble Cu^I complexes. Moreover, the Cu_3N catalyst supported on a magnetic microsphere is recyclable, thus it can be applied to living and environmentally benign systems. This novel nitride can be considered as the next generation catalyst. It is expected to have considerable potential for use in a wide range of toxic-free click chemistry applications such as imaging and labelling of bio-molecules on live cells.

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