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## COMMUNICATION

## $Cu_2O$ acting as a robust catalyst in CuAAC reactions: water is the required medium $\ensuremath{^\dagger}$

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 $Cu_2O$  as the catalyst in water was found to be quite robust for the azide-alkyne cycloaddition (AAC) reaction, which was verified by a wide variety of applicable azides and alkynes. Water was proved to play an essential role because of a significant rate acceleration compared with reactions using organic solvents and conducted under neat conditions. The high catalytic performance of  $Cu_2O/H_2O$ system was further argued by decreasing the catalyst loading to ppm levels.

Since the seminal discovery of the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) by the groups of Sharpless and Meldal independently, this 'near-perfect' bond-forming reaction has found a myriad of applications in chemistry, biology, and materials science.<sup>1</sup> A plethora of copper catalytic systems have been utilized to catalyze this transformation including the combination of copper with other elements such as Cu(II)/sacrificial reducing agent, Cu(0)/oxidizing agent or Cu(I)/auxiliary ligand, and the use of Cu(I) species alone.<sup>2</sup> Despite these catalytic systems available, it still appeals as a more simple and practical catalyst for this reaction. Compared with other cuprous species, Cu<sub>2</sub>O is the most readily available and above all an inexpensive catalyst. For a long time, the surface of Cu<sub>2</sub>O has been assumed to be the catalytically active species in metallic Cu(0)-catalyzed AAC reactions,<sup>3</sup> supported by experimental evidence; for example, the catalytic activity of metallic Cu by washing with dilute HCl showed a dramatic drop.<sup>3a</sup> Unfortunately, reactions directly catalyzed by Cu<sub>2</sub>O powder were usually met with incomplete conversion and poor yields even after longer reaction times.<sup>4</sup> Until now, the catalytic capability of Cu<sub>2</sub>O in the CuAAC reactions has yet been thoroughly exploited because of lacking appropriate reaction conditions.

As our continued interest in developing and applying smart organic reactions to label biomolecules under bio-compatible conditions,<sup>5</sup> we noted that Cu<sub>2</sub>O has been emerging as a versatile catalyst for organic reactions such as coupling and cycloaddition reactions, some of which can be performed in water,<sup>6</sup> so we envisaged that water might be a required medium for Cu<sub>2</sub>O-AAC reactions. Further studies realized this hypothesis. In this context, we wish to report that Cu<sub>2</sub>O as the catalyst in water is quite robust for the CuAAC reactions, which was verified by the wide range of applicable organic azides and alkynes. Water was proved to play an essential role in Cu<sub>2</sub>O-AAC because a significant rate acceleration was observed in the presence of water compared with reactions using organic solvents and conducted under neat conditions. The high catalytic efficiency of Cu<sub>2</sub>O/H<sub>2</sub>O system was further argued by catalyst loadings as low as 100 part per million (ppm) under neat conditions. A plausible mechanism on the water-acceleration effect was also tentatively suggested. During our preparation of this manuscript, Kong and coworkers reported polyvinylpyrrolidone (PVP) stabilized Cu<sub>2</sub>O nanoparticles as catalyst for the CuAAC reaction in water, however, an additional operation for preparing the PVP-coated Cu<sub>2</sub>O nanoparticles was required; moreover, only a limited set of azides and alkynes were tested in their protocol.<sup>7</sup>

Initially, the survey of reaction parameters including copper catalysts and solvents was performed using the cycloaddition of tosyl azide 1a with phenylacetylene 2a as a model reaction, because N-sulfonyl triazoles 3 have been proved convenient precursors of azavinyl carbenes in metal-catalyzed transannulation,<sup>8</sup> while only a few of procedures for their synthesis are available to date.4b,9 Therefore it is highly desirable to search for a simple, practical and efficient catalyst system. As shown in Table 1, in the presence of 20 mol% lutidine, CuI promotes the cycloaddition both in CHCl<sub>3</sub> and in water; without the lutidine, the full conversion can not occur in water (entries 1-3). CuCl could result in a complete conversion with a good yield, but would require a longer reaction time (entry 4). Other cuprous salts and complexes, and cupric compounds showed little or no catalytic effect, similar to the situation without catalyst (entries 5-9). To our delight, Cu<sub>2</sub>O catalyzed this reaction in water within a very short period of time, affording an excellent yield of 3a (entry 10). Noticeably, there was no amide by-product formed in this process through the threecomponent reactions of alkynes, sulfonyl azides and H<sub>2</sub>O as reported by Chang et al.<sup>10</sup> Using high purity Cu<sub>2</sub>O (99.99%)

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 Table 1
 Cycloaddition of tosyl azide 1a with phenylacetylene 2a under varying conditions<sup>a</sup>

	$\mathbb{O}_{\tilde{O}}^{O} \mathbb{N}_{3} + = $	Cat. Solvent, R	r⊤ –∕⊂)– <sup>0</sup> sö	−N. N <sup>≈</sup> N
	1a 2a			3a
Entry	Cat.	Solvent	Time (h)	Yield (%) <sup>b</sup>
1	CuI <sup>c</sup>	CHCl <sub>3</sub>	12	80
2	CuI <sup>c</sup>	$H_2O$	12	79
3	CuI	$H_2O$	12	$45(55)^d$
4	CuCl	$H_2O$	24	70
5	CuBr	$H_2O$	12	trace
6	$[(IPr)_2Cu]PF_6$	$H_2O$	12	0
7	CuCl <sub>2</sub>	$H_2O$	12	0
8	CuO	$H_2O$	12	0
9	no	$H_2O$	12	0
10	Cu <sub>2</sub> O	$H_2O$	4	90
11	$Cu_2O^e$	$H_2O$	3	91
12	Cu <sub>2</sub> O	DMSO	12	trace
13	Cu <sub>2</sub> O	CHCl <sub>3</sub>	12	$20 \ (80)^d$
14	$Cu_2O$	THF	12	trace
15	Cu <sub>2</sub> O	$CH_3OH$	12	trace

<sup>*a*</sup> Reactions were performed with phenylacetylene (1.2 mmol), tosyl azide (1 mmol), and [Cu] (10 mol%) in solvent (1 mL) at room temperature. <sup>*b*</sup> Isolated yields. <sup>*c*</sup> 20 mol% lutidine was added. <sup>*d*</sup> Recovery of tosyl azide in bracket, determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>*e*</sup> High purity of Cu<sub>2</sub>O (99.99%) was used.

only slightly increased the rate, thus negating the influence of metal impurities (entry 11). In contrast, the representative polar, nonpolar, and protonic organic solvents instead of water all gave poor yields or trace amount of triazole **3a** (entries 12–15). Water was therefore established as an appropriate reaction medium for efficient  $Cu_2O$ -AAC reactions.<sup>11</sup>

Next, the reaction scope catalyzed by Cu<sub>2</sub>O in water was investigated. As shown in Table 2, a wide variation of azides and alkynes efficiently fused and produced the corresponding N-sulfonyl triazoles 3 and N-aryl/alkyl triazoles 4 in good to excellent yields. For the synthesis of N-sulfonyl triazoles 3, either varying the substituent on the phenyl acetylene or using fused aromatic alkynes did not induce appreciable changes in the reaction efficiency (**3b–3g**). By comparison, the reaction of aliphatic alkynes is a little slower, albeit yielding triazoles 3h-3n in good to high yields. A range of functional groups including halo-, cyclopropyl-, ethoxy-, amide, ether and double bonds were well tolerated. In addition to the tosyl azide, 4-chlorophenyl, 2-naphthyl, methyl, as well as bulky camphor sulfonyl azides were all suitable to this Cu<sub>2</sub>O-catalyzed procedure in water (30-3r). The chemoselective formation of triazole 4a, leaving the sulfonyl azide intact, demonstrated a much higher reactivity for alkyl azide. Thus, the reactions for the synthesis of N-aryl/alkyl triazoles 4 generally proceeded much faster, and also displayed higher functional group tolerance, for example, hydroxyl, ester, and triethylsilyl groups were all tolerated (4b-4j). These results demonstrated that Cu<sub>2</sub>O as catalyst in water is quite robust for AAC reactions, featuring a wide scope of substrates, clean conversion and high reaction efficiency in open-air conditions.

The outstanding catalytic performance of  $Cu_2O$  under an 'in water' environment led us to investigate the effect of water, as well as the possibility of decreasing the amount of catalyst used in the transformation. As shown in Table 3, only a trace amount of

trizaole 3a can be detected from the reaction mixture of alkyne 1a with tosyl azide 2a in the presence of 10 mol% Cu<sub>2</sub>O under neat conditions in 6 h, and most starting materials were left, where the reaction has been carried out in a glove box to minimize the impact of water (entry 1). Once small amount of water (100 µl, 5.5 mmol) was added, the conversion guickly completed within 2.5 h, yielding 89% of 3a (entry 2), so the rate acceleration is not simply a consequence of the increased concentration of the reacting species. Undoubtedly, water plays a crucial role in the Cu<sub>2</sub>O-AAC reaction. Next, we varied the amount of Cu<sub>2</sub>O and the reaction temperature in the presence of 100  $\mu$ l H<sub>2</sub>O. It was found that a slight increase in the reaction temperature can compensate for the decrease in reaction rate caused by reducing the catalyst. Delightfully, a small amount (100 ppm) of Cu<sub>2</sub>O still effectively catalyzed a complete conversion within 12 h at 50 °C, yielding 87% of 3a. This is comparable with the catalytic efficiency of some Cu(I) complexes (entries 3-5).<sup>12</sup> The results listed in Table 4 show some of the azide-alkyne reactions under neat conditions in the presence of a trace amount of water (100 µl) at low Cu<sub>2</sub>O loading (100 ppm). All of reactions proceeded smoothly, affording good to excellent yields of the corresponding triazoles 3 and 4.

Water appears to act as an activator for Cu<sub>2</sub>O catalyst. To gain some insight into the activation pathway of water, we carried out a deuterium experiment. Reaction of tosyl azide **1a** with phenylacetylene **2a** in D<sub>2</sub>O offered the desired triazole **3a-D** with 92% *d*-incorporation at the 5-position (eqn (1)). Based on this information as well as the results of theoretical calculation on the reaction mechanism from other groups,<sup>2,13</sup> we tentatively suggested that water might actively take part in the formation of the transion-state complex of azide and alkyne on the surface of Cu<sub>2</sub>O, and somehow stabilize it, finally assist the reaction by speeding up the protiolysis step that cleaves the Cu–C bond of Cu-triazolyl intermediate, leading to the regeneration of the catalytically active Cu(1) species.

$$1a + 2a \xrightarrow[D_2O, RT, 8h]{0} \xrightarrow[S_1]{0} \xrightarrow[S_1]{$$

In conclusion, we have demonstrated that Cu<sub>2</sub>O acted as a robust catalyst in water for CuAAC reactions making a wide variety of triazoles, without additional stabilizing ligands. Due to the simplicity and practicality of the Cu<sub>2</sub>O/H<sub>2</sub>O catalyst system, our findings are striking in terms of further advancing the application of CuAAC click chemistry, particularly under 'in water' conditions. Further studies to clarify the mechanism of the water-accelerated Cu<sub>2</sub>O-AAC reaction in combination with theoretical calculations are underway.

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 Table 2
 Cu<sub>2</sub>O-catalyzed azide-alkyne cycloaddition with a wide variety of alkynes and azides in water<sup>a</sup>

" (a) *Reagents and Conditions*: alkynes (1.2 mmol), azides (1.0 mmol),  $Cu_2O$  (0.1 mmol), water (1 mL), RT; (b) The 1,4-regioselectivity of **4b** was confirmed by an NOE study; (c) The reaction for **4g** was performed at 50 °C.

 
 Table 3
 Condition optimization for the cycloaddition of phenylacetylene 1a with tosyl azide 2a under neat conditions<sup>a</sup>

Entry	Cu <sub>2</sub> O (mol%)	Water $(\mu l)^b$	Temp. (°C)	Time (h)	Yield (%)
1	10	0	RT	6	traced
2	10	100	RT	2.5	89
3	1	100	40	5	91
4	0.1	100	50	7	88
5	100 ppm	100	50	12	87

<sup>*a*</sup> Reactions were performed with tosyl azide **1a** (0.5 mmol), phenylacetylene **2a** (0.6 mmol). <sup>*b*</sup> Water was used as an additive. <sup>*c*</sup> Isolated yields. <sup>*d*</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture.

Table 4 Cu<sub>2</sub>O-AAC reaction under neat conditions<sup>a</sup>



 $^a$  Reagents and Conditions: alkynes (0.6 mmol), azides (0.5 mmol), Cu\_2O (100 ppm), water (100  $\mu$ l), 50 °C.

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