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Reusable Cu_2O/PPh_3/TBAB System for the Cross-Couplings of Aryl Halides and Heteroaryl Halides with Terminal Alkynes

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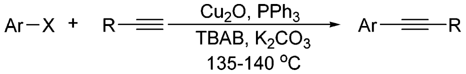
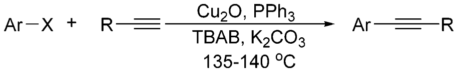


$$Ar{-}X + R{-}{\equiv} \xrightarrow[\substack{TBAB,\ K_2CO_3\\ 135\text{-}140\ ^{\circ}C}]{Cu_2O,\ PPh_3} Ar{-}{\equiv}{-}R$$

An efficient and reusable Cu_2O/PPh_3/TBAB (n-Bu_4NBr) system for the cross-coupling reactions of aryl and heteroaryl halides with terminal alkynes has been developed. Four types of Cu_2O, including bulky Cu_2O, cubic Cu_2O nanoparticles, octahedral Cu_2O nanoparticles, and spherical Cu_2O nanoparticles, were examined, and the octahedral Cu_2O nanoparticles were found to be the most effective catalyst for the reaction. In the presence of the octahedral Cu_2O nanoparticles, PPh_3, and TBAB, a variety of aryl and heteroaryl halides were reacted with alkynes including alkynols smoothly in moderate to good yields. Noteworthy is that the Cu_2O/PPh_3/TBAB system can be recovered and reused several times without loss of any activities.

Recently, much attention has been attracted to the use of copper complexes as the catalysts for the Sonogashira-type cross-coupling of aryl halides with terminal alkynes.[1,2] This is because palladium complexes, the most commonly used catalysts for the Sonogashira-type cross-coupling reaction, are considerably expensive, which limits their application in industry.[3] Recent studies show that ligated copper halides by PPh_3,[2a] 1,10-phenanthroline,[2b,e] *N*,*N*-dimethylglycine,[2c] ethylenediamine,[2d] 2-aminopyrimidine-4,6-diol,[2f] and tertiary amines[2g,h] are effective catalysts in the Sonogashira reaction, while Cu_2O is a less active. Miura and co-workers,[2a] for instance, have reported the first catalytic Sonogashira-type cross-couplings between aryl iodides or vinyl iodides with terminal alkynes using CuI/PPh_3 as the catalytic system and DMF as the solvent, but the Cu_2O/PPh_3 catalytic system provided a rather low yield of the Sonogashira product after 20 h even in the reaction of iodobenzene with phenylacetylene at 120 °C. On the other hand, the reported catalytic systems were not recovered and reused because of the harmful organic solvents (often DMF) in all of these copper-catalyzed transformations. Furthermore, alkynols were found to be unsuitable substrates, and heteroaryl halides as the substrates remain unexplored.[1,2] Recently, the ligand-free copper nanocluster-catalyzed Sonogashira reaction was developed by Rothenberg and co-workers. However, no recycling of the copper nanoclusters process was tested, and the scope was still limited to the activated aromatic bromides.[2i] Very recently, we have also reported solventless $Cu(OAc)_2$-catalyzed couplings between aryl halides and terminal alkynes using TBAF as a base and 4,6-dimethoxypyrimidin-2-amine as a ligand, and only aryl iodides and the activated aryl bromides were suitable substrates for the Sonogashira coupling reaction.[2f] From the point of economy and environment, the development of some efficient and reusable copper catalytic systems for the solventless Sonogashira reaction of a wide range of aryl halides is still challenging. Here, we wish to report the combination of the octahedral Cu_2O nanoparticles with PPh_3 and TBAB as an efficient and reusable system for the Sonogashira-type cross-coupling reaction under solventless conditions (eq 1). It is noteworthy that the scope of the substrates is expanded to heteroaryl halides and alkynols.



$$Ar{-}X + R{-}{\equiv} \xrightarrow[\substack{TBAB,\ K_2CO_3\\ 135\text{-}140\ ^{\circ}C}]{Cu_2O,\ PPh_3} Ar{-}{\equiv}{-}R \qquad (1)$$

Although many shapes of Cu_2O nanoparticles, such as octahedral,[4] cube,[5] wire, rod, and unformed amorphism,[6] were prepared, few papers have been reported on the use of Cu_2O

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[1] For special reviews on copper-catalyzed cross-couplings, see: (a) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int Ed.* **2000**, *39*, 2632. (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (d) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.

[2] For papers on the Sonogashira cross-coupling reaction catalyzed by a catalytic amount of copper, see: (a) Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716. (b) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (c) Ma, D, Liu, F. *Chem. Commun.* **2004**, 1934. (d) Wang, Y. F.; Deng, W.; Liu, L.; Guo, Q. X. *Chin. Chem. Lett.* **2005**, *16*, 1197. (e) Saejueng, P.; Bates, C. G.; Venkataraman, D. *Synthesis* **2005**, 1706. (f) Xie, Y.-X.; Deng, C.-L.; Pi, S.-F.; Li, J.-H.; Yin, D.-L. *Chin. J. Chem.* **2006**, *24*, 1290. (g) Guo, S.-M.; Deng, C.-L.; Li, J.-H. *Chin. Chem. Lett.* **2007**, *18*, 13. (h) Li, J.-H.; Li, J.-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, M.-B.; Hu, X.-C. *J. Org. Chem.* **2007**, *72*, 2053. (i) Thathagar, M. B.; Beckers, J.; Rothenberg, G. *Green Chem.* **2004**, *6*, 215. (j) Li, J.-H.; Li, J.-L.; Xie, Y.-X. *Synthesis* **2007**, 984.

[3] For reviews, see: (a) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998. (b) Miyaura, N. *Cross-Coupling Reaction*; Springer: Berlin, 2002. (c) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 2004. (d) Doucei, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (e) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.

[4] For representative papers on the preparation of the octahedral Cu_2O nanoparticles, see: (a) Xu, H.; Wang, W.; Zhu, W. *J. Phys. Chem. B* **2006**, *110*, 13829. (b) Ng, C. H. B.; Fan, W. Y. *J. Phys. Chem. B* **2006**, *110*, 20801.

[5] For representative papers on the preparation of the cubic Cu_2O nanoparticles, see: (a) Guo, L.; Murphy, C. J. *Nano Lett.* **2003**, *3*, 231. (b) Zeng, X.-W.; Zhang, Y.-H.; Luo, C.-C.; Zeng, Y.-W.; Wang, Y.-G. *Chin. J. Inorg. Chem.* **2005**, *21*, 1515. (c) Singh, D. P.; Neti, N. R.; Sinha, A. S. K.; Srivastava, O. N. *J. Phys. Chem. C* **2007**, *111*, 1584.

[6] For representative papers on the preparation of the other shapes of Cu_2O nanoparticles, see: (a) Cao, M.; Hu, C.; Wang, Y.; Guo, Y.; Guo, C.; Wang, E. *Chem. Commun.* **2003**, 1884. (b) Zhang, J.; Liu, J.; Peng, Q.; Wang, X.; Li, Y. *Chem. Mater.* **2006**, *18*, 867. (c) Wu, W.-T.; Wang, Y.; Shi, L.; Pang, W.; Zhu, Q.; Xu, G.; Lu, F. *J. Phys. Chem. B* **2006**, *110*, 14702. (d) Yao, W.-T.; Yu, S.-H.; Zhou, Y.; Jiang, J.; Wu, Q.-S.; Zhang, L.; Jiang, J. *J. Phys. Chem. B* **2005**, *109*, 14011.

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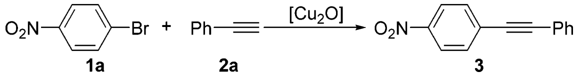
TABLE 1. Screening Conditions[a]



entry	[Cu_2O]	ligand	yield (%)[b]
1	cubic Cu_2O nanoparticles	P(*o*-tol)$_3$ (**L1**)	57
2	bulky Cu_2O	P(*o*-tol)$_3$ (**L1**)	55
3	spherical Cu_2O nanoparticles	P(*o*-tol)$_3$ (**L1**)	63
4	octahedral Cu_2O nanoparticles	P(*o*-tol)$_3$ (**L1**)	78
5	octahedral Cu_2O nanoparticles		trace
6[c]	octahedral Cu_2O nanoparticles	PPh_3 (**L2**)	90
7	octahedral Cu_2O nanoparticles	PCy_3 (**L3**)	54
8	octahedral Cu_2O nanoparticles	P(2,6-diMeC_6H_4)$_3$ (**L4**)	55
9	octahedral Cu_2O nanoparticles	P(*n*-Bu)$_3$ (**L5**)	48
10	octahedral Cu_2O nanoparticles	$POPh_3$ (**L6**)	70
11	octahedral Cu_2O nanoparticles	1,1′-bipyridinyl (**L7**)	41
12	octahedral Cu_2O nanoparticles	DABCO (**L8**)	65
13	cubic Cu_2O nanoparticles	PPh_3 (**L2**)	76
14	bulky Cu_2O	PPh_3 (**L2**)	73
15	spherical Cu_2O nanoparticles	PPh_3 (**L2**)	81
16[d]	octahedral Cu_2O nanoparticles	PPh_3 (**L2**)	91
17[e]	octahedral Cu_2O nanoparticles	PPh_3 (**L2**)	81
18[f]	octahedral Cu_2O nanoparticles	PPh_3 (**L2**)	35

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.7 mmol), [Cu] (10 mol %), ligand (20 mol %), K_2CO_3 (1 mmol), and TBAB (1.5 g) at 135−140 °C for 24 h. [b] Isolated yield. [c] Average yield of three runs. [d] At 120 °C for 48 h. [e] Cs_2CO_3 (1 mmol) instead of K_2CO_3. [f] Et_3N instead of K_2CO_3.

nanoparticles in organic synthesis.[7] Thus, further application of them as catalysts in organic synthesis should be intensively pursued. Very recently, we have developed the cubic Cu_2O nanoparticles combined with P(*o*-tol)$_3$ as an alternative Stille cross-coupling catalytic system in TBAB.[7a] We then attempted to apply the cubic Cu_2O nanoparticles/P(*o*-tol)$_3$ (**L1**)/TBAB system in the Sonogashira-type reaction of 1-bromo-4-nitrobenzene (**1a**) with phenylacetylene (**2a**). To our delight, a moderate yield of the target product **3** was isolated after 24 h (entry 1). It was found that the yield of **3** was reduced slightly using the bulky Cu_2O (entry 2). These results prompted us to further evaluate the copper catalyst. After a series of trials, we observed that the octahedral Cu_2O nanoparticles were highly active in the Sonogashira reaction (Table 1, entries 1−4). In the presence of the octahedral Cu_2O nanoparticles, **L1**, and TBAB, the yield of **3** was enhanced to 78% (entry 4). Subsequently, a series of other ligands were evaluated, and PPh_3 (**L2**) provided the highest yield (entries 5−12). Without any ligands, substrate **1a** was treated with alkyne **2a**, the octahedral Cu_2O nanoparticles, K_2CO_3, and TBAB at 135−140 °C for 24 h to afford a trace amount of **3**, whereas the yield was increased sharply to 90% when PPh_3 (**L2**) was added (entries 5 and 6). Interestingly, the Cu_2O/**L2**/TBAB system could be recovered and reused at least three times without any loss of activity. The results of three runs showed that they were almost consistent in yields and rates (entry 6; run 1 = 88%; run 2 = 90%; and run 3 = 93%). The results showed that the cubic Cu_2O nanoparticles, the spherical Cu_2O nanoparticles, and the bulky Cu_2O were still inferior to the octahedral Cu_2O nanoparticles even in the presence of **L2** (entries 6 and 13−15). Finally, both the reaction temperature and base effects were investigated (entries 6 and 16−18). It turned out that K_2CO_3 at 135−140 °C provided the best results (entry 6). Note that high yield of the target product **3** is still achieved when the reaction can be conducted at 120 °C after prolonging the reaction time (entry 16).

As listed in Table 2, a variety of aryl halides could undergo the reaction with terminal alkynes smoothly under the standard reaction conditions, demonstrating the versatility of the octahedral Cu_2O nanoparticles. Aryl iodides **1b**−**1f**, whether electron-deficient or electron-rich, all worked well with alkynes **2a**−**2e** bearing aryl, heteroaryl, alkyl, or hydroxy groups in the presence of the octahedral Cu_2O nanoparticles, PPh_3 (**L2**), K_2CO_3, and TBAB (entries 1−11). Moreover, the Cu_2O/**L2**/TBAB system in these couplings could be reused at least three times without loss of any activity. 1-Iodo-2-methylbenzene (**1d**), for instance, reacted with alkyne **2a** efficiently to give similar results in five runs using the recovered system (entry 5). *p*-Iodoanisole (**1e**), a deactivated substrate, was also coupled with alkynes **2a**−**2e**, respectively, to afford the target products **8**−**12** in moderate to good yields (entries 6−10). It is interesting to reveal that the reaction between 2-iodobenzaniline (**1f**) and alkyne **2a** gave the corresponding 2-(2-phenylethynyl)benzenamine **13**, not the often reported 2-phenyl-1*H*-indole,[2,3] in a 50% yield (entry 11). It was found that the standard conditions were also effective for the reaction of another activated aryl bromide **1g** (entry 12). Although higher loadings of Cu_2O were required, moderate yields were still achieved in the couplings of the less active bromides **1h** and **1i** (entries 13−15). While the reaction of bromobenzene **1h** with alkyne **2a** produced the corresponding desired product **4** in a rather low yield at a loading of 10 mol % of Cu_2O, the yield of **4** was increased to 55% in the presence of 20 mol % of Cu_2O (entries 13 and 14). Gratifyingly, the coupling of 1-chloro-4-nitrobenzene (**1j**) with alkyne **2a** was conducted successfully in high yield in the presence of Cu_2O, **L2**, K_2CO_3, and TBAB (entry 16). Unfortunately, both chlorides **1k** and **1l** were not suitable substrates even in the presence of 20 mol % of Cu_2O (entries 17 and 18).

To our delight, heteroaryl bromides and chlorides are suitable substrates for the Sonogashira reaction under the standard conditions (Table 3). In the presence of the octahedral Cu_2O nanoparticles, PPh_3 (**L2**), K_2CO_3, and TBAB, 3-bromopyridine

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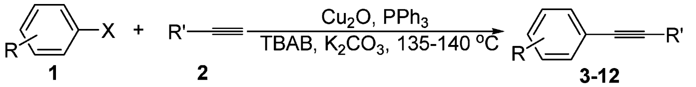
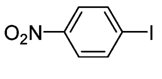
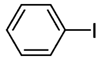
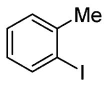
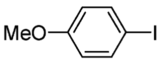
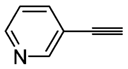
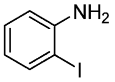
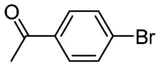
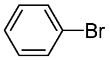
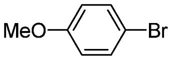
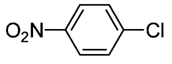
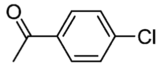
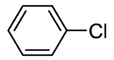
(7) For selected papers, see: (a) Li, J.-H.; Tang, B.-X.; Tao, L.-M.; Liang, Y.; Zhang, M.-B. *J. Org. Chem.* **2006**, *71*, 7488. (b) White, B.; Yin, M.; Hall, A.; Sergey, D. L.; Rahman, T.; Turro, N.; O'Brien, S. *Nano Lett.* **2006**, *6*, 2095.

TABLE 2. Octahedral Cu_2O Nanoparticles/PPh_3 (L2)-Catalyzed Cross-Couplings of Aryl Halides (1) with Terminal Alkynes (2) in TBAB[a]



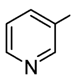
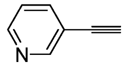
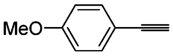
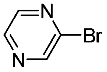
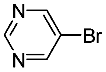
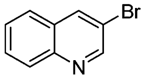
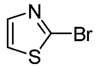
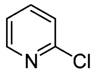
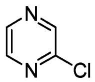
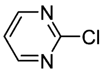
entry	aryl halide	alkyne	recycle no	time (h)	yield (%)[b]
1	 (**1b**)	Ph—≡ (**2a**)		20	88 (**3**)
			1	20	91 (**3**)
			2	20	93 (**3**)
			3	20	92 (**3**)
			4	20	95 (**3**)
2	 (**1c**)	(**2a**)		24	96 (**4**)
3	(**1c**)	n-C_5H_{11}—≡ (**2b**)		36	95 (**5**)
4	(**1c**)	≡—$(CH_2)_2OH$ (**2c**)		36	93 (**6**)
5	 (**1d**)	(**2a**)		24	83 (**7**)
			1	24	85 (**7**)
			2	24	85 (**7**)
			3	24	84 (**7**)
			4	24	88 (**7**)
6	 (**1e**)	(**2a**)		20	95 (**8**)
			1	20	93 (**8**)
			2	20	96 (**8**)
7	(**1e**)	(**2b**)		36	98 (**9**)
8	(**1e**)	(**2c**)		36	61 (**10**)
9	(**1e**)	≡—CH_2OH (**2d**)		36	66 (**11**)
10	(**1e**)	 (**2e**)		36	71 (**12**)
11	 (**1f**)	(**2a**)		24	50 (**13**)
12	 (**1g**)	(**2a**)		26	90 (**14**)
13	 (**1h**)	(**2a**)		30	23 (**4**)
14[c]	(**1h**)	(**2a**)		30	55 (**4**)
15[c]	 (**1i**)	(**2a**)		36	40 (**4**)
16	 (**1j**)	(**2a**)		30	83 (**3**)
17[c]	 (**1k**)	(**2a**)		30	26 (**14**)
18[c]	 (**1l**)	(**2a**)		36	10 (**4**)

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.7 mmol), octahedral Cu_2O nanoparticles (10 mol %), **L2** (20 mol %), K_2CO_3 (1 mmol), and TBAB (1.5 g) at 135−140 °C. [b] Isolated yield. [c] Octahedral Cu_2O (20 mol %) and ligand (40 mol %).

(**1m**) was reacted with alkyne **2a**, **2b**, **2e**, or **2f** smoothly to afford the corresponding products **15**, **16**, **18**, and **12** in moderate to good yields (entries 1, 2, 4, and 5). However, alkynol **2c** was an unsuitable substrate for the reaction with bromide **1m** (entry 3). The other heteroaryl bromides **1n**−**q** also underwent the reaction successfully in moderate to good yields under the same conditions (entries 6−9). Although 2-chloropyridine (**1r**) provided a low yield, the other two heteroaryl chlorides **1s** and **1t** worked well with alkyne **2a** to give the target products in high yields (entries 10−12). It is worth noting that the Cu_2O/**L2**/TBAB system in the couplings of **1m** and **1s** with **2a** could also be recovered and reused (entries 1 and 11).

In conclusion, we have developed a novel copper catalytic system for the Sonogashira cross-coupling reaction. In the presence of the octahedral Cu_2O nanoparticles, **L2**, K_2CO_3, and TBAB, a variety of aryl and heteroaryl halides could perform

TABLE 3. The Cu_2O/PPh_3 (L2)/TBAB System for the Reactions of Heteroaryl Halides (1) with Terminal Alkynes (2)[a]

entry	aryl halide	alkyne	recycle no	time (h)	yield (%)[b]
1	 (**1m**)	Ph—≡ (**2a**)		24	83 (**15**)
			1	24	84 (**15**)
			2	24	88 (**15**)
2	(**1m**)	n-C_5H_{11}—≡ (**2b**)		24	69 (**16**)
3	(**1m**)	≡—$(CH_2)_2OH$ (**2c**)		24	trace (**17**)
4	(**1m**)	 (**2e**)		24	82 (**18**)
5	(**1m**)	 (**2f**)		24	74 (**12**)
6	 (**1n**)	(**2a**)		26	48 (**19**)
7	 (**1o**)	(**2a**)		24	46 (**20**)
8	 (**1p**)	(**2a**)		24	87 (**21**)
9	 (**1q**)	(**2a**)		36	43 (**22**)
10	 (**1r**)	(**2a**)		31	19 (**23**)
11	 (**1t**)	(**2a**)		24	90 (**19**)
			1	24	91 (**19**)
			2	24	95 (**19**)
			3	24	91 (**19**)
			4	24	98 (**19**)
12	 (**1s**)	(**2a**)		24	76 (**24**)

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.7 mmol), octahedral Cu_2O nanoparticles (10 mol %), **L2** (20 mol %), K_2CO_3 (1 mmol), and TBAB (1.5 g) at 135−140 °C. [b] Isolated yield.

the coupling with terminal alkynes efficiently in moderate to excellent yields. Furthermore, the Cu_2O/**L2**/TBAB system could be reused several times without loss of activity. Noteworthy is that the couplings of alkynols are successful under the present conditions. Efforts to apply the catalytic system in other cross-coupling transformations are underway in our laboratory.

Experimental Section

Typical Experimental Procedure for the Cu_2O/PPh_3/TBAB (*n*-Bu_4NBr) System for the Cross-Coupling Reactions of Aryl and Heteroaryl Halides with Terminal Alkynes. A mixture of aryl halide **1** (0.5 mmol), alkyne **2** (0.7 mmol), pyramid-like Cu_2O nanoparticles (10 mol %), PPh_3 (L2; 20 mol %), K_2CO_3 (2 equiv), and TBAB (1.5 g) was stirred at 135−140 °C for the desired time (indicated in Table 2) until complete consumption of starting material was monitored by TLC. After the reaction was finished, diethyl ether was poured into the mixture, then washed with water, extracted with diethyl ether, dried with anhydrous Na_2SO_4, and evaporated under vacuum, and the residue was purified by flash column chromatography (hexane or hexane/ethyl acetate) to afford the desired coupled product.

After initial experimentation, the residue (the Cu_2O nanoparticles/PPh_3/TBAB system) was then solidified (evaporated in vacuo and cooled) and subjected to a second run of the Sonogashira reaction by charging with the same substrates (aryl halide, alkyne, and K_2CO_3).

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Supporting Information Available: Analytical data and spectra (^1H and ^{13}C NMR) for all the products **3**−**16**, **18**−**22**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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