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# Exposure to Air Boosts CuAAC Reactions Catalyzed by PEG-stabilized Cu Nanoparticles

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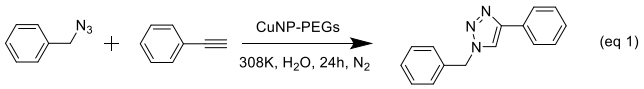
**New PEG-stabilized CuNP catalysts are designed upon Cu(II) reduction with sodium naphthalenide in MeCN followed by simple purification using the salting-out effect. Their catalytic activity in CuAAC is boosted upon exposure 30 min in air producing $Cu_2O$ NPs. These NPs are also supported on SBA-15 providing excellent recyclable heterogeneous catalysts that are applied in low amounts for efficient "click" functionalization.**

Among the various "click" reactions[1] Cu-catalyzed azide alkyne cycloaddition (CuAAC)[2] (eq 1) undisputedly dominates with applications spanning over organic,[3] polymer,[4] biomedical[5] and materials[6] chemistry.



(eq 1)

Since the early report of the use of $CuSO_4$ + Na ascorbate,[7] a large variety of metal catalysts have been published with the aim to decrease the amount of toxic Cu sources and improve the greenness of the reaction medium and conditions.[2-8] Transition metal nanoparticles (NPs), in particular those of noble metals, are excellent ligand-free catalysts in green solvents for many reactions.[9] Among these nanocatalysts, biometal NPs of the first-raw late transition metals are attracting increasing attention, although they are traditionally believe to be inferior catalysts compared to noble transition metal NP catalysts. Along this line, the finding by a number of research groups that CuNPs and Cu nanomaterials are active catalysts for the CuAAC reaction is of particular interest, because these catalysts avoid the use of costly and eventually toxic ligands.[9] CuNPs are usually formed by reduction of a Cu salt by a reductant such as $NaBH_4$ in the presence of a stabilizer, and the resulting CuNPs are supposed to contain zero-valent Cu,[10,11] although Cu nanomaterials under both Cu(I)[12] and Cu(II)[13] oxidation states have also been reported with catalytic activity for this reaction.[10-13] Molecular CuAAC catalysts have clearly been shown to be active as Cu(I) derivatives,[2,10,12] but the oxidation state that is actually most active in nanomaterials is often not so well defined. Cu(0) nanomaterials might be active in the Cu(0) state[10,11] or, as they are easily oxidized in particular in air, their catalytic activity can be due to Cu(I)[10,12] or Cu(II).[10,13] Cu(II) catalysts have been proposed for click reactions, but the possibility of their *in situ* reduction to Cu(I), in particular by azido derivatives or other substrates, cannot be underestimated.

Here we report new PEG-stabilized, recyclable, homogeneous and heterogeneous CuNP catalysts of the CuAAC reactions including applications to various biomolecule functionalization with low Cu amounts. In the same time we also wish to shed light on the problem on the optimized Cu oxidation state in CuNPs for "click" catalysis by comparing the catalytic activity in CuAAC reactions of these new Cu(0)NPs with those obtained upon exposure to air. In particular, we have now examined the catalytic activity of Cu(0)NPs synthesized by reduction of $CuSO_4 \cdot 5H_2O$ by the strong reductant sodium naphthalenide and stabilized by polyethylene glycol (PEG-2000, eq 2).

$CuSO_4$ + 2 Na naphthalenide + PEG → Cu(0)NP-PEG + $Na_2SO_4$ + 2 naphthalene (eq 2)

Sodium naphthalenide, with a redox potential $E^\circ_{NaNaph/NaNaph^-}$ of -3.1V vs. NHE in THF[14] has recently been used successfully for the reduction of early transition metal salts to the corresponding zero-valent NPs.[15] We show herein that the catalytic activity of CuNPs synthesized using this method is boosted upon exposure to air.

Whereas various stabilizers such as *N*,*N*-dimethylformamide, cetyltrimethylammonium bromide, alkylthiolates, phosphines are toxic, poly(ethylene glycol) (PEG) has emerged as one of the most promising nanocomponents in bio-materials and green chemistry.[16] Indeed, PEGs are currently used as carriers of anticancer drugs, with efficiency related to the enhanced permeability and retention effect.[17]

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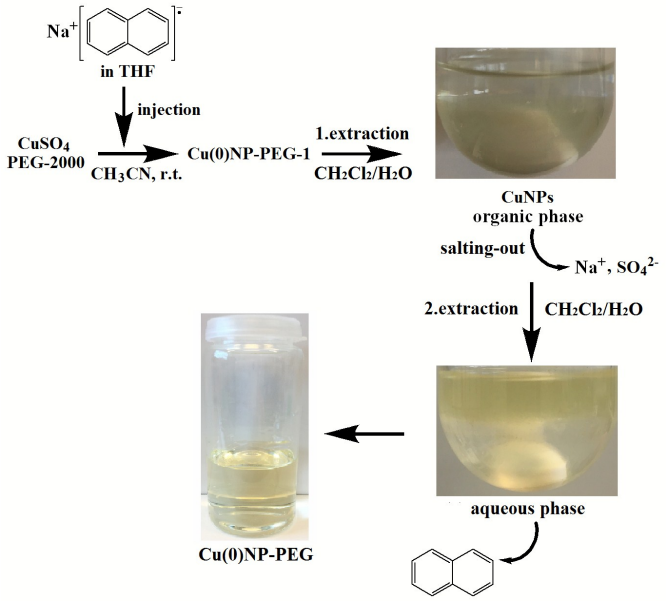


Figure 1. Synthesis and purification of Cu(0)NP-PEG NPs by salting-out under $N_2$.

Thus we have used PEG-2000 to stabilize Cu(0)NP prepared by reduction of $CuSO_4 \cdot 5H_2O$ sodium-naphthalenide in $CH_3CN$. These Cu(0)NPs (noted Cu(0)NP-PEG-1 before purification) have been purified by simple extraction with a mixture of $CH_2Cl_2$ and degassed $H_2O$ under $N_2$. In this first extraction, the Cu(0)NPs are soluble in the organic phase, due to the salting-out effect of $Na^+{}_2SO_4{}^{2-}$ in the aqueous phase. This allowed removing the colorless aqueous solution containing $Na^+{}_2SO_4{}^{2-}$ formed during the synthesis of the CuNPs. In a second extraction of the organic phase by degassed water, the CuNPs were transferred to the aqueous phase, leaving naphthalene in the organic phase that was also well separated in this way (Figure 1).

The absence of absorption band in the UV-vis. spectra (Figure S1) showed that these purified CuNPs were zero-valent Cu species (noted Cu(0)NP-PEG). On the other hand upon exposure to air for several minutes these CuNPs were characterized by the apparition of a UV-vis. band at 360 nm for $Cu_2O$ and noted Cu(I)NP-PEG.[18] Indeed UV-vis. spectroscopy was very useful to monitor this oxidation in air (Figure S2). These changes appeared to be complete after 30 min, no further change being observed after one day or one week (Figure S3).

The XPS spectra showed an absorption for Cu(0) or Cu(I), although contrary to UV-vis. it was not possible to distinguish between Cu(0) and Cu(I) using XPS. On the other hand, it allows distinguishing Cu(0/I) from Cu(II). Only tiny traces of Cu(II) due to CuO are observed after one week. The Cu 2p spectrum showed the Cu 2p3/2 and 2p1/2 peaks (Figure S4). The fitting of the Cu 2p3/2 part of the spectrum revealed the presence of Cu(I) or Cu(0) at around 932.1 eV, and the small component at around 934.5 eV attributed to Cu(II).[19]

The TEM of Cu(I)NP-PEG (Figure 2a, histogram in Figure S5) shows that the average NP size is 3.2 nm, with a maximum distribution around 2.5-3 nm and a few NPs around 4-5 nm. Because the crystallinity of large NPs is better than that of

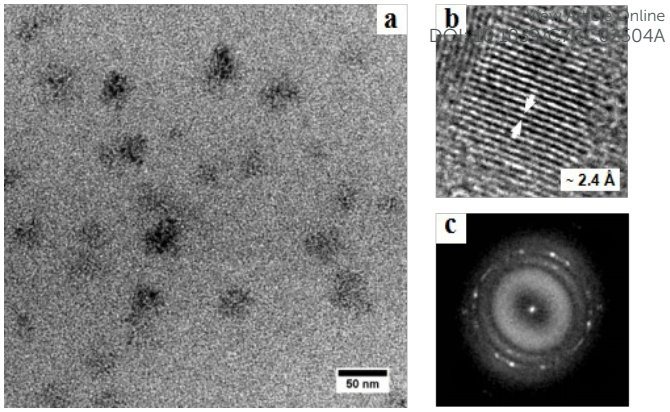


Figure 2. (a) TEM of the Cu(I)NP-PEG catalyst. (b) Detail of a 4.8 nm NP observed in Fig S6 and (c) corresponding Fast Fourier Transformation of the HRTEM image shown in Fig S6.

small ones, two NPs of 4 nm (SI Figure S8) and 4.8 nm (Figure 2b) respectively were selected in the HRTEM both showing the clear lattice fringes. The lattice spacing is about 2.4 Å, assuming that the crystallographic plane of the $Cu_2O$ nanocrystal is {111}. This indicates that the Cu(0)NP-PEG surface was oxidized by $O_2$ to form $Cu_2O$ NPs. The Fast Fourier Transformation of the HRTEM image (Figure S6) further shows that a good crystallinity was achieved in this case.

The CuNPs were examined for their catalytic activity in the CuAAC reaction in neat water. There were dramatic differences between the catalytic activities of raw Cu(0)NP-PEG-1, purified Cu(0)NP-PEG and air oxidized Cu(I)NP-PEG. For instance with 50 ppm Cu, the isolated yields of the click reactions between PhCCH and $PhCH_2N_3$ for these 3 types of CuNP-PEGs were respectively traces (<1%), 21% and 72% (Table 1). The first conclusion is that pure aqueous Cu(0)NP-PEG performs better in this catalytic application than the Cu(0)NP-PEG-1 dissolved in water before these purification steps, because these side products inhibit the surface of non-purified Cu(0)NP-PEG-1. The second conclusion is that aerobically oxidized Cu(I)NP-PEG is a much better catalyst than before oxidation in air, and con- version raised from 80% with 50 ppm to 100% (95% yield) with 100 ppm Cu (TON = 9500; TOF = 396 $h^{-1}$).

The scope of applicability of this low level amount of Cu(I)NP-PEG catalyst was explored with CuAAC reactions between various alkynes and organic azides in water. Good yields were obtained in the CuAAC of a wide variety of alkynes with organic azides (Table S1). In addition after the reactions the "click" products were obtained by simple extraction–washing–filtration without silica chromatography, because they are water-insoluble solids, and the excess alkyne was removed by simple washing with the solvent.

The catalyst Cu(I)NP-PEG was supported and immobilized onto SBA-15 using the sol-immobilization method, and this material was dried at 50°C (ICP content: 0.06 wt%). The evaluation of the NP size distributions of the Cu(I)NP-PEG after immobilization on the support is displayed in Figure S9 and

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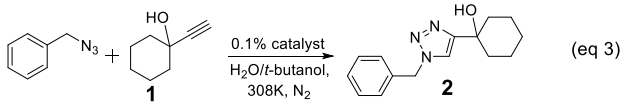
Table 1. CuAAC reaction (eq 1) catalyzed by CuNP-PEGs.[a]

| Catalysts | Amount [b] | Conversion (%) [c] | Yield (%) [d] | TON | TOF ($h^{-1}$) |
|---|---|---|---|---|---|
| Cu(I)NP-PEG [e] | 100 ppm | 100 | 95 | 9500 | 396 |
| Cu(0)NP-PEG | 100 ppm | 74 | 65 | 6500 | 271 |
| Cu(0)NP-PEG-1 | 100 ppm | 50 | 40 | 4000 | 167 |
| Cu(I)NP-PEG [e] | 50 ppm | 80 | 72 | 14400 | 600 |
| Cu(0)NP-PEG | 50 ppm | 32 | 21 | 4200 | 175 |
| Cu(0)NP-PEG-1 | 50 ppm | trace | trace | - | - |
| Cu(I)NP-PEG [f] | 100 ppm | 100 | 97 | 9700 | 404 |
| Cu(I)NP-PEG [f] | 50 ppm | 84 | 75 | 15000 | 625 |

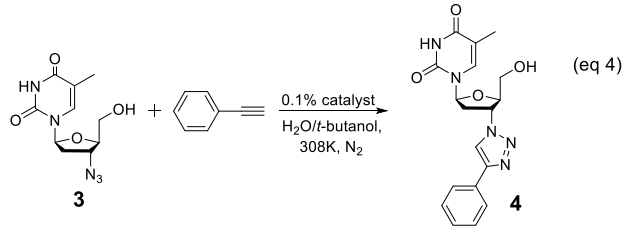
[a] Reaction conditions: 0.5 mmol of benzyl azide, 0.505 mmol of phenylacetylene, 2 mL degassed $H_2O$, 35°C, 24 h, under $N_2$. [b] Amount of catalysts used in the CuAAC reduction. [c] $^1H$ NMR conversion. [d] Isolated yield. [e] Cu(I)NP-PEG (exposed to air 30 min before catalysis) work-up in deionized $H_2O$. [f] Cu(I)NP-PEG (exposed to air 1 day before catalysis) work-up in deionized $H_2O$.

reveals that the average particle size of the supported catalyst Cu(I)NP-PEG@SBA-15 is 2.5 nm, i.e. smaller than unsupported Cu(I)NP-PEG. This indicates that the SBA-15 support prevents Cu(I)NP-PEG aggregation and better stabilizes very small Cu(I)NP-PEG@SBA-15 than unsupported Cu(I)NP-PEG. Recycling experiments using 300 pm of Cu(I)NP-PEG@SBA-15 provided isolated yields larger than 85% during at least five successive recycling experiments (Table S2), showing the good stability of the catalyst Cu(I)NP-PEG@SBA-15. Following the catalytic reaction, the residual solution after centrifugation was used to test the CuAAC reaction.



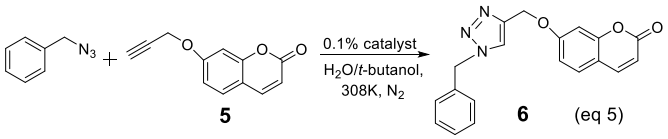

(eq 3)

(1) Catalyst: Cu(I)NP-PEG, 48h, isolated yield: 81.5%;
(2) Catalyst: Cu(I)NP-PEG@SBA-15, 24h, isolated yield: 87.8%




(eq 4)

(1) Catalyst: Cu(I)NP-PEG, 48h, isolated yield: 87.4%;
(2) Catalyst: Cu(I)NP-PEG@SBA-15, 24h, isolated yield: 91.8%




(eq 5)

(1) Catalyst: Cu(I)NP-PEG, 48h, isolated yield: 88%;
(2) Catalyst: Cu(I)NP-PEG@SBA-15, 24h, isolated yield: 92.7%

Traces of the final 1,2,3-triazole product were observed by thin-layer chromatography only after the first catalytic run, and the residual solution from other catalytic runs did not provide any more traces of this reaction product, indicating that catalyst leaching did not occur after the first use of the supported catalyst.

The catalyst Cu(I)NP-PEG@SBA-15 was also successfully used to prepare functional biomedical materials. The "click" reaction between 1-ethynylcyclohexanol (1), the precursor of ethinamate, a depressant drug that is an active metabolite of the central nervous system,[20] and benzyl azide provided **2** in good isolated yield (87.8%) with only 0.1% Cu in 50% aq. *t*-butanol at 35 °C for 24 h (eq 3). Another key natural product, 3'-deoxy-3-azidothymidine (AZT, zidovudine, **3**), is a nucleoside analogue reverse transcriptase inhibitor, and it was the first approved antiviral product for the treatment of human immunodeficiency virus (HIV).[21] The 3'-azi-do group of AZT has provided potential application to HIV RT binding.[22] Its "click" functionalization has been shown to be a convenient tool for the synthesis of new nucleoside inhibitors with low to submicromolar potencies against HIV-1,[23,24] new fluorescent markers, and cytostatic agents.[25,26] Here, the "click" reaction between zidovudine **3** and phenylacetylene using 0.1% Cu from Cu(I)NP-PEG@SBA-15 in 50% *t*-butanol at 35 °C for 24 h provided **4** in 91.8% isolated yield (eq 4). Cu(I)NP-PEG@SBA-15 was also applied to synthesize "click"-triazole functionalized 7-(propargyloxy) coumarin **6** from **5** in $H_2O$/ *tert*-butanol. Coumarin derivatives are often used in the perfume industry. Moreover, they are fluorophores and have recently been employed as fluorescent probes to visualize the metabolism of cysteine in living cells.[27] In this case (eq 5), 92.7% isolated yield was achieved with 0.1% Cu from the catalyst Cu(I)NP-PEG@SBA-15. Moreover, note that these three functional "click" reactions catalyzed by the supported catalyst Cu(I)NP-PEG@SBA-15 yielding compound **2**, **4** and **6** work in higher yield with less reaction time than with the unsupported catalyst Cu(I)NP-PEG. The interfacial effect within the supported catalyst plays an important role in the "click" functionalization of the biomedical products.

## Conclusion

In conclusion, the synthesis and purification of new PEG-stabilized homogeneous and heterogeneous nano-catalysts CuNP-PEG for "CuAAC" reactions has been achieved. The purified aqueous catalyst Cu(0)NP-PEG performs better than the crude catalyst Cu(0)NP-PEG-1 dissolved in water before salting-out process, because these steps help purifying the side-products on the CuNP surface and expose more catalytic active sites for "click" substrates. Aerobic oxidation of Cu(0)NP-PEG to Cu(I)NP-PEG further largely improves the catalytic activity, indicating that $Cu_2O$ NPs are the real "CuAAC" catalyst. This shows that among CuNPs and Cu-oxide NPs, the highest activity is by far exhibited by $Cu_2O$ NPs resulting from rapid aerobic oxidation of Cu(0)NPs. Both Cu(0) NPs and $Cu_2O$ NPs are active, but the present study highlights the superiority of the latter. This catalyst Cu(I)NP-PEG was heterogenized on SBA-15 for efficient recycling and was successfully applied in

"CuAAC" reactions between various azides and alkynes including functionalization of compounds of biomedical interest. These principles of biometal nanocatalyst design could be extended to various other catalysts in the close future.

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