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Highly Efficient and Stable Atomically Dispersed Cu Catalyst for Azide-Alkyne Cycloaddition Reaction

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In this study, we report a highly stable and efficient single-atom Cu dispersed on N-doped porous carbon as a superior catalyst for azide-alkyne cycloaddition reaction. A broad set of 1,4-disubstituted 1,2,3-triazoles was synthesized in high to excellent yields with good tolerance of various functional groups in a cost-effective, environment-friendly manner. Parallel studies show that the single-atom Cu with unique coordination structure exhibits superior catalytic activity to the metallic Cu nanoparticles analogue. Remarkably, the single-atom Cu catalyst demonstrates robust stability and can be reused several times without variations in activity and regioselectivity.

Introduction

Copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction is undoubtedly one of the most powerful click reactions.[1] To date, CuAAC has an incredible breadth of versatility and application in the fields ranging from material science, polymer chemistry, biochemistry, to drug discovery, owing to the high catalytic efficiency and atomic economy as well as the excellent orthogonality of the azide and alkyne functional groups.[2] A number of homogeneous and heterogeneous Cu(I) catalysts have been developed for AAC reaction.[3] However, both homogeneous and heterogeneous Cu(I) catalyst possess their respective inherent drawbacks, making their applications challenging in practical scenario. For example, (i) The thermodynamically unstable active Cu(I) species. Cu(I) is easily oxidized to catalytically inactive Cu(II) species or disproportionated to a mixture of Cu(II) and Cu(0), thereby reducing the reaction efficiency or even terminating the reaction. To maintain the high level of Cu(I) at all times during the reaction, addition of a large excess of reducing agents or external ligands is necessary to protect or stabilize Cu(I) from oxidation and/or disproportionation.[4] Such treatments further complicate the work-up procedure and also reduce the cost-efficiency. (ii) The difficulty of separation of the catalyst from the final product for homogeneous CuAAC. The contamination of copper within the final products is a big problem in polymer science and bioconjugation, because the residual Cu not only decreases the quality of polymers with color change and easy degradation but also is cytotoxic to live cell or organisms.[5] (iii) The low catalytic efficiency for the heterogeneous Cu catalysts. The catalytic activity for those currently developed heterogeneous Cu catalysts is far from satisfactory due to the issues of diffusion and steric hindrance.[1a,6] Therefore, it is urgently needed to develop a highly stable and efficient heterogeneous Cu catalyst for the AAC reaction.

Single-atom catalysts (SACs) have recently drawn considerable attention in the fields of heterogeneous catalysis and energy conversion, and were regarded a potential to bridge homogeneous and heterogeneous catalysis.[7] SACs have distinct advantages, such as atomic dispersion, maximized utilization of metals, and easy of separation. In particular, the unique structural and electronic features with special oxidation state stemming from unsaturated coordination metal sites offer the single-atom metal catalysts more fascinating catalytic performance.[8] A number of single-atom Cu catalysts have been developed for electrochemical nitrogen reduction reaction (NRR),[9] photo/electrochemical CO_2 reduction reaction (CRR),[10] oxygen reduction reaction (ORR),[11] and other industrial catalytic reactions (e.g., CO oxidation,[12] dehydrogenation of propane,[13] acetylene semihydrogenation,[14] oxidation of benzene[15]). They generally demonstrate remarkably increased catalytic activity, selectivity and stability in comparison with their Cu nanocrystalline catalysts or metal salts under comparable conditions. Nonetheless, to our knowledge, single-atom Cu catalyst for AAC reaction has not been explored yet.

Very recently, we have reported an atomically dispersed Cu on N-doped porous carbon with coordinately unsaturated Cu-N_2 sites (labelled as Cu_1/NC-800) as a superior catalyst for the oxidative Glaser-Hay coupling of terminal alkynes to deliver a variety of (un)asymmetric 1,3-diynes.[16] We found that the

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special coordination environment and oxidation state of Cu active sites with N-doped carbon provided preferential adsorption and activation of terminal alkynes to form the key intermediate Cu^{δ}-acetylide species, which synergistically boosted the catalytic activity and selectivity. Previous experimental and computational studies reveal that the formation of Cu^{δ}-acetylide intermediate is a rate-determining step for CuAAC reaction.[17] As such, we expect that the single-atom catalyst Cu_1/NC-800 can be a good candidate as a heterogeneous catalyst for AAC reaction and might make a great advance for expedient synthesis of 1,4-disubstituted 1,2,3-triazoles.

In this study, we investigated the catalytic performance for the AAC reaction using Cu_1/NC-800 as the catalyst. An outstanding activity and excellent regioselectivity to the targeted 1,4-disubstituted 1,2,3-triazole products with a broad set of alkynes and azides was achieved under mild conditions in a cost-effective and sustainable manner. Meanwhile, the catalyst Cu_1/NC-800 remained highly stable in catalytic activity and selectivity upon successive reuses without detection of Cu leaching, thereby avoiding the contamination of copper within the final products. Furthermore, a parallel study using the supported Cu nanoparticles (NPs) dispersed on N-doped carbon as the catalyst (labelled as Cu NPs/NC-900) demonstrates the distinct advantage in catalytic performance and the potential for practical application of the catalyst Cu_1/NC-800 in AAC reaction.

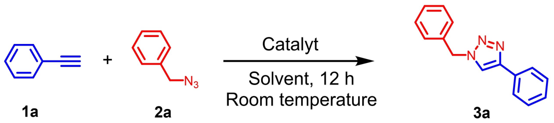
Results and Discussion

As illustrated in our previous work,[16] the catalyst Cu_1/NC-800 was prepared through a facile and inexpensive one-pot pyrolysis method using biochar and copper salt as starting materials. The catalyst Cu NPs/NC-900 was synthesized according to the same procedure to Cu_1/NC-800 with exception of pyrolysis temperature at 900 °C. The Cu loading contents in two catalysts were determined to be 1.28 and 1.37 wt%, respectively, by inductively coupled plasma atomic emission spectroscopy (ICP-AES). The formation of single-atom Cu with coordinately unsaturated $Cu-N_2$ sites in Cu_1/NC-800 was unambiguously confirmed by XRD, HR-TEM, AC HAADF-STEM, and XAFS in our previous work.[16]

In contrast, upon increasing the pyrolysis temperature to 900 °C, metallic Cu nanoparticles were formed and well-dispersed on N-doped carbon. HR-TEM images (Figure 1a and b) show that Cu NPs with uniform size were homogeneously dispersed on carbon material. XRD pattern (Figure 1c) of Cu NPs/NC-900 shows an intensive and broad diffraction peak at around 26°, corresponding to the characteristic (002) plane of graphitic carbon. Besides, three diffraction peaks situated at 43, 51, 63° were observed, which belong to the reflections of metallic Cu (111), (200), and (220) planes (JCPDS # 04-0836). Cu $2p_{3/2}$ XPS spectrum (Figure 1d) shows a sharp peak at 932.4 eV, suggesting the metallic Cu^0 oxidation state.[18] The near-edge feature of Cu NPs/NC-900 (Figure 1e) is very close to Cu foil, further indicating the Cu^0 oxidation state. An intensive peak at 2.20 Å, a typical value for Cu–Cu bond, in the FT-EXAFS spectrum in the R space (Figure 1f) was observed, which verifies the formation of metallic Cu NPs. The lower intensity of FT for Cu NPs/NC-900 compared with Cu foil suggests the formation of Cu NPs too. All these results demonstrate the formation of metallic Cu NPs in the catalyst Cu NPs/NC-900. In addition, comparison among N 1s XPS spectrum (Figure S1), BET analysis (Figure S2 and S3), and elemental analysis (Table S1) reveals that there are no big differences in the types and content of N, surface area and pore size distribution between the catalyst Cu_1/NC-800 and Cu NPs/NC-900.

With both catalysts Cu_1/NC-800 and Cu NPs/NC-900 in hand, we next assessed their catalytic performance for AAC reaction. We started to optimize the reaction conditions using cycloaddition of phenylacetylene with benzyl azide as the benchmark reaction in the presence of Cu_1/NC-800 (Table 1). After comprehensive screening, we found that complete conversion with exclusive regioselectivity to 1-benzyl-4-phenyl-1,2,3-triazole (**3 a**) was achieved when the reaction was conducted using 20 mg (2 mol% of Cu) of Cu_1/NC-800 in acetonitrile as solvent under air at room temperature for 12 h (entry 10). Poor or no reactivity was detected when the reaction was performed using other solvents including alcohols (MeOH, EtOH, *i*PrOH, tBuOH), THF, dioxane, $CHCl_3$, toluene, and H_2O instead of CH_3CN under otherwise identical conditions (entries 1–9), indicating the solvent has a critical role on the reactivity. The reaction proceeded under argon atmosphere led to a rather reduced reactivity (entry 12), suggesting that air can effectively boost the reaction. No reaction took place at all in the absence of the catalyst Cu_1/NC-800 or using NC-800 as the catalyst (entries 13 and 14). As a contrast, when the reaction was performed using Cu NPs/NC-900 as the catalyst under the equal conditions, a

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst [2 mol % of Cu]	Solvent	GC Yield **3 a** [%][b]
1	Cu_1/NC-800	MeOH	6
2	Cu_1/NC-800	EtOH	3
3	Cu_1/NC-800	Isopropanol	trace
4	Cu_1/NC-800	*t*BuOH	trace
5	Cu_1/NC-800	H_2O	20
6	Cu_1/NC-800	THF	trace
7	Cu_1/NC-800	Dioxane	0
8	Cu_1/NC-800	$CHCl_3$	3
9	Cu_1/NC-800	Toluene	trace
10	Cu_1/NC-800	CH_3CN	>99
11	Cu NPs/NC-900	CH_3CN	69
12[c]	Cu_1/NC-800	CH_3CN	47
13[d]	NC-800	CH_3CN	0
14[e]	Blank	CH_3CN	0

[a] Reaction conditions: phenylacetylene (0.2 mmol), benzyl azide (0.2 mmol), catalyst (2 mol % of Cu), solvent (2 mL), room temperature, under atmospheric air. [b] Determined by GC using an internal standard sample and confirmed with its corresponding authentic sample. [c] Under argon atmosphere. [d] Using NC-800 as the catalyst instead of Cu_1/NC-800. [e] In the absence of catalyst.

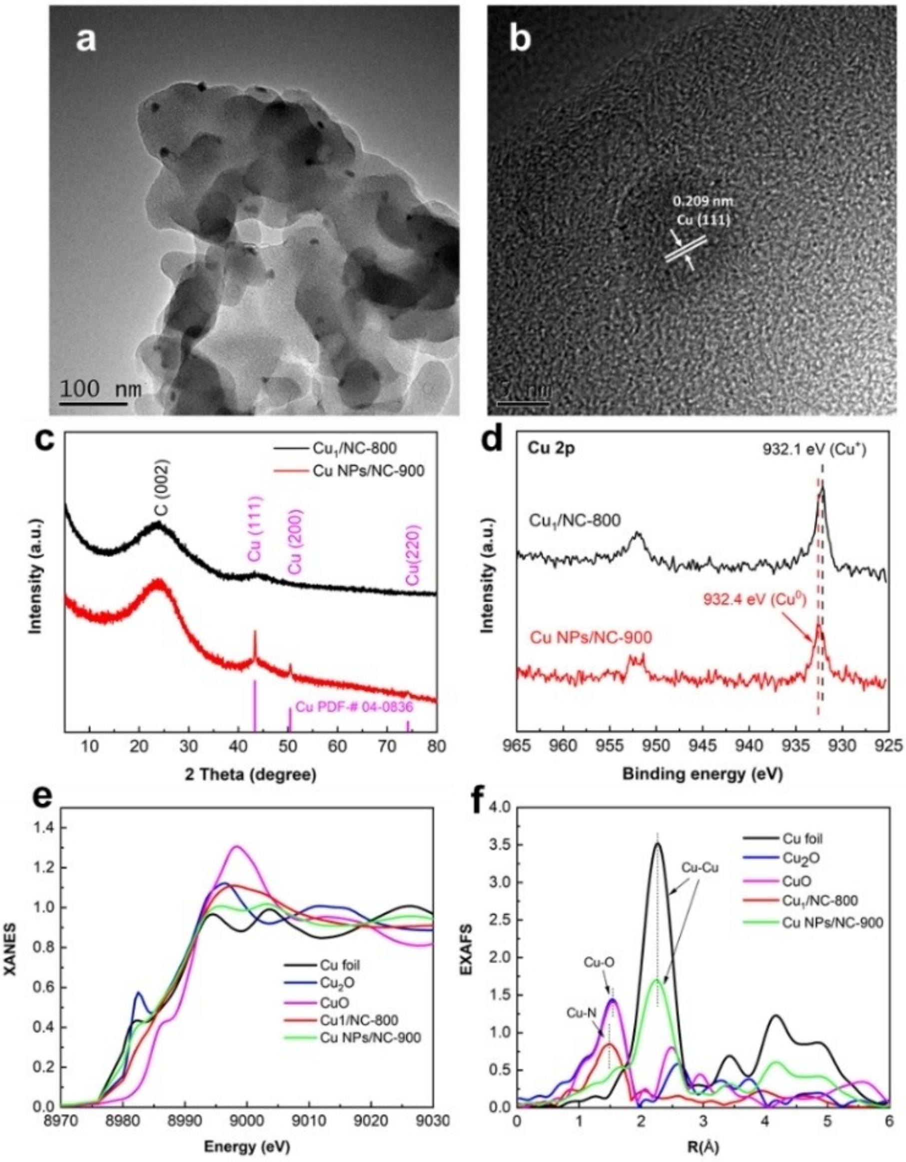


Figure 1. (a, b) HR-TEM images of Cu NPs/NC-900; (c) XRD pattern and (d) Cu $2p_{3/2}$ XPS spectra of Cu_1/NC-800 and Cu NPs/NC-900; (e) Cu K-edge X-ray absorption near-edge structure (XANES) and (f) FT-k^3-weight extended X-ray absorption fine structure (EXAFS) spectra of Cu_1/NC-800 and Cu NPs/NC-900 and the reference samples.

considerably lower reactivity was observed (entry 11). This result indicates that the single-atom Cu catalyst Cu_1/NC-800 is more active than its metallic Cu NPs/NC-900, highlighting the advantage of SACs for AAC reaction.

To uncover the difference in catalytic activity between Cu_1/NC-800 and Cu NPs/NC-900, we performed the control experiments. Kinetic studies (Figure S4) show that an induction period is required for the AAC reaction catalyzed by Cu NPs/NC-900, while this phenomenon is not observed for Cu_1/NC-800. It is quite reasonable because Cu species are in zero oxidation state in Cu NPs/NC-900 as proved by XRD, HR-TEM, XPS, and XAS, which need to be oxidized to catalytically active Cu^+ to facilitate the AAC reaction.[19] Furthermore, the initial reaction rate for Cu NPs/NC-900 is rather slower than that of Cu_1/NC-800, indicating the nature of Cu NPs/NC-900 with lower reactivity for AAC reaction compared with Cu_1/NC-800. Our previous studies have revealed that the catalyst Cu_1/NC-800 with coordinately unsaturated Cu-N_2 active sites has a stronger adsorption of terminal alkyne than metallic Cu NPs on the support, which subsequently promotes the formation of the key intermediate Cu$^{\delta}$-acetylide species with assistance from the weak bonding interaction between the adjacent pyridinic-N site and acetylenic proton of alkyne via the N···H bond.[16] This might account for the higher reaction rate of the single-atom Cu catalyst. Indeed, ^{1}H NMR spectroscopy (Figure S5) shows that the chemical shift of acetylenic proton in phenylacetylene gradually shifted to a high field with increasing the reaction time for the reaction of phenylacetylene with Cu$_1$/NC-800, further verifying the interaction between acetylenic proton and the catalyst. H_3PO_4-poison experiment (Figure S6) reveals that the pyridinic-N as a basic site in the porous carbon plays a critical role for the reactivity, where a significant reduced activity or no reactivity was observed when H_3PO_4 was added into the reaction mixture. Given nearly no difference in N type and content as well BET surface area and pore volume for both catalysts, we believe that the unique coordination and oxidation structure of the single-atom Cu essentially boosts the catalytic kinetics and overall activity for the AAC reaction.

We further investigated the stability of the catalysts Cu$_1$/NC-800 and Cu NPs/NC-900 under the optimized conditions. After completion of the reaction, the catalyst was separated by centrifugation and washing with acetonitrile for next use. The catalyst Cu$_1$/NC-800 could be recycled for at least 8 times without variations in the catalytic activity and selectivity (Figure 2a), demonstrating the robust stability. The filtration experiment was also conducted to disclose any possible Cu leaching from the catalyst. No further consumption of phenylacetylene and benzyl azide was observed after filtering off the catalyst at around 40% conversion (Figure S7). In contrast, it was found that the catalytic activity decreased gradually in each recycle for the catalyst Cu NPs/NC-900, while the excellent regioselectivity to the desired product was remained (Figure 2b). The stability was further reflected by the Cu contents for both catalysts after recycling. ICP-AES analysis (Table S2) reveals that nearly no loss of Cu loading content was observed for the used Cu$_1$/NC-800, while around 20% of Cu leached out from the fresh Cu NPs/NC-900. Furthermore, no obvious change in the oxidation state and structure of single-atom Cu was observed for the used Cu$_1$/NC-800 (Figure S8 and S9). In addition, the catalyst Cu$_1$/NC-800 also allows for gram-scale synthesis of 1-benzyl-4-phenyl-1,2,3-triazole **3 a** under the optimized conditions (Scheme S1), further highlighting the practicability of this protocol.

We subsequently explored the generality of this method for the synthesis of various 1,4-disubstituted 1,2,3-triazoles. Overall, a broad set of 1,4-disubstituted 1,2,3-triazoles was successfully synthesized in an efficient and exclusively regioselective manner, as shown in Table 2. Various aryl-, alkyl-, heteroaryl-terminal alkynes could efficiently undergo cycloaddition with benzyl azide to deliver their corresponding 1,4-disubstituted 1,2,3-triazoles in high to excellent yields. Aryl alkynes substituted by electro-rich (*p*-Me and *p*-OMe) (**1 b** and **1 c**) groups gave higher yields than those with electro-deficient substituents (*p*-Cl, *p*-NO$_2$, *p*-CHO, and *p*-COOMe) (**1 d**–**g**). Heteroaryl alkynes, e.g., 3-ethynylpyridine (**1 h**) and 2-ethynylthiophene (**1 i**), worked well to give rise to their respective 1,4-triazoles in 89 and 82% yields, respectively. Alkyl alkynes including 1-hexylene (**1 k**), ethynyltrimethylsilane (**1 l**), 2-methylbut-3-yn-2-ol (**1 n**), (prop-2-yn-1-yloxy)benzene (**1 o**) and 1-ethynylcyclohex-1-ene (**1 j**) also reacted with benzyl azide smoothly to produce their corresponding 1,4-triazoles in good yields. Remarkably, mestranol (**1 m**), a biologically active compound, could be cycloadded with benzyl azide to give its desired product in decent yield. Likewise, a family of azides ranging from substituted benzyl azides, ethyl 2-azidoacetate, 2-azidoethan-1-ol could efficiently cycloadd with various terminal alkynes, exclusively affording their corresponding 1,4-triazoles in good to high yields. Importantly, random combination of both azides and terminal alkynes is successful for the

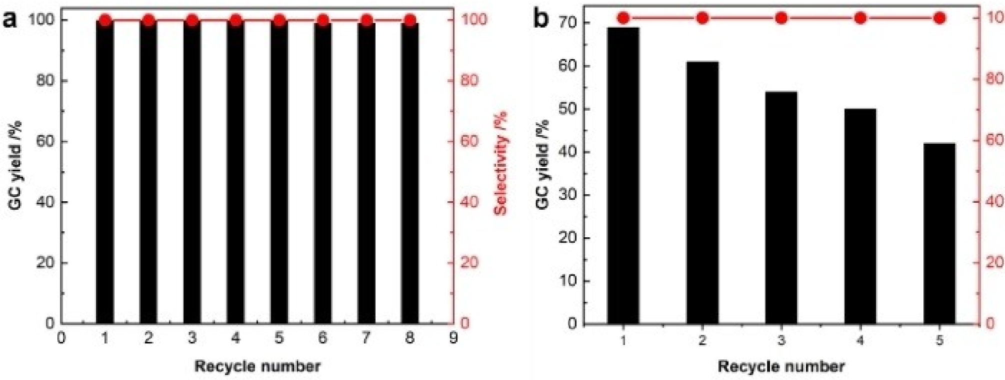
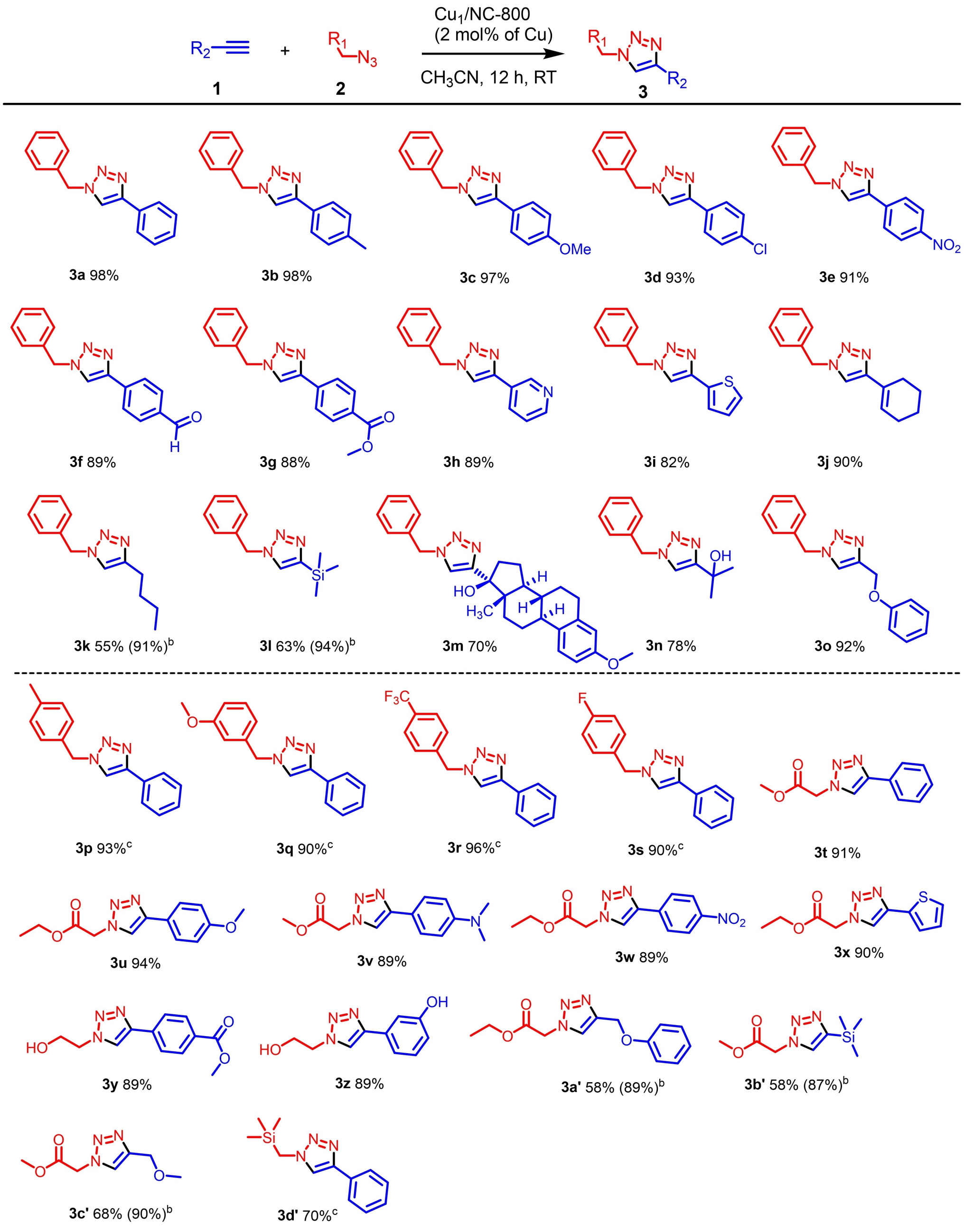


Figure 2. Stability of the catalysts Cu$_1$/NC-800 (a) and Cu NPs/NC-900 (b) for the benchmark reaction under the optimized conditions.

Table 2. Substrate Scope.[a]



[a] Reaction conditions: alkyne 1 (0.2 mmol), azide 2 (0.2 mmol), Cu_1/NC-800 (2 mol% of Cu), CH_3CN (2 mL), room temperature, 12 h, under air atmosphere. [b] 24 h instead of 12 h. [c] Alkyne 1 (0.2 mmol), benzyl bromide (0.22 mmol), NaN_3 (0.2 mmol), CH_3CN (2 mL), 60 °C, 18 h. Isolated yields are given.

construction of more functional 1,4-triazoles (**3 u**–**d'**). It should be pointed out that a facile one-pot cascade reaction of terminal alkyne, benzyl bromide and NaN_3 to efficiently and regioselectively synthesize 1,4-triazoles (**3 p-s**) under slight variation of the optimized conditions could be accomplished. Notably, the reactions proceeded in the present catalysis system are very clean. After completion of the reaction, the pure targeted products could be readily obtained via simple separation of the catalyst and evaporation of the solvent without requirement of chromatography column for purification, making this protocol more time-saving, environment-friendly, and cost-effective.

Conclusion

In summary, we have demonstrated a highly active and stable single-atom Cu catalyst with coordinately unsaturated Cu-N_2 sites for the azide-alkyne cycloaddition reaction for the first time. A broad spectrum of 1,4-disubstituted 1,2,3-triazoles was efficiently and regioselectively synthesized, and various functional groups are well tolerated. Importantly, the single-atom Cu catalyst demonstrates strong stability in catalytic activity and structure, without the detection of Cu leaching from the catalyst after several successive recycles. This work provides a new stable heterogeneous Cu catalyst for expedient synthesis of 1,4-disubstituted 1,2,3-triazoles in simple, cost-effective, and sustainable manner and also expands the application of the single-atom catalyst for organic transformations.

Experimental Section

Materials. Unless otherwise noted, all reagents were purchased commercially from Sigma-Aldrich, or Aladdin and used as received without further purification. The fresh bamboo shoots were obtained from Anhui Taiping Test Centre, International Centre for Bamboo and Rattan, Anhui Province, China. All operations were carried out in an argon atmosphere using glovebox and Schlenk techniques unless otherwise specified.

Preparation of catalysts. The catalysts were prepared via a facile tandem hydrothermal-pyrolysis process. Typically, fresh bamboo shoots were first cut into small slices, dried and ground into powder followed by the hydrothermal carbonization (HTC) process in a Teflon-inner stainless-steel autoclave with deionized water at 180 °C. In this step, the bamboo shoots were converted into biochar. The resulting brown biochar was filtered, washed thoroughly with deionized water, and then dried under vacuum at room temperature. Next, the obtained solids were homogeneously mixed with copper nitrate solution at 60 °C for 2 h. Finally, the resulting material was heated under N_2 atmosphere to 800 and 900 °C, respectively, with a heating rate of 5 °C min^{-1}. The pyrolysis was maintained under N_2 for 2 h at the target temperature and then cooled to room temperature. The obtained catalysts were denoted as Cu_1/NC-800 and Cu NPs/NC-900.

General procedures for CuAAC reaction. A 25 mL glass tube was charged with a magnetic stirring bar, azide (0.2 mmol), alkyne (0.2 mmol), Cu_1/NC-800 (20 mg, 2 mol% of Cu), 2 mL CH_3CN as solvent. The reaction was stirred for 12 h at room temperature under atmospheric air. After completion of the reaction, the organic phase was analyzed by GC to measure the conversion and selectivity. The products were purified by flash chromatography column on silica gel using appropriate eluents to obtain the isolated yields. For these reactions with up to 95% conversion of starting material, chromatography column is not needed, the pure products could be obtained by simple filtration of the catalyst and evaporation of the solvent. The obtained products were structurally confirmed by NMR.

Recyclability of the catalysts for the benchmark reaction. The benchmark reaction was chosen to investigate the recyclability of the catalyst Cu_1/NC-800 and Cu NPs/NC-900. A 25 mL reaction tube was charged with a magnetic stirring bar, phenylacetylene (0.2 mmol) and benzyl azide (0.2 mmol), Cu_1/NC-800 (2 mol% of Cu), CH_3CN (2 mL). The reaction was stirred at room temperature under atmospheric air for 12 h. After completion of the reaction, the catalyst was carefully collected by centrifugation and washing with CH_3CN followed by drying under vacuum for next use.

Gram-scale CuAAC reaction. A 100 mL round-bottom flask was charged with a magnetic stirring bar, phenylacetylene (5 mmol) and benzyl azide (5 mmol), Cu_1/NC-800 (2 mol% of Cu), CH_3CN (50 mL). The reaction was stirred at room temperature for 12 h under atmospheric air. The pure product **3a** was obtained via simple separation of the catalyst and evaporation of the solvent.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Single-atom catalyst · CuAAC reaction · 1,4-disubstituted 1,2,3-triazoles · heterogeneous Cu catalysis · carbon material

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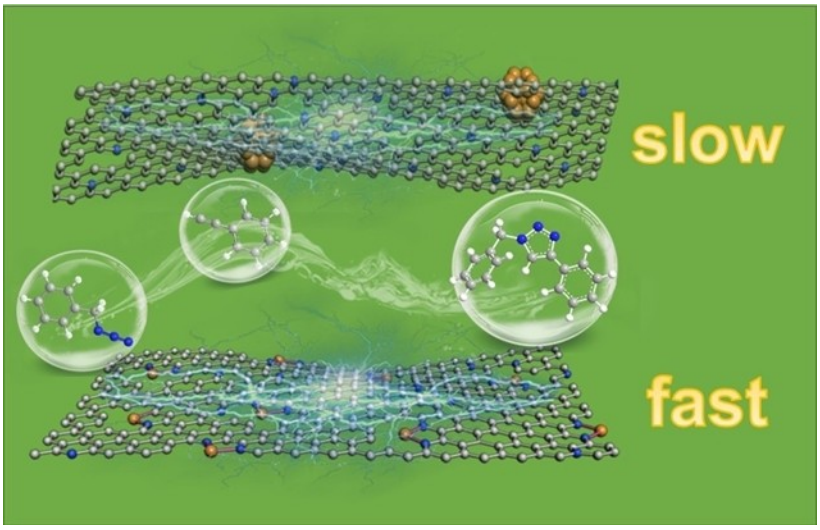

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1 – 8

Highly Efficient and Stable Atomically Dispersed Cu Catalyst for Azide-Alkyne Cycloaddition Reaction

Single-atom catalysis: A single-atom Cu dispersed on N-doped carbon exhibits superior catalytic activity for efficient and selective AAC reaction to access a broad set of 1,4-disubstituted 1,2,3-triazoles in a facile and environmentally-benign manner. Single-atom Cu catalyst demonstrates both higher reactivity and stronger stability than the supported Cu nanoparticles under the same reaction conditions.