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LETTER

Synthesis of a heterogeneous Cu(OAc)$_2$-anchored SBA-15 catalyst and its application in CuAAC reaction

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A novel dinuclear Cu(OAc)$_2$-anchored SBA-15 catalyst was synthesized by simple proton exchange of a carboxyl functionalized mesoporous SBA-15 silica with Cu(OAc)$_2$ in water. XAFS and EPR spectra were utilized to probe its structure. Such Cu(II) solid material exhibited excellent catalytic activity for azide-alkyne cycloaddition reaction in water without addition of either reductant or base.

Since the seminal works of the independent groups of Sharplesss [1] and Meldal [2] in 2002, the copper-catalyzed cycloaddition reaction of organic azides and terminal alkynes to form 1,4-disubstituted 1,2,3-triazoles (CuAAC reaction) have gained tremendous attention among the scientists from different disciplines. It provides a robust and regio-selective route to link two functionalized building blocks together under mild conditions, and to date has become a prevailing reaction with valuable applications in the fields of medicinal chemistry,[3] biochemistry,[4] polymer and material science,[5] as well as catalyst design.[6]

Commonly, CuAAC reaction was performed with Cu(I) species as the real catalyst, which could be either directly derived from Cu(I) salts, or *in situ* generated through reduction of Cu(II) salts, or oxidation of Cu(0) clusters.[7] Nevertheless, other than Cu(I) catalyst systems, there also have been some reports of the direct use of Cu(II) salts (or complexes) [8] and copper nanoparticles [9] as catalysts for the titled reaction. Taking cosideration of simply product(s)/catalyst seperation, potential catalyst reuse as well as great decrease of the toxic copper metal remain in end products, in recent years, the development of copper-supported solid materials as heterogeneous catalyst for CuAAC reaction was received much attention.[10] On the other hand, great progress has been made on the mechanism research in this field over the past years, a majority of which suggested that the reaction was preferably cooperative catalyzed by two copper atoms on the basis of a series of experimental [11] and computational [12] studies as well as the isolation of key intermediates.[13] In contrast to monocopper catalytic pathway, transition state with dicopper significantly reduced the activation energy of the reaction, thereby promoting the catalysis. With the idea of the synergistic cooperation of two copper atoms in CuAAC catalysis, more recently, a few structure-defined dinuclear copper catalysts were designed, synthesized and consequently applied in CuAAC reaction.[14] However, all of these catalytic systems were homogeneous and inherently suffered from the difficulty in removing the catalysts from product streams and incapability of reuse. Furthermore, a majority of them required expensive and/or special ligands to stabilize copper species and limited the application in organic solvent under inert gas atmospheric condition.

In this letter, we reported the synthesis of a novel dinuclear Cu(II) solid catalyst (**Cu@SBA-15-PTAA**) and its application in azide-alkyne cycloaddition reaction in water without addition of any reductant and base. The detailed preparing procedure of **Cu@SBA-15-PTAA** was elucidated in Scheme 1, which was confirmed by FT-IR method (Figure S1, ESI+). Firstly, the surface of SBA-15 silica was modified with organic *tert*-butyl ester groups through a conventional silane coupling reaction, followed by hydrolyzation with H_3PO_4 to provide a carboxylic functionalized mesoporous SBA-15 silica (**SBA-15-PTAA**).[15] Then, the resulted **SBA-15-PTAA** underwent a proton exchange process with Cu(OAc)$_2$ in water, affording the desired solid catalyst **Cu@SBA-15-PTAA** as a bluish solid. The supported Cu(II) amount was 1.29 mmol/g measured by atomic absorption spectrophotometer. In combination of acid capacity of **SBA-15-PTAA** (1.28 mmol/g based on thermo-gravimetric and potentiometrictitration analyses, see Figures S2 and S3, ESI+), we could find that the anchoring of Cu(OAc)$_2$ on **SBA-15-PTAA** to form **Cu@SBA-15-PTAA** with a 1:1 complex.

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Electronic Supplementary Information (ESI) available: Experimental procedures, FT-IR, TGA, Acid capacity determination, N_2 sorption of prepared solid materials, optimizing the reaction conditions, recycling the catalyst, mechanism studies, ^1H and ^{13} NMR date and spectra of prepared 1,4-disubstituted 1,2,3-triazoles. See DOI: 10.1039/x0xx00000x

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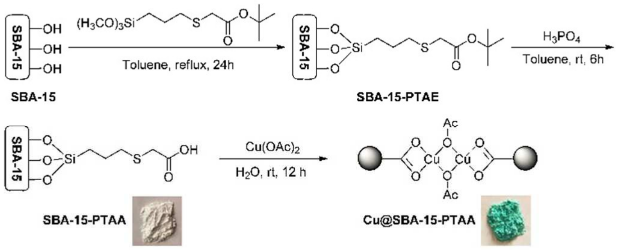

Scheme 1 The synthesis of $Cu(OAc)_2$-anchored SBA-15 catalyst (**Cu@SBA-15-PTAA**).

The architecture information of this novel catalyst was characterized by X-Ray reflective diffraction (XRD), high resolution transmission electron microscopy (HR-TEM) and N_2 sorption measurements. The small-angle XRD and TEM in Figure 1 showed that the structure of the well-ordered mesoporous SBA-15 remained intact after the immobilization process. Nevertheless, the XRD peak intensity of **Cu@SBA-15-PTAA** was a slight lower than those of **SBA-15** and **SBA-15-PTAA**, which could be attributed to the lowering local order after anchoring $Cu(OAc)_2$ at the surface. The N_2 sorption isotherms of **Cu@SBA-15-PTAA** showed a typical type IV isotherm with a very large hysteresis loop in the 0.5 to 0.8 P/P_o range (Figure S4, ESI+), also accounting for the ordered mesopore. Using a BJH model, the BET surface area, pore volume and pore size of **Cu@SBA-15-PTAA** was calculated to be 411 m^2/g, 0.58 cm^3/g and 49.6 Å, respectively. These values were obviously less than those of their parent **SBA-15** and **SBA-15-PTAA** (Table S1, ESI+), suggesting the Cu-sites inside the channels of **SBA-15** in some extent.

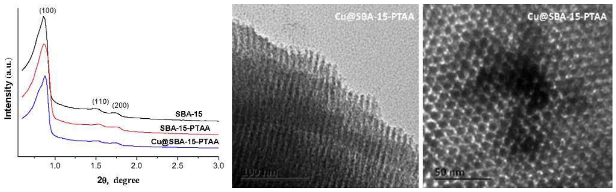

Figure 1 XRD patterns and HR-TEM images of Cu@SBA-15-PTAA

In addition, we also used XAFS spectroscopy, which serves as a powerful tool for the metal structure characterization,[16] to study the local structure of the resulted copper catalyst. As shown in Figure 2a, the XANES spectrum of **Cu@SBA-15-PTAA** was similar to that of $Cu(OAc)_2$, which indicated the valency of copper in **Cu@SBA-15-PTAA** was +2. Then, the comparison of $Cu(OAc)_2$ and **Cu@SBA-15-PTAA** in EXAFS parts shown in Figure 2b revealed that the coordination environments of $Cu(OAc)_2$ and **Cu@SBA-15-PTAA** were similar from the local structure parts. Furthermore, we also fitted the EXAFS spectra of **Cu@SBA-15-PTAA**. The fitting results (Table S2, ESI+) revealed that four oxygen atoms coordinated to one Cu(II) species. The average bond length of Cu-O bond was 1.96 Å. Based on the well-known dimeric structure of $Cu(OAc)_2$,[17] the literature reports [18] and our fitting results, the structure of **Cu@SBA-15-PTAA** was assigned in Scheme 1, which was a dinuclear species and each Cu(II) was coordinated with four oxygen atoms. Furthermore, we also used EPR spectroscopy to probe the heterogeneous copper catalyst. When performing the EPR experiment of **Cu@SBA-15-PTAA**, a strong EPR signal was observed (Figure 2c), which was similar to the previous reported Cu(II) species.[18a] This result suggested that single-electron existed, which was in accordance with the Cu(II) in the heterogeneous catalyst .

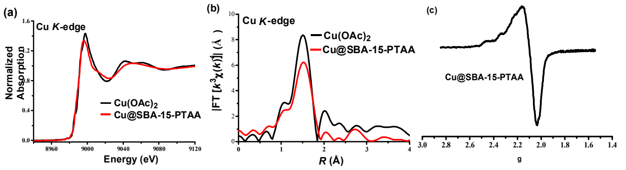

Figure 2 XAFS spectra of **Cu@SBA-15-PTAA** and $Cu(OAc)_2$ (a) XANES spectra, (b) EXAFS spectra, (c) EPR spectrum.

We were delighted to find that the newly prepared dinuclear copper(II) solid exhibited excellent catalytic activity in the cycloaddition reaction of azides and terminal alkynes in water without the requirement of any external reductant and base.[19] As the results shown in Scheme 2, with 2 mol% of **Cu@SBA-15-PTAA** as catalyst, a wide range of substituted phenylacetylenes, aliphatic acetylenes and heteroaromatic acetylenes could smoothly react with benzyl azide and phenyl azide at 50 °C to afford their corresponding cycloaddition product, 1,4-disubstituted 1,2,3-triazoles, in excellent yields (91-99%) with appropriate reaction time. A diversity of functional groups, such as NH_2, Br, NO_2, OH, alkynyl, and COOEt, were well tolerated and could be potentially utilized for further transformations. Interestingly, by employing 1,4-diethynyl benzene as substrate, only mono-cyclization addition product was obtained. The exclusive chemoselectivity on the mono-cyclization of 1,4-diethynyl benzene could be attributed to the pore size control of catalyst that restrained the formation of much larger di-cyclization addition product. The cycloaddition product **2ag** could be potentially used for further CuAAC reaction to achieve unsymmetric di-1,2,3-triazoles. When 2-ethynylpyridine and 2-ethynylthiophene were used as cycloaddition substrates, a relatively higher reaction temperature (70 °C) was required for the cmpletion reaction. We reckoned that the lower reactivity of these two substrates might be ascribed to the coordination action of the generated products **3ap** and **3aq** with catalytic Cu(II) species, which restrained the reaction to some extent. We also found that the catalyst **Cu@SBA-15-PTAA** was competent in one-pot multicomponent reaction of benzyl bromide/chloride, NaN_3 and phenyl alkyne for 1,4-disubstituted 1,2,3-triazole synthesis in water (Scheme 3). It was noteworthy to point out that irrespective of the nature of alkynes and azides, an exclusive 1,4-regioselectivity was observed in all these reactions under the catalysis of **Cu@SBA-15-PTAA** in water.

The recyclability of **Cu@SBA-15-PTAA** was further studied. Since the catalytic reaction was heterogeneous and performed in neat water without any additive reagent, therefore, the yielded product could be conveniently separated from the reaction mixture by simple extraction with common organic solvent (such as ethyl acetate, CH_2Cl_2), while the catalyst remaining in aqueous phase could be served for next run. It was observed that the catalyst could be reused at least 5 times

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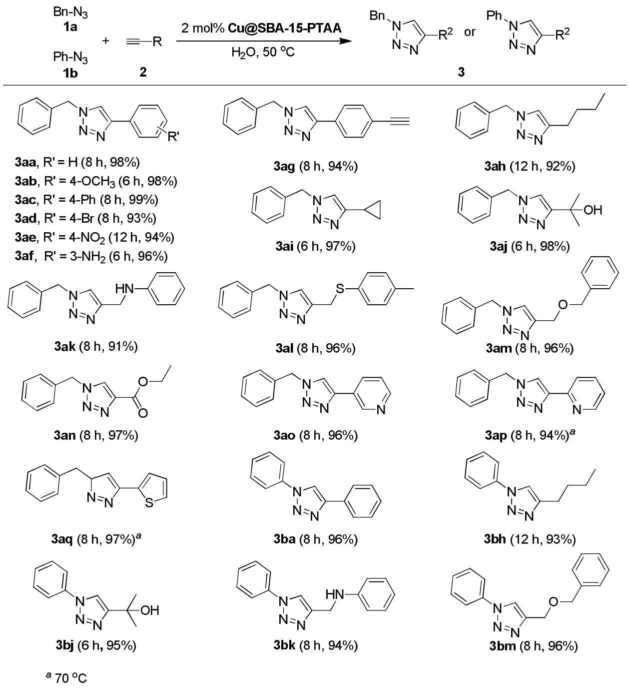
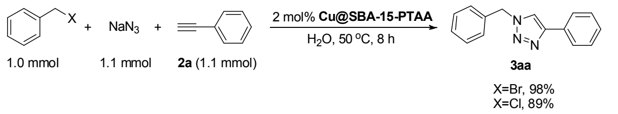
(Table S4, ESI+). Furthermore, we characterized the recovered catalyst by XRD and EPR analyses, performed the leaching test and measured the Cu content of the reused catalyst.[20] All of these experiments signified that the catalyst was very stable during the course of reaction and Cu(II) was tightly grafted on the **SBA-15-PTAA** support. In order to check the heterogeneous nature of the catalyst, a hot filtration test was also carried out. The result showed that nearly no further reaction proceeded after filtering the catalyst from the reaction mixture.[20]

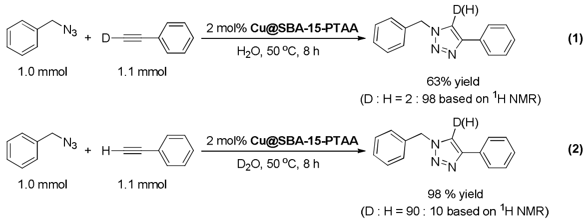


Scheme 2 Cycloaddition reaction of azides and alkynes. Reaction conditions: **1a** or **1b** (1.0 mmol), **2** (1.1 mmol), catalyst, H_2O (2 mL), isolated yields.



Scheme 3 One-pot multicomponent azide-alkyne cycloaddition reaction

In order to well understand this **Cu@SBA-15-PTAA**-catalyzed cycloaddition process, we then turned our attention to mechanistic studies. At first, kinetic experiments of the cycloaddition reaction were carried out with the reaction of benzyl azides and phenyl acetylene. The results (Figure S4, ESI+) showed that no obvious induction period was observed for the reaction. In combination with the fact that the color of **Cu@SBA-15-PTAA** maintained blue during the overall reaction process and no a threshold amount of phenyl acetylene homo-coupling product was detected in product profiles based on HPLC analyses, we can conclude that the possibility of generation of Cu(I) species as real catalyst during this catalytic process could be convincingly ruled out.[14a] Furthermore, two deuterium-exchange experiments were performed and the results were shown in Scheme 4. One experiment, that using 1-deuterium-substituted phenyl alkyne as substrate, led to a remarkably lower yield (63%) and the percentage of 5-deuterated 1,2,3-triazole in final product was about 2% (eq. 1, Scheme 4). In another experiment, replacement of H_2O with D_2O as reaction medium did not affect the yield. However, the ratio of 5-D/5-H products reached to 9 : 1 (eq. 2, Scheme 4). These phenomena indicated that the reaction involved C-D bond cleavage and it might be the rate-determining step in the catalytic cycle.



Scheme 4 Deuteration experiments

Based on above experimental results and clued by previous reports,[21] a possible stepwise mechanism was proposed. As shown in Figure 3, firstly, benzyl azide and phenyl acetylene respectively coordinated with two adjacent Cu(II) cations of **Cu@SBA-15-PTAA**. Then, under the reaction conditions (50 °C in water), the C-H band of phenyl acetylene was cleaved to form a Cu(II)-acetylide intermediate, accompanying with the diassociation of Cu-O bond of **Cu@SBA-15-PTAA**. In this case, the solvent water acted as base and promoted the conversion. As the Cu(II)-acetylide intermediate generated, it immediately reacted with the neighboring benzyl azide, forming a copper metallocycle species. The latter was unstable and immediately contracted to afford 1,2,3-triazole ring. Finally, proto demetallation occurred through internal proton delivery to release the produced 1,2,3-triazole and regenerate the catalyst. If the reaction was carried out in D_2O, D-H exchange occurred before the protodemetallation step and the corresponding deuterium product was resulted. The exclusive regio-selectivity to 1,4-isomers was attributed to the selective coordination of Cu(II) cation to N^3 of benzyl azide.

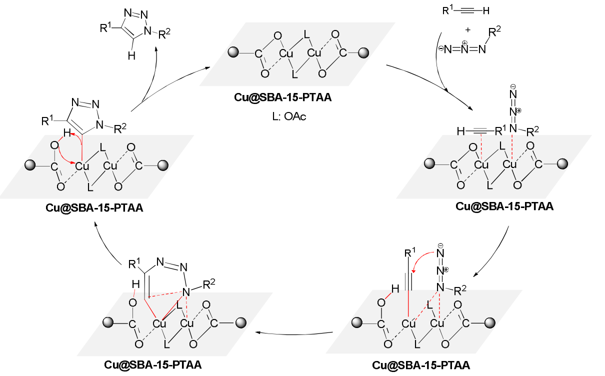


Figure 3 Plausible reaction mechanism for 1,4-disubstituted 1,2,3-triazole formation with **Cu@SBA-15-PTAA** catalyst

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In summary, we have obtained a new dinuclear copper(II) solid catalyst (**Cu@SBA-15-PTAA**) by simple proton exchange of carboxyl functionalized mesoporous SBA-15 silica with $Cu(OAc)_2$ in water at room temperature. Its actual structure and architecture information were characterized by FT-IR, XRD, HR-TEM, N_2 sorption, EXAFS and EPR. The resulted **Cu@SBA-15-PTAA** could be directly utilized for the catalysis of CuAAC reaction in water without the requirement of any reductant and base. Moreover, we found that the **Cu@SBA-15-PTAA** in water could be reused at least for five times. The mechanism studies revealed that the cycloaddition process was directly catalyzed by Cu(II) species and the unique dinuclear copper(II) structure of **Cu@SBA-15-PTAA** played a crucial role on its catalytic activity. The convenient operation, easy preparation of **Cu@SBA-15-PTAA** as well as its excellent recyclibility make this method attractive for practical applications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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