

Copper immobilized on biomimetic assembled calcium carbonate/carboxymethylcellulose hybrid: a highly active recoverable catalyst for CuAAC reactions

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Abstract

A novel copper immobilized on biomimetic assembled carboxymethylcellulose/ calcium carbonate hybrid (Cu^{II}@CMC/CaCO₃) as an efficient heterogeneous catalyst for the synthesis of 1,2,3-triazoles has been described herein. The fabrication of Cu^{II}@CMC/CaCO₃ is accomplished through a bioinspired mineralization process using sodium carboxymethylcellulose (CMC-Na) as the template and ion exchange agent, while the metathesis, nucleation, assemble, hybridization, and immobilization of Cu(II) occurred by successful treatment with CaCl₂, Na₂CO₃, and CuSO₄ in water at room temperature. The resultant Cu^{II}@CMC/CaCO₃ hybrid was well characterized by various analyses such as FT-IR, XRD, SEM, EDX, EDX-mapping, TEM, and TGA techniques. In the presence of low copper loading of Cu^{II}@CMC/CaCO₃ hybrid, benzylic halides, azide, and alkynes proceeded smoothly to afford 1,4-disubstituted 1,2,3-triazoles in high yields. The catalyst can be conveniently recovered from the reaction mixture by filter and reused for at least 5 consecutive runs with a slight drop in its catalytic activity. The remarkable activity and stability of the catalyst may be attributed to the coordination of both carboxyl and hydroxyl groups of the hybrid of CMC/CaCO₃.

Keywords Biomimetic synthesis \cdot Carboxymethylcellulose/calcium carbonate hybrid \cdot Copper \cdot CuAAC reaction

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Introduction

1,2,3-Triazoles are stable N-rich five-membered heterocyclic architectures for tolerating moisture, air, light, harsh conditions, and metabolism in living organisms and proved to be versatile synthetic intermediates for agricultural chemicals, pharmaceuticals, and functional materials [1-3]. The most powerful tool for the synthesis of 1,2,3-triazoles is based on the 1.3-dipolar cycloaddition of alkyne and azide. The first uncatalyzed 1,3-dipolar cycloaddition of alkyne and azide afforded a mixture of 1,4- and 1,5-substituted 1,2,3-triazoles, respectively, under harsh condition first reported in 1893 by Michael and later modified by Huisgen (Scheme 1) [4]. In 2002, Sharpless and Meldal independently discovered the Cu-catalyzed 1,3-Huisgen reaction with high regioselectivity to produce the exclusively the 1,4-disubstituted isomer under mild reaction conditions [5, 6]. These Cu-catalyzed azide-alkyne cycloadditions were later defined as CuAAC reactions, or more commonly referred to as click reactions (Scheme 1). Since then, the CuAAC reaction has been established to be a powerful tool in organic synthesis, medicinal chemistry, polymer chemistry, and surface modifications owing to its unique features such as high efficiency, mild conditions, excellent yields, and high regioselectivity [7-10]. In recent years, several reviews have thoroughly highlighted the progress of CuAAC reactions and a plethora of homogeneous and heterogeneous catalysis have been documented in the literature [10-13]. This CuAAC reaction is typically accomplished using homogeneous copper(I) sources such as CuI, CuBr, and CuCl [14]. However, Cu(I) species are easily oxidized to Cu(II), and/or disproportionate to Cu(0) and Cu(II) owing to its thermodynamic instability [15]. To overcome this problem, ligand stabilized Cu(I) catalytic system has been developed. In particularly, a series of ligands such as PPh_3 , iminopyridine, nitrogen ligands, N-heterocyclic carbene have been successfully employed to protect Cu(I) intermediates from oxidation and disproportionation, and hamper undesired side-product formation [15, 16]. Recent research results indicated that homogeneous Cu(II) salts like CuSO₄, CuCl₂, and Cu(OAc)₂, etc., together with a reductant (usually sodium ascorbate) could be adopted as catalysts for CuAAC reactions. Despite their excellent catalytic performance, there are one or more disadvantages such as the use of excess organic solvent, low yields, long reaction times, high temperature, tedious isolation, introduction of stabilizing ligands, requirement of excessive reducing agent, and severely contamination of the product with transition metal catalyst and possible ligand residues.

Heterogeneous catalysis has salient features such as easy recovery and good recyclability. Therefore, it is not surprising that many attempts have been made on heterogenization of homogeneous catalyst on an insoluble support material in recent years to aim to separation and reuse of the CuAAC catalysts from the reaction mixture in more effective ways to tackle the obstacles of homogeneous catalysis. Recently, the pace



Scheme 1 Thermal Huisgen's reaction and Cu-catalyzed azide-alkyne cycloaddition

of researches in the scope of heterogeneous catalysis for CuAAC is so fast that many reported heterogeneous copper catalysts have documented in the literature [13, 15, 17, 18]. For instance, magnetic Cu^{II}-CMC-Fe₃O₄ hybrid materials [19], cuttlebone@ CuCl₂ [20], Cu(I)/microporous Schiff base network [21], NovaPEGBimPy₂/CuSO₄ [22], the copper(I) complex of polymer-supported tris(triazolyl)methanol [23], thermoresponsive P(TBTACu-co-NIPAM) catalyst [24], nano-ferrite-glutathione-copper [25], Cu^{II}-hydrotalcite [26], Cu(OH)_x/TiO₂ [27], ionic polymer supported copper(I) [28], copper-alginates [29], TG-TBTA-CuPF₆ [30], CuI/Amberlyst A-21 catalyst [31], Cu/C [32], etc., have been documented.

Noticeably, among the homogeneous Cu(II) catalytic system, the effect of counterion of Cu(II) salts was independently studied using CuCl₂, CuSO₄, and Cu(OAc)₂ by L. Zhu et al.[33] and M. L. Kantam et al. [34]. Although three counterions gave satisfactory yields, the activity of these systems was found to depend on the nature of the counter-ion in the order: $AcO^->CI^->SO_4^{2-}$. Unlike CuSO₄ and CuCl₂, Cu(OAc)₂ is the best catalyst in *t*-BuOH to afford highest yields in shortest time. Even so, there is no report of using supported Cu(OAc)₂ as a catalyst for CuAAC reactions.

Recently, natural biominerals have emerged as viable alternatives to conventional support materials, as robust, readily available, high-surface-area heterogeneous catalyst supports. Some literature studies reported the use of naturally biominerals as supports for immobilization of metal catalysts, like oyster shell powder-supported CuBr (OSPs-CuBr) [35], oyster shell powder (OSP)-supported CuCl₂ (OSP-CuCl₂) [36], pearl shell powder-supported palladium (Pd/shell powders, Pd/SP) [37], and Ag nanoparticle-loaded eggshell (Ag NPs/eggshell) [38], which demonstrate that these catalysts are promising for various organic reactions such as CuAAC reactions, A₃ couplings, reductive homocoupling of aromatic halides, benzene oxidation, and so on. The research results clearly showed that these naturally biomineral-supported metal catalysts exhibit superior catalytic activity compared with the unsupported counterparts. The remarkable catalytic activity has been attributed to the chelation of metal species with the surface chitin, protein molecules of the supported naturally biomimetic powders. Therefore, the excellent catalytic performance of Cu(OAc)₂ for CuAAC reactions and metal catalysts immobilized on natural biominerals has deeply impressed and afforded us important inspiration for catalysts design and synthesis.

Sodium carboxymethylcellulose (CMC-Na), one water-soluble cellulose derivatives bearing a plenty of $-COO^-Na^+$ groups and -OH groups on its molecular chain, is capable of exchanging and thus chelating with metal cations [39, 40]. Thus, negatively charged carboxylate groups are suggested to have the ability to serve as a template to chelate calcium ions and induce the nucleation of the related CaCO₃ biominerals in nature. Based on combination of these properties, we here wish to report a novel biomimetic approach for preparation of Cu^{II}@CMC/CaCO₃ catalyst in which CMC-Na backbone/side carboxylic and hydroxyl groups have a large impact not only on the mineralization of CaCO₃ but also on the immobilization of metal catalyst and further modulate their catalytic activity. The catalytic activity and recyclability of the Cu^{II}@CMC/CaCO₃ catalyst have been examined using the CuAAC reactions (Scheme 1).

Results and discussions

Preparation and characterization of Cu^{ll}@CMC/CaCO₃ catalysts

Initially, in the achievement of this purpose was the fabrication of $Cu^{II}@CMC/CaCO_3$ hybrid catalyst. The catalyst was prepared by a facile biomimetic self-assemble method using CMC-Na as template and exchange reagent successively treated with CaCl₂ and Na₂CO₃ in water to control—nucleate and induce the growth of CMC-Na/CaCO₃ hybrid, followed by the Cu(II) immobilization on CMC-Na/CaCO₃ hybrid by the ion exchange reaction of CMC-Na trapped in CaCO₃ with CuSO₄ solution being achieved. The preparation approach is depicted in Scheme 2.

Next, the biomimetic self-assembled Cu^{II}@CMC/CaCO₃ catalysts were well characterized by ICP-AES, FT-IR, XRD, SEM, EDX, TEM and TGA techniques.

The FT-IR of CMC-Na, Na-CMC/CaCO₃, and Cu^{II}@CMC/CaCO₃ are shown in Fig. 1. In curve a, the broad band around 3492 cm⁻¹ confirms the O–H bond vibration, and peak located around 2915 cm⁻¹ can be assigned to the asymmetric and



Scheme 2 Schematic preparation of $Cu^{II}@CMC/CaCO_3$ via self-assemble process between carboxylate groups of CMC-Na with calcium and copper ions

symmetric C–H stretching modes [41]. The characteristic absorption peaks at 1459 and 1421 cm⁻¹ of CMC-Na are assigned to the carboxylate ($-COO^-Na^+$) asymmetric and symmetric stretching vibration [41]. The peak at 1053 cm⁻¹ is attributed to C–O–C bond vibration [41]. In curve b, and c, the sharp peaks appeared at 875 cm⁻¹, and 707 cm⁻¹ are related to characteristic Ca–O bond of calcite CaCO₃, which is basically consistent with the vibration absorption peaks of Ca–O in the literature [41]. Compared to curve a, the characteristic –COO⁻ peaks of Na-CMC/CaCO₃ and Cu^{II}@CMC/CaCO₃ are turned broad and red shifted to1498 cm⁻¹ and 1438 cm⁻¹, respectively, illustrating the interactions of CMC with CaCO₃ and coordination of CMC with Cu(II) ions.

Figure 2 shows XRD patterns of CMC-Na, surface-modified Na-CMC/CaCO₃ and Cu^{II}@CMC/CaCO₃. In curve b and c, diffraction peaks of (012), (104), (110), (113), (202), (018), (116), and (122) came from a typical calcite of CaCO₃ crystal [41]. These peaks do not change in Cu^{II}@CMC/CaCO₃, indicating that the immobilization of Cu(II) does not damage the crystal structure of CaCO₃. Although all peaks are very well matched with the calcite structure, the broaden peaks in curve c may be caused by vigorous hybridization of CMC with CaCO₃ and interaction of Cu(II) with CMC/CaCO₃ hybrids in molecular level. Moreover, Cu(II)-related peaks were not detected in the XRD pattern of the catalyst which implies that Cu(II) was dispersed in the CMC matrix as an amorphous form.

The SEM images of the surface morphology of fresh and the $Cu^{II}@CMC/CaCO_3$ after third use are shown in Fig. 3. The SEM images clearly show that all these $Cu^{II}@CMC/CaCO_3$ catalysts have similar microparticles microstructures in varying sizes and shapes with rough surface. This rough texture affords crucial functions to enlarge its contact area and thus increases the loading amount of Cu(II) cations as well as facilitate the better mass transfer. However, microparticles with slight changes are visible after three times reuse (image b) in CuAAC reaction.

Energy-dispersive X-ray spectroscopy (EDX) analysis provides the local information of various elements. The existence of metallic elements Ca, Cu and non-metallic



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Fig. 3 The SEM of fresh catalyst (a) and the catalyst after the third use (b)

elements C, O is clearly shown in Fig. 4. Obviously, the presence of these elements has been successfully anchored on the CMC/CaCO₃.

The element mapping for the selected area of $Cu^{II}@CMC /CaCO_3$ hybrid is shown in Fig. 5 which shows that C, O, Ca and Cu are dispersed in a relatively uniform form in $Cu^{II}@CMC/CaCO_3$ catalyst. These maps distinctly confirmed the existence of C, O, Ca, and Cu throughout the hybrid material in a homogeneous dispersion.

The TEM images of the fresh catalyst $Cu^{II}@CMC/CaCO_3$ and the $Cu^{II}@CMC/CaCO_3$ catalyst after third use are presented in Fig. 6. As can be seen, the $Cu^{II}@CMC/CaCO_3$ is amorphous with black color showing $CaCO_3$ core surrounded by gray and fluffy CMC shell. The particle size is measured by ImageJ software. The average size of the fresh and the used $Cu^{II}@CMC/CaCO_3$ catalyst is in the scope of 100–105 nm and 105–120 nm, respectively, showing a slight aggregation of used catalyst.

In most cases, the CuAAC reaction is performed on thermal conditions. The stability of the $Cu^{II}@CMC/CaCO_3$ was assessed by the thermogravimetric analysis



Fig. 4 The EDX of Cu^{II}@CMC/CaCO₃

(TGA). The TGA curves of the CMC-Na, and $Cu^{II}@CMC/CaCO_3$ are depicted in Fig. 7. As can be seen from curve a, the incipient weight loss of CMC-Na occurred at the range of 50–100 °C ascribed to the release of physically adsorbed moisture; the sharply weight loss in the region between 300 and 325 °C is attributed to the decomposition of CMC. By comparison with CMC-Na, the main weight loss of $Cu^{II}@CMC/CaCO_3$ observed in the scope of 250–300 °C is ascribed to the decomposition of CMC, implying that $Cu^{II}@CMC/CaCO_3$ is not a physical mixture of Cu^{2+} with CMC/CaCO₃, but a metal complex. Moreover, the $Cu^{II}@CMC/CaCO_3$ presented higher ash content, which is the desired copper residue. The TGA results indicate that $Cu^{II}@CMC/CaCO_3$ hybrid has good thermal stability from room temperature to 250 °C and thus can be performed in the described experimental conditions.

Application of Cu^{II}@CMC/CaCO₃ hybrids in CuAAC reaction for the synthesis of 1,2,3-triazoles

The CuAAC reaction is generally performed using a catalytic amount of Cu (II) with a reducing agent such as sodium ascorbate. The direct use of Cu(I) or its clusters is also possible; however, there is formation of undesirable alkynealkyne homocoupling product. To obtain the optimal reaction conditions for CuAAC reactions, the reaction of benzyl bromide (1.0 mmol), phenyl acetylene (1.0 mmol), sodium azide (1.2 mmol), sodium ascorbate (10 mol%) was chosen as a model to systematically evaluate under various conditions including solvent, the loading amount of catalyst, and reaction temperature. The results are summarized in Table 1. At the beginning, different solvents were screened to select the suitable solvent. Protic polar solvents including EtOH, 75% EtOH, *t*-BuOH, aqueous *t*-BuOH, MeOH, and H_2O as well as aprotic polar solvents including



Fig. 5 The element mapping of catalyst Cu^{II}@CMC/CaCO₃

CH₃CN, DMF, and DMSO afforded moderate to high product yields (Table 1, entries 2–16), while poor yield was observed in toluene (Table 1, entry 1). Based on the screening findings, H₂O was chosen as the most suitable solvent for further applications. Subsequently, the catalytic amount of the Cu^{II}@CMC/CaCO₃ was explored. It was found that 2 mol% of Cu is the optimal amount of the catalyst



Fig. 6 The TEM images of fresh catalyst (a) and catalyst after third use (b)



because it gave the best yield (Table 1, entry 12). Moreover, no significant promotion in the yield was observed increasing the amount of catalyst to 3 mol% and even to 4 mol% (Table 1, entries 13 and 14). On the contrary, decreasing the amount of catalyst reduced the yield of the product (Table 1, entry 11). As expected, in the absence of the catalyst, no desired product was found (Table 1, entry 10). These results indicated that the catalyst played a crucial role in the reaction. Finally, having optimized the solvent and dose of catalyst for the model reaction, we proceeded to investigate the adoption of different temperatures including 70, 50, and 25 °C. Decreasing the reaction temperature from 70 to 50 and 25 °C, the yields decreased from 93 to 80 and 63%, respectively (Table 1, entries 12–16). These findings had considerable negative impact on the product yields. Therefore, the optimal condition was that of benzyl bromide (1.0 mmol), phenyl acetylene (1.0 mmol), sodium azide (1.2 mmol), sodium ascorbate Table 1 Optimization of the reaction conditions^a



Entry	Solvent	Amount of catalyst (mmol% of Cu)	Temp. (°C)	Time (h)	Yield ^b (%)
1	Toluene	2.0	70	9	Trace
2	MeCN	2.0	70	4	62
3	DMF	2.0	70	3	75
4	DMSO	2.0	70	3	78
5	EtOH	2.0	70	3	76
6	75% EtOH	2.0	70	2	82
7	t-BuOH	2.0	70	3	80
8	H ₂ O/t-BuOH (4/1, v/v)	2.0	70	2	90
9	MeOH	2.0	70	2	65
10	H ₂ O	0	70	2	NP ^c
11	H ₂ O	1.0	70	2	80
12	H ₂ O	2.0	70	1	93
13	H ₂ O	3.0	70	1	93
14	H ₂ O	4.0	70	1	93
15	H ₂ O	2.0	50	2	80
16	H ₂ O	2.0	25	6	63

^aReaction conditions: benzyl bromide (1.0 mmol), phenyl acetylene (1.0 mmol), sodium azide (1.2 mmol), sodium ascorbate (10 mol%), $Cu^{II}@CMC/CaCO_3$ (catalytic amount of Cu), solvent (3 mL) at 70 °C

^bIsolated yields

^cNP refers to no production

(10 mol%), and Cu^{II}@CMC/CaCO₃ (2 mol% of Cu) in H₂O (3 mL) at 70 °C for specific time indicated by TLC.

With the optimal condition established, the domain of the reactions using a wide range of benzyl halides, various alkynes, and sodium azide were explored, and the obtained results are summarized in Table 2. In this catalytic system, different benzyl halides bearing either electron-donating or electron-withdrawing substituents proceed well to afford the desired products in good-to-excellent yields. The results illustrate that the electronic factors of the substrates do not have significant effect on the product yields attributing to the high catalytic activity of $Cu^{II}@CMC/CaCO_3$ hybrid catalyst. Notably, benzyl chloride took a slightly prolonged time as compared with that for aryl bromide counterparts due to its lower reactivity (Table 2, entries 1 and 2, 7 and 8, 13 and 14). Furthermore, aliphatic halides (Table 2, entries 22–23) and aliphatic alkyne (Table 2, entry 24) could work and produced the corresponding products in moderate to good yields.

Table 2 $Cu^{II}@CMC/CaCO_3$ -catalyzed synthesis of 1,4-disubstituted 1,2,3-triazoles through one-pot CuAAC reactions^a

_	+ NaN ₃ + R ₂	$= \frac{Cu^{II}@CMC/CaCO_3}{H_2O, \text{ sodium ascorbate}}$			R ₁ R ₂	
R ₁ —\ X						
1		3			4	
Entry	R ₁	R ₂	X	Time (h)	Yield ^b (%)	Product
1	Ph	Ph	Br	1	93	4a
2	Ph	Ph	Cl	1.5	89	4a
3	4-F-C ₆ H ₄ -	Ph	Cl	2.5	85	4 b
4	3-F-C ₆ H ₄ -	Ph	Cl	3	82	4 c
5	4-Cl-C ₆ H ₄ -	Ph	Cl	3	87	4d
6	3-Cl-C ₆ H ₄ -	Ph	Cl	3	88	4 e
7	3-CH ₃ -C ₆ H ₄ -	Ph	Cl	3	90	4f
8	4-CH ₃ -C ₆ H ₄ -	Ph	Br	2.5	88	4g
9	$4-NO_2-C_6H_4-$	Ph	Br	4	83	4h
10	$4-OCF_3-C_6H_4-$	Ph	Br	2.5	88	4i
11	4-Br-C ₆ H ₄ -	Ph	Br	1.5	91	4j
12	4-Br-C ₆ H ₄ -	Ph	Cl	2.5	84	4j
13	Ph	4-Me-C ₆ H ₄ -	Br	2.5	88	4k
14	Ph	4-Me-C ₆ H ₄ -	Cl	4	86	4k
15	$4-NO_2-C_6H_4-$	4-Me-C ₆ H ₄ -	Br	6	80	41
16	4-OCF ₃ -C ₆ H ₄ -	$4-\text{Me-C}_6\text{H}_4-$	Br	4	82	4m
17	$4-Br-C_6H_4-$	4-Me-C ₆ H ₄ -	Br	2.5	87	4n
18	3-Cl-C ₆ H ₄ -	4-Me-C ₆ H ₄ -	Br	3	84	4o
19	Ph	2-Py	Br	2	88	4p
20	4-Br-C ₆ H ₄ -	2-Py	Br	2.5	90	4 q
21	4-CN-C ₆ H ₄ -	2-Py	Br	3	82	4r
22	C ₂ H ₅ -	Ph	Ι	5	43	4 s
23	CNCH ₂ -	Ph	Br	5	52	4t
24	Ph	Oct	Br	5	83	4u

^aReaction conditions: benzyl halide (1.0 mmol), alkyne (1.0 mmol), sodium azide (1.2 mmol), sodium ascorbate (10 mol%), Cu^{II}@CMC/CaCO₃ (2.0 mol% of Cu), solvent (H₂O, 3 mL) at 70 °C ^bIsolated yields

The recyclability of $Cu^{II}@CMC/CaCO_3$ catalyst was examined using the model reaction under the optimal condition. At the end of the reaction, $Cu^{II}@CMC/CaCO_3$ catalyst was separated and reused directly in the subsequent run without any further treatment. As seen from Fig. 8, slight dropping of the catalytic performance was observed after each run. Notably, the copper content of the used catalyst after three cycles was measured to be 3.508 mmol/g by ICP analysis, by comparison with the data of fresh catalyst (4.040 mmol/g); a slight Cu leaching from catalyst was

observed. Thus, the product yields decrease seemed to be the tiny amounts of Cu leaching and slight aggregation of catalyst (Figs. 3b, 6b, 8).

Proposed mechanism for the carboxyl-chelation assisted CuAAC reaction

Based on the dinuclear copper mechanism proposed by Fokin et al. [42], we postulate the plausible carboxylic-modulated mechanism for the CuAAC (Scheme 3). Initially, the Cu(I) species is formed in situ from Glaser coupling [43] initiated by Cu(II) species in Cu^{II}@CMC/CaCO₃ precatalyst. The Cu(I) species interact with terminal alkyne to generate copper–acetylide intermediate (**A**) and release a proton. Secondly, the complex (**A**) reacts with azide which is activated by another Cu(I) species to form the dinuclear copper intermediate (**B**). Thirdly, rearrangement of intermediate (**B**) leads to the formation of the copper metalated triazolide (**C**) and release of the catalytic Cu(I) species. Finally, the intermediate (**C**) captures a proton to produce the corresponding triazole and regenerate the Cu(I) species. Noticeably, CMC in this catalytic cycle provide the carboxylic groups to tune the activity of Cu(I) species on the catalyst.

Conclusion

In this work, we have successfully developed an efficient biomimetic approach for the preparation of Na-CMC/CaCO₃ biomimetic minerals and further employed it as a support to anchor Cu(II) to assemble Cu^{II}@CMC/CaCO₃ nanohybrid catalyst using carboxymethylcellulose as a template and ion exchanger as well as modulator of catalytic performance. The as-prepared biomimetic nanocatalyst is well characterized by ICP, FT-IR, SEM, EDX, TEM, XPS, and TGA analyses. It has been certified that Cu^{II}@CMC/CaCO₃ clearly exerts versatile catalytic activity toward the CuAAC reactions. The remarkable activity and stability of the catalyst have been ascribed to the coordination of both carboxyl and hydroxyl groups of the hybrid of CMC/CaCO₃. Moreover, there is no obvious loss of the catalytic activity when the



Fig. 8 Recyclability of $Cu^{II}@CMC/CaCO_3$ catalyst in the model reaction

Copper immobilized on biomimetic assembled calcium...



 $\label{eq:Scheme 3} Scheme 3 \ Conceivable \ catalytic \ pathway \ of \ the \ carboxyl-chelated-copper-catalyzed \ CuAAC \ reaction \ based \ on \ Fokin's \ proposal$

catalyst is reused up to 5 runs. Therefore, high catalytic performance, reusability of catalyst, wide substrate scope, short reaction time, and mild condition are the salient features of this green catalytic process, which makes it more competitive for practical applications.

Experimental

Materials and methods

Sodium carboxymethylcellulose (CMC-Na, Mw 250,000) was purchased from commercial sources and used without further treatment; all other chemicals were AR or CP grade and used as received.

Melting points were measured by Electrothermal X_6 microscopic digital melting point apparatus. All reactions were performed on magnetic agitator type WH 220. The copper content of catalyst was measured by PerkinElmer Optima 20,000 V Inductively coupled plasma spectrometer. The copper content of catalyst was measured by PerkinElmer Optima 20,000 V Inductively coupled plasma spectrometer. Flourier transform infrared spectra (FT-IR) were recorded on a Nicolet 6700 spectrophotometer in KBr pellet. Scanning electron microscopy (SEM) were tested with Philips XL 30E scanner, and energy-dispersive spectroscopy (EDX) was conducted with a Hitachi SU8010 instrument. X-ray powder diffraction (XRD) data were collected on an MSALXRD2 diffractometer under ambient conditions using Cu Ka radiation in a range of Bragg's angles (20–80 °C). Transmission electron microscopy (TEM) was validated by TEM-100CX instrument. Thermogravimetric analysis (TGA) was gained on a SDTQ 600 equipment. X-ray photoelectron spectroscopy (XPS) was acquired on a Thermo ESCALAB 250XI spectrometer with monochromatic Al K α radiation. ¹H NMR (300 MHz) spectra were recorded by a Bruker-300 Avance Spectrometer with CDCl₃ as solvent with TMS as internal standard.

Biomimetic preparation of Cu^{II}@CMC/CaCO₃ hybrid catalyst

Firstly, $CaCl_2$ (2.2 g, 20 mmol) was slowly mixed with CMC-Na solution (0.4 wt%, 500 mL) under vigorously agitation at room temperature for 1 h to obtain a clear solution. Secondly, the Na₂CO₃ solution (20 mmol, 500 mL) was quickly poured into the as-prepared CMC/CaCl₂ mixture with constant stirring at room temperature for 30 min. Then, the white CMC-Na/CaCO₃ microspheres were separated by centrifugation at 3000 r/min for 5 min and then washed with a large amount of deionized water till the filtrate turned to neutral. The collected white powders were then dried in the vacuum to constant weight. Finally, the resultant CMC-Na/CaCO₃ hybrid (1.0 g) was immersed in 0.1 mol/L Cu(OAc)₂·H₂O for 72 h under mild agitation at room temperature to ensure the completion of metathesis of Cu(II) with CMC-Na/CaCO₃. The blue solid was separated from the solution by suction and washed with deionized water and ethanol successively and thoroughly, then dried in vacuum to constant weight to provide Cu^{II}@CMC/CaCO₃ as blue powders. The loading Cu content was determined by coupled plasma (ICP-AES) analysis to be 4.040 mmol/g.

General procedure for the one-pot CuAAC reaction

A mixture of benzyl halides (1.0 mmol), terminal alkynes (1.0 mmol), NaN₃ (1.2 mmol), sodium ascorbate (10 mol%), a catalytic amount of Cu^{II}@CMC/CaCO₃ catalyst (2.0 mol% of Cu), and 3.0 mL H₂O were charged into a flask. The reaction mixture was heated at 70 °C for a specific time with constant stirring. The progress was tracked by TLC. After completion of the reaction, ethyl acetate was added to the flask and the catalyst was filtered by suction, washed with enough ethyl acetate, and dried in vacuum for the next run. The resulting mixture was washed with brine and dried over anhydrous Na₂SO₄ and evaporated in vacuum using a rotary evaporator to obtain the crude product. The desired pure products were further purified by recrystallization with ethanol/H₂O mixed solvent. All the products are known, and

their melt point and ¹H NMR data were found to be consistent with those reported in the literature.

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