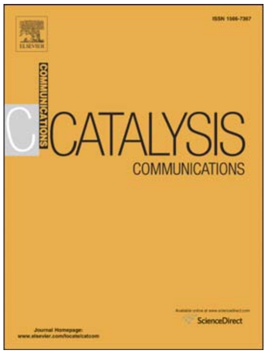

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A highly efficient synthesis of *N*-glycosyl-1,2,3-triazoles using a recyclable cellulose-copper (0) catalyst in water

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Abstract:

Cellulose supported copper (0) was used as a highly active heterogeneous catalyst to synthesize *N*-glycosyl-1,2,3-triazoles from glycosyl azides and alkynes. Cellulose-Cu(0) catalysed the cycloaddition reaction to produce the corresponding products in good to excellent yields in water. This heterogeneous catalyst has the advantages of high catalytic reactivity and low copper leaching. The separation and reuse of the catalyst are easy and efficient.

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1. Introduction

The Cu (I)-catalysed azide-alkyne cycloaddition (CuAAC) to generate 1,2,3-triazoles has been one of the most desired examples of click chemistry, which was proposed in 2001 by Sharpless and co-workers [1-3]. The applications of this approach have dramatically increased in different areas, such as drug discovery [4], material science [5] and chemical biology [6]. Cu(I) salts in the presence of a base or Cu(II) salts that are coupled with reducing agents are commonly used catalyst systems for this reaction. Despite many obvious advantages, the CuAAC reaction has a non-ignorable limitation: there is a significant amount of toxic, coloured, and expensive copper complexes, which are difficult to remove from the end products [7]. Immobilizing the copper catalyst on a heterogeneous support is one of the main strategies to circumvent the aforementioned problems [7]. Therefore, various heterogeneous supports have been applied to immobile types of copper catalysts to improve this click-type reaction, such as organic polymers [8], zeolites [9], charcoal [10-11], alumina [12], silica [13], magnetic materials [14] and polysaccharides [15-16]. In particular, supported copper nanoparticles can make the reaction more efficient [17]. Among these supports, polysaccharides have obvious advantages for environment-friendly chemistry because they are abundant in nature, biodegradable, and nontoxic. Cellulose is the most common polysaccharide, and the use of cellulose as a metal-supported material for catalytic reactions has been explored in some cases [18-21]. However, the application of this heterogeneous catalyst in click chemistry, particularly for specific substrates, such as drug, sugar, and so on, requires further improvement.

Click chemistry is also a powerful tool for carbohydrate drug development [22]. *N*-glycosyl-1,2,3,-triazole derivatives, which are prepared from easily available glycosyl azides and alkynes by the CuAAC reaction, exhibit various activities [23-24]. Our group has synthesized a series of glucosyl triazoles in a $CuSO_4$ and sodium ascorbate system [25]. However, when this method was used to synthesize other glycosyl triazoles, such as arabinosyl derivatives, the yield was not satisfactory. In fact, because of the complexities of the carbohydrate configurations, the conditions of the CuAAC reaction for diverse glycosyl azides and alkynes are not always moderate. In several cases, the reaction has high temperatures, a long reaction time and a low yield [22, 26-27]. To our surprise, there are few reports on the development or application of the new catalytic method to synthesize glycosyl triazoles [28-29].

Continuing our longstanding interest in catalysis and carbohydrate chemistry [30-31], herein, we describe an efficient and recyclable catalytic system for the CuAAC reaction using a cellulose-supported Cu(0) catalyst (cellulose-Cu(0)) and its application in the synthesis of *N*-glycosyl triazoles.

2 Experimental

2.1. Materials

Microcrystalline cellulose was purchased from J&K Scientific (Shanghai, China). $Cu(NO_3)_2·3H_2O$, and sugars and alkynes were purchased from Aladdin Reagent (Shanghai, China). Other chemicals were commercially obtained and used without prior purification.

2.2. Catalyst preparation

Microcrystalline cellulose (5 g) was suspended in 50 mL of water. To this suspension, 1.0 g of $Cu(NO_3)_2·3H_2O$ was added and stirred for 15 min. Then, hydrazine hydrate (80%, 1.5 mL) was slowly added dropwise to the above reaction mixture under continuous stirring for 12 h at room temperature. The catalyst was filtered in a nitrogen atmosphere, washed several times with distilled water and acetone and dried in vacuum at 50 °C [18].

2.3. Characterization

ICP-AES metal determinations were performed using a Perkin-Elmer Optima 3100 XL inductively coupled plasma atomic emission spectrometer. X-ray photoelectron spectrographs (XPS) were recorded using an ESCALAB-250Xi instrument. The melting points were recorded using a X5-Data microscopic melting point apparatus. ^1H NMR and ^{13}C NMR spectra were recorded using a Bruker Advance 500 spectrometer at ambient temperature. GC-MS and ESI-HRMS were acquired using Agilent 5975 and Agilent 1290-6530 UPLC-Q-TOF spectrometers. Transmission electron microscopy (TEM) images were taken using a FEI T20 microscope.

2.4. Synthesis of 2,3,4-tri-O-acetyl-α-L-arabinopyranosyl azide

1,2,3,4-Tetra-*O*-acetyl-α/β-L-arabinopyranose (16.24 g, 50 mmol), 125 mL of CH_2Cl_2 and 5.5 mL of water were added to a flask with an ice-water bath. Then, phosphorus tribromide (21.87 g, 80 mmol) was slowly dropped into the mixture while stirring. The reaction was performed at 0 ^{o}C for 12 h and monitored using TLC (petroleum ether- ethyl acetate=2:1). After the reaction completed, the reaction solution was diluted with 250 mL of CH_2Cl_2. The organic layer was washed with cold water (250 mL×2), saturated with $NaHCO_3$ (250 mL×2), and brined. Then, the organic phase was dried with Mg_2SO_4, filtered and evaporated under reduced pressure to generate 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl bromide (crude product). The crude residue was purified by recrystallization from diethyl ether, and white needle-like crystals were obtained (12 g, 70% yield).

A mixture of 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl bromide (16.96 g, 50 mmol), sodium azide (6.5 g, 10 mmol), Tetrabutylammonium hydrogen sulphate (TBAHS, 2.55 g, 7.5 mmol, 1 M aq Na_2CO_3 (300 mL) and CH_2Cl_2 (250 mL) was stirred in a round bottomed flask for 2 h. The reaction was monitored using TLC (petroleum ether- ethyl acetate=3:1). After the reaction completes, the solution was poured into a beaker containing CH_2Cl_2 (250 mL), stirred and separated. The organic layer was washed with water (250 mL×3) and brine (250 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL×3). The combined organic layers were dried ($MgSO_4$) and filtered and the solvent was evaporated under reduced pressure to yield crude 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl azide. A white solid (16 g) was obtained by recrystallization using EtOH in an 85% yield.

2.5. General experimental procedure to synthesize N-glycosyl triazoles

Azide (1.0 mmol) and alkyne (1.0 mmol) were suspended in 1.0 mL of water, and the cellulose-Cu(0) catalyst (137 mg, 0.730 mmol copper per gram, 10 mol %) was added. The reaction was performed at 60 ^{o}C and monitored using the thin-layer chromatographic technique. After the reaction completed, the mixture was allowed to cool to room temperature. Then, the reaction mixture was filtered, and the filter was subsequently washed with ethyl acetate (3×5 mL). The organic extracts were combined, washed with water and dried over $MgSO_4$. The solvent was removed, and further purification was performed using column chromatography.

2.6. Catalyst recycling experiment

The reactions were performed for 12 h. After the post treatment process of the reaction, the catalyst was recovered, washed with water and acetone twice, and dried in vacuum for 3 h at 50 °C. Then, it was reused for the next cycle.

3. Results and discussion

3.1. Catalyst synthesis and characterization

Cellulose-Cu(0) was prepared following the method reported by Reddy's group [18]. To characterize the cellulose-Cu(0) catalyst, we studied the oxidation state of the Cu of the catalyst using XPS (Fig. 1 A). The binding energy of Cu 2p3/2 showed a peak at 932.68 eV, which is typically attributed to Cu(0) [18]. The TEM analysis shows that the average diameter of the copper nanoparticles was approximately 5-10 nm and that the dispersion of Cu particles on the cellulose support was good (Fig. 2). ICP-AES analysis was applied to measure the copper-loading levels of the prepared catalyst, which shows the presence of 0.730 mmol of copper per gram.

Fig.1

Fig.2

3.2. Synthesis and characterization of glycosyl azides

Scheme 1

After preparing and characterizing the cellulose-Cu(0) catalyst, we focused on evaluating the catalyst reactivity for the catalysing synthesis of *N*-glycosyl triazoles (Scheme 1 A). First, we synthesized glycosyl azides as the corresponding substrate. According to the reported method [32], β-glucopyranosyl azide **1b**-**1c** was obtained through treatments of compound **4b**-**4c** with $TMSN_3/SnCl_4$ (Scheme 1 C). However, when we used this method to synthesize arabinopyranosyl azide, a new challenge emerged. The pure desired product α-L-arabinopyranosyl azide could not be obtained through recrystallization or chromatography. The ^1H NMR spectrum of the arabinopyranosyl azide that was obtained through this synthesis route showed impure signals that always accompanied the pure ones (see supplementary information). To solve this problem, another reported synthesis route [33] was used (Scheme 1 B), and the results were satisfying. *O*-acetyl-α-L-arabinopyranosyl azide **1a** was prepared from per-*O*-acetyl-L-arabinose **4a** through bromination and a substituted reaction of azide, and the single configuration product was obtained with recrystallization. The impure signals disappeared in the ^{1}H NMR analysis of **1a**, and the value of the vicinal coupling constant of the anomeric proton (*J*=7.96) confirmed the α-configuration of **1a** (see supporting information) [34].

3.3. Catalytic studies

In our previous studies, we found that the coupling of $CuSO_4$ with the reducing agent Na-ascorbate, which is one of the most commonly used catalytic systems for CuAAC, did not efficiently catalyse the reaction of *O*-acetyl-α-L-arabinopyranosyl azide **1a** and phenyl acetylene **2a**: only a 54% yield of the arabinopyranosyl triazole **3a** was obtained after a 24-hour reaction (Table 1, entry 10). Hence, the cycloaddition of **1a** and **2b** was performed as a model reaction to test the catalytic activities of the prepared cellulose-Cu(0) catalyst. First, the model reaction was accomplished in different media with 10% mol of cellulose-Cu(0) at room temperature, and the results were encouraging (Table 1, entries 1-6). Compared with the typical catalyst (Table 1, entry 10), cellulose-Cu(0) performed well in all of the selected solvents, among which acetonitrile was the most appropriate reaction media for the model reaction. Water is the ideal environmentally friendly reaction solvent, but cellulose-Cu(0) was less efficient in water than in other organic solvents, such as dichloromethane and acetonitrile. In consideration of green-chemistry, we attempted to improve the catalytic activity of cellulose-Cu(0) in water and found that when the temperature reached 60 °C, a satisfactory yield of the desired product was obtained (Table 1, entry 7). In addition, only a small quantity of the product was obtained when cellulose and CuI or $Cu(NO_3)_2$ were added *in situ* (Table 1, entry 8-9).

Table 1

To study the effect of catalyst loading, three parallel reactions were performed with 1 mol %, 5 mol %, and 10 mol % cellulose-Cu(0) loading. The yields of **3a** were detected using GC-MS after 3, 6, 12, and 24 hours. The study reveals that reducing the amount of cellulose-Cu(0) causes a decrease in product yields (Fig. 3). However, a long reaction time can minimize the negative effect of the low catalyst dosage. An excellent yield can be obtained using only 1 mol % catalyst after a 24-hour reaction.

Fig.3

To further investigate the scope of the cycloaddition reactions catalysed by cellulose-Cu(0), we performed the reactions with different glycosyl azides and terminal alkynes under the optimized reaction conditions (water as the solvent, 10 mol% of cellulose-Cu(0) as the catalyst, and completing the reaction at 60 °C in 12 h). The results are summarized in Table 2. The results show that this method has a good compatibility for various substituted glycosyl azides. The reaction of α-L-arabinopyranosyl azide and β- D-glucopyranosyl azides with phenyl acetylene had a similarly good yield (Table 2, entries 1, 6 and 11). Different phenyl-acetylene-bearing groups smoothly reacted with glycosyl azides to afford the corresponding products in good to high yields. The electronic effect of phenyl acetylene on the reaction was not evident (Table 2, entries 1-3, 6-8 and 11-13). We also used 3-butyn-1-ol as an aliphatic reactant and obtained a favourable result (Table 2, entries 4, 9 and 14). The heterocycle-substituted compound, which was 2-pyridyl acetylene, afforded the corresponding products (**3e**, **3j** and **3o**) in excellent yields (92%-94%).

Table 2

Recoverability and reusability are important indicators of the supported catalyst evaluation. When water is used as the reaction media, both the product and the cellulose-Cu(0) catalyst are insoluble, so after the reaction completed, the catalyst was separated by filtration with the product and unreacted reactants. The catalyst was sequentially washed with ethyl acetate, water and acetone, and the dried catalyst could be used for the next cycle. There was no significant loss of catalyst in quantity. Then, the reusability of the catalyst was examined in the cycloaddition reaction, and the results are shown in Fig. 4. These studies indicate that cellulose-Cu(0) maintains its catalytic activity after five reuses. However, the yields of the fifth cycle decreased by approximately 10 percent compared to that of the first use of the catalyst. Copper leaching from the heterogeneous catalyst may decrease the catalyst activity. The reaction solution of every cycle was analysed using ICP-AES, and a notably small amount of copper ions (0.3-1.9 ppm) was detected. The results show that the copper leaching was negligible and did not affect the catalyst activity. Thus, we speculate that the change of the valence state of the used catalyst may be responsible for the slight yield decrease. To verify this speculation, XPS was used to scan the spent cellulose-Cu(0) catalyst, and two peaks at 933.28 and 934.88 eV were found (Fig. 1 B). These peaks indicate that the reused cellulose-Cu(0) contains Cu(I) and Cu(II). The clear effect of the oxidation states of the catalyst and the catalytic activities require further investigation.

Fig.4

Although there are many reports on the synthesis and applications of *N*-glycosyl-1,2,3-triazoles, few new catalysts or methods have been applied to synthesize glycosyl triazoles. The reported protocols to synthesize *N*-glycosyl-1,2,3-triazoles are summarized in Table 3. The typical catalytic system, which is Cu_2SO_4 with Na-ascorbate or CuI with DIPEA, requires a long reaction time or a high temperature to perform the reaction. The complex of Cu and ligands is a more efficient catalyst for the reaction. However, considering the environmental and economic benefits, the supported Cu catalyst has a unique advantage. Our developed protocol is easy to operate and more efficient and adaptable than the commonly used system to synthesize glycosyl triazoles.

Table 3

4. Conclusion

In conclusion, we have reported a simple, efficient and eco-friendly protocol that uses cellulose-Cu(0) as a catalyst for the heterogeneously catalysed cycloaddition reaction of glycosyl azides with terminal alkynes to generate the corresponding triazoles in good to excellent yields. The reaction was performed in water, and no external ligand or base was required. The cellulose-Cu(0) catalysts in this catalytic system are easily recoverable and efficiently reusable.

Acknowledgments

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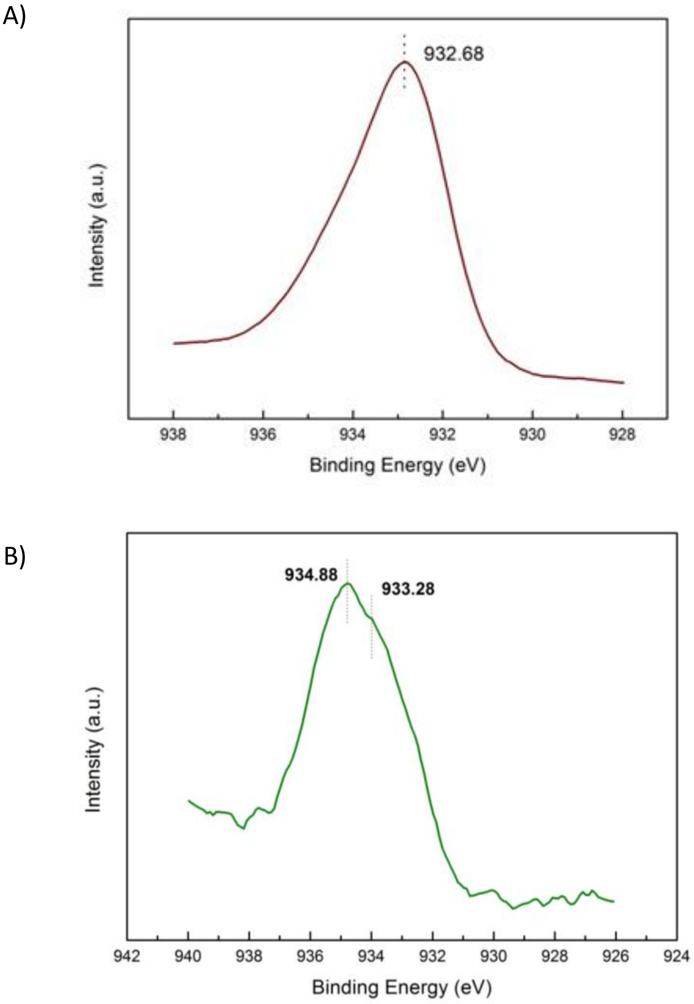


Fig.1 A) XPS spectrum of the cellulose-Cu(0) catalyst B) XPS spectrum of the spent cellulose-Cu(0) catalyst

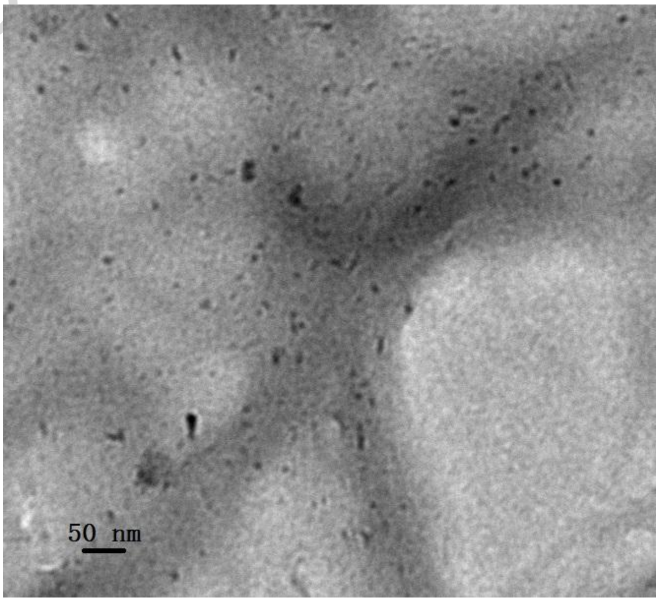
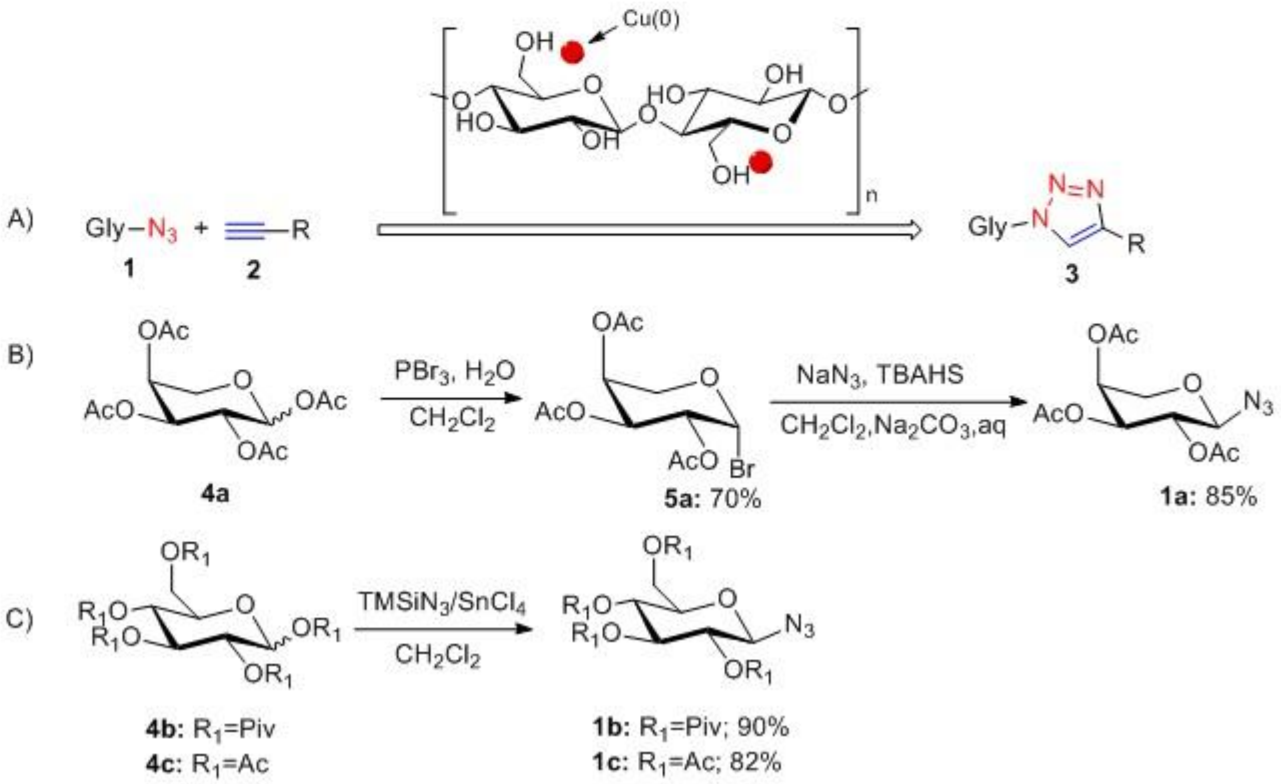


Fig.2 TEM images of cellulose-Cu(0)



Scheme 1 A) Cellulose-Cu(0) catalyzed the cycloaddition of glycosyl azides and terminal alkynes; B) Synthesis of arabinopyranosyl azide; C) Synthesis of glucopyranosyl azide

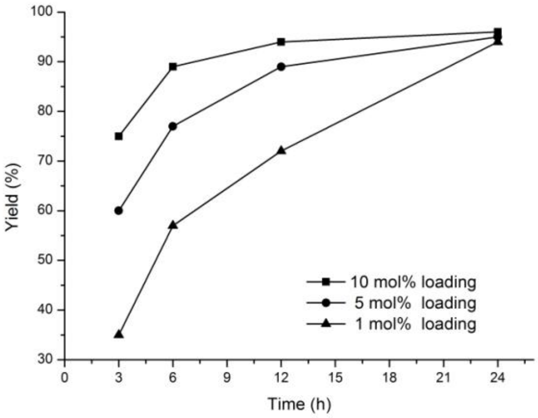


Fig. 3 Influence of different cellulose-Cu(0) loading. Reaction conditions: **1a** (0.5 mmol), phenyl acetylene **2a** (0.5 mmol), cellulose-Cu(0) ,water (1 mL), at 60 °C. GC-MS yield (using n-dodecane as an internal standard).

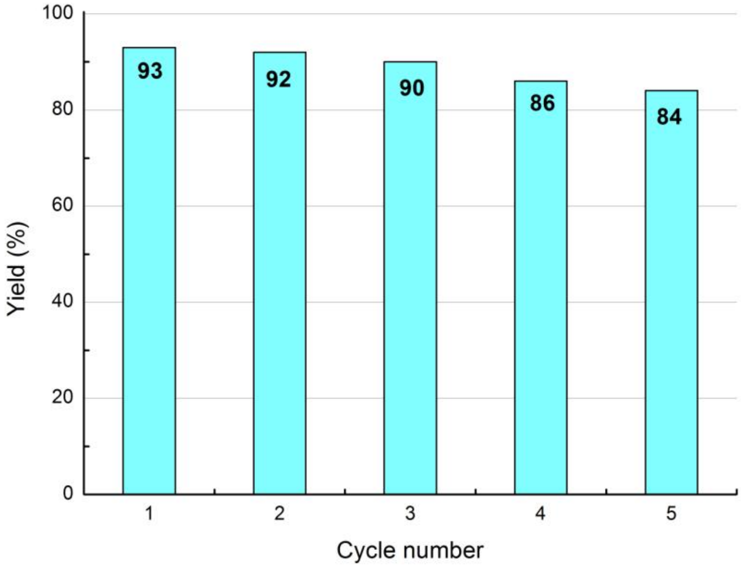
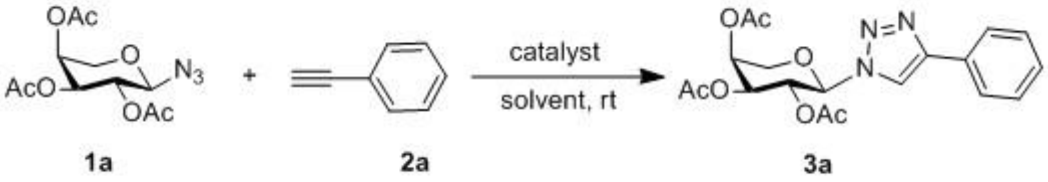


Fig. 4 Recycling of the cellulose-Cu(0) in the synthesis of **3a** (Table 2, entry 1). The Cu in reaction solution for each cycle was: 0.3, 0.3, 0.7, 1.2, 1.9 ppm.

Table 1 Optimization of reaction conditions [a]



Entry	Catalyst (mol %)	Solvent	Time (h)	Yield (%)[b]
1	cellulose-Cu(0) (10%)	Dichloromethane	10	92%
2	cellulose-Cu(0) (10%)	Toluene	10	89%
3	cellulose-Cu(0) (10%)	Ethanol	10	67%
4	cellulose-Cu(0) (10%)	Acetonitrile	10	93%
5	cellulose-Cu(0) (10%)	Acetone	10	92%
6	cellulose-Cu(0) (10%)	Water	10	81%
7	cellulose-Cu(0) (10%)	Water	12	93% [c]
8	$Cu(NO_3)_2\cdot3H_2O$ (10%), cellulose [d]	Acetonitrile	24	Trace
9	CuI (10%), cellulose [d]	Acetonitrile	24	Trace
10	$CuSO_4\cdot5H_2O$, sodium ascorbate	*t*-Butanol/H_2O	24	54 %

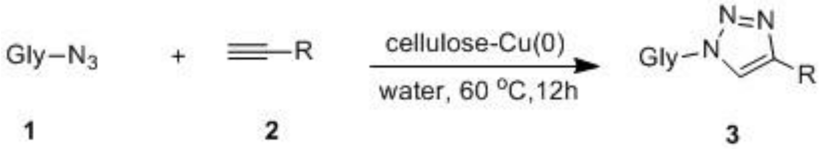
[a] Reaction conditions: *O*-acetyl-*α*-L-arabinopyranosyl azide **1a** (1 mmol), phenyl acetylene **2a** (1 mmol), catalyst (10 mol %), solvent(1 mL), at room temperature.

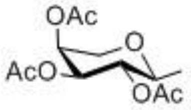
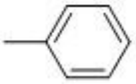
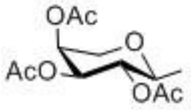
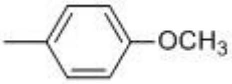
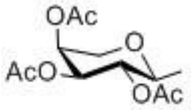
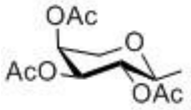
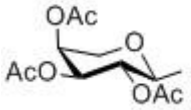
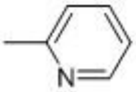
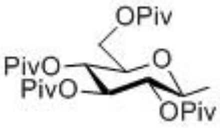
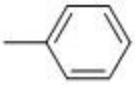
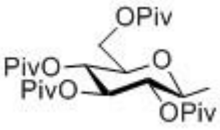
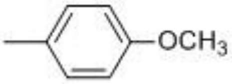
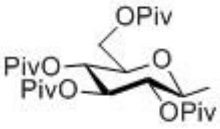
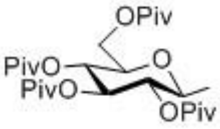
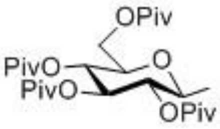
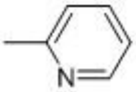
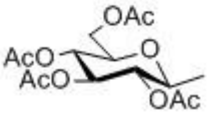
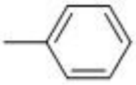
[b] Isolated yield.

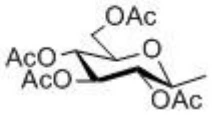
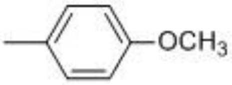
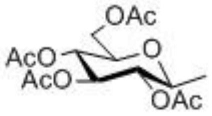
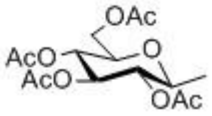
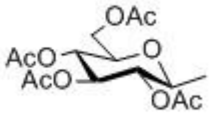
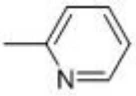
[c] The reaction was performed at 60 °C.

[d] 100 mg cellulose was added.

Table 2 Reaction between glycosyl azides and alkynes [a]



Entry	Gly	R	Product	Yield(%)
1			**3a**	93
2			**3b**	84
3			**3c**	87
4		$-(CH_2)_2OH$	**3d**	89
5			**3e**	94
6			**3f**	89
7			**3g**	83
8			**3h**	85
9		$-(CH_2)_2OH$	**3i**	85
10			**3j**	92
11			**3k**	90

12			**3l**	80
13			**3m**	85
14		$-(CH_2)_2OH$	**3n**	83
15			**3o**	94

[a] Reaction conditions: *O*-acetyl-*α*-L-arabinopyranosyl azide **1a** (1 mmol), phenyl acetylene **2a** (1 mmol), cellulose-Cu(0) (10% mmol), water (1 mL), at 60 °C.

[b] Isolated yield.

Table 3 Comparison of the developed protocol with other reported method in the synthesis of glycosyl triazoles

No.	Glycosyl azide	Alkyne	Catalyst (mol%)	Conditions	Time (h)	Yield (%)	Ref.
1	glucopyranosyl azide	phenyl acetylene	$CuSO_4 \cdot 5H_2O$ 20% , sodium ascorbate	H_2O/EtOH, 70 ^oC	24	60	27
2	xylopyranosyl azide	phenyl acetylene	CuI 50%, *i*Pr_2NEt	DMF,N_2, 100 ^oC	1	80	26
3	glucopyranosyl azide	2-methylbut-3-yn-2-ol	Functionalized chitosan-CuI 0.1%	H_2O/EtOH, 70 ^oC	12	99	15
4	glucopyranosyl bromide, NaN_3	phenyl acetylene	Cu nanoparticles on activated carbon 0.5%	H_2O, 100 ^oC	16	70	29
5	arabinopyranosyl azide	phenyl acetylene	$C_3H_7COOCu(PPh_3)_2$ 1%	CH_2Cl_2, rt	5	98	28
6	glycopyranosyl azide	phenyl acetylene	cellulose-Cu(0) 10%	H_2O, 60 ^oC	12	90-93	this work

Graphical abstract

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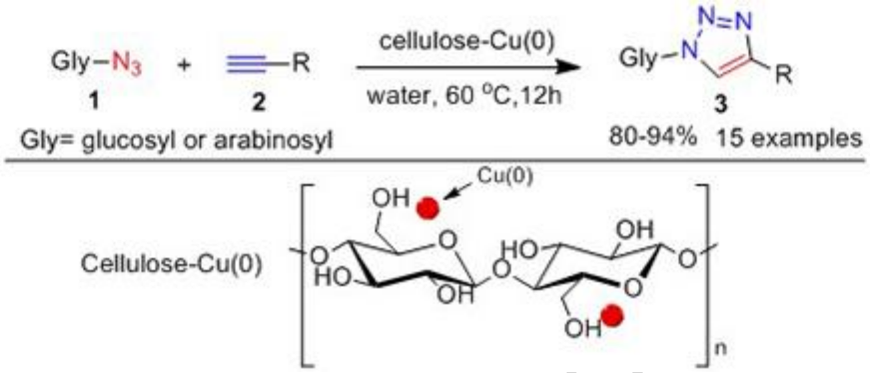

Highlights

►Cellulose supported Cu nanoparticles were prepared as a heterogeneous catalyst.

►Cellulose-Cu(0) catalyzed the reaction of glycosyl azides and alkynes efficiently.

►The catalytic reaction was carried out in water without external ligands or base.

►The heterogeneous catalyst was easily recoverable and efficiently reusable.