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### COMMUNICATION

# Cellulose-Immobilized NHC–Cu(I) Complex: An Efficient and Reusable catalyst for Multicomponent Synthesis of 1,2,3-Triazoles

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A novel cellulose supported copper NHC complex has been prepared by the reaction of cellulose supported imidazolium salt with copper(I) iodide. The catalyst is active in the synthesis of 1,2,3triazoles *via* a one-pot reaction of an alkyl/benzyl halides or tosylates and terminal alkynes, with sodium azide in water.

Huisgen 1,3-dipolar cycloadditions are exergonic fusion processes that unite two unsaturated reactants and provide fast access to an enormous variety of five-membered heterocycles.<sup>1</sup> The cycloaddition of azides and alkynes to give triazoles is arguably the most useful member of this family.<sup>2</sup> The classical method for their synthesis involved thermal 1,3-dipolar cycloaddition.<sup>3</sup> However, this procedure was associated with elevated temperature, low yields and lack of selectivity. Independent discoveries by Sharpless et al. and Meldal et al. demonstrated that in the presence of a Cu(I) catalyst, this cycloaddition could be performed regioselectively, affording exclusively the 1,4 disubstituted 1,2,3-triazoles.<sup>2,4</sup> This chemistry has found wide application in various disciplines including materials science, chemical biology, and medicinal chemistry.<sup>5</sup> Several members of the 1,2,3-triazole family have indeed shown interesting biological properties, such as antiallergic, anti-bacterial, and anti-HIV activity.6

During the last 20 years, *N*-Heterocyclic Carbenes (NHCs) have been extensively studied in organometallic synthesis and catalysis.<sup>7</sup> As strong  $\sigma$ -donors and weak  $\pi$ -acceptors, the NHC ligands have a stronger interaction with the metal center compared to phosphine ligands, thereby enhancing the stability of NHC complexes toward heat and moisture.<sup>8</sup> Recently, several papers were reported about the remarkable activity of supported and unsupported [(NHC)CuX] complexes (X=Cl, Br) in the 1,3-dipolar Huisgen cycloaddition.<sup>9</sup> Such catalytic systems have already been applied to the preparation of triazole-containing carbanucleosides, porphyrins, and platinum-based

anticancer drugs, as well as to the development of a latent catalyst for this transformation.  $^{10}\,$ 

Recently, biopolymers such as alginate, cellulose, chitosan, gelatine, starch and wool have been used as supports for catalytic applications.<sup>11</sup> Several interesting features of the biopolymers for example, bio-degradable, environmentally safe, high sorption capacity, physical and chemical versatility make them attractive to use as supports.

Abdelmouleh *et al.* reported the surface modification of cellulose (CL) fibers with silanes coupling agents.<sup>12</sup> Recently, Koga et al. reported in situ modification of cellulose paper with 3-aminopropyltrimethoxysilane for catalysis Knoevenagel condensation between aldehydes or ketones and active methylene compounds.<sup>13</sup>

Based on the understanding described above, herein, we report the synthesis of novel heterogeneous catalyst containing NHC anchored in CL, as well as its application for the multicomponent 1,3-dipolar cycloaddition of terminal alkynes and organic azides generated in situ from sodium azide and different organic halides or tosylates.

The process for the preparation of CL supported copper NHC complex is schematically described in Scheme 1. First, the grafting of the imidazolium salt (NHC ligand precursor) onto the CL support followed by reaction with sub-stoichiometric amount of copper(I) iodide and sodium *tert*-butoxide, to afford NHC-Cu/CL



Scheme 1. Schematic description for the preparation of NHC-Cu/CL

FT-IR spectroscopy of CL-IL showed a new medium absorption band at 1572 cm $^{-1}$  for C=N stretching (Fig. 1).

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Thermogravimetric analysis (TGA) was further used to study the thermal behavior and stability of the NHC-Cu/CL. TGA indicates the catalyst stable up to 231 °C. (Fig. 2).

The morphology of Fig. 3a-c shows representative SEM images of the as-received CL and NHC-Cu/CL. The density and distribution of the NHC-Cu group on the NHC-Cu/CL nanocomposite were evaluated by quantitative energy dispersive X-ray spectroscopy (EDS) mapping. As can be seen in Fig. 3d–g, rather than only being located at the edges of the graphene sheets, the elements Cu, Cl, I and Si were found to be uniformly dispersed on the whole surface of the NHC-Cu/CL nanocomposite indicating the homogeneous distribution of the NHC-Cu.



Fig. 1 FT-IR spectra of cellulose (blue), grafted imidazolium salt (red), and NHC-Cu/CL (green).





Fig. 3 SEM images of (a) CL and (b-c) NHC-Cu/CL, and corresponding quantitative EDS elemental mapping of (d) Cu, (e) Cl (f) I and (g) Si.

The catalytic activity of the NHC-Cu/CL composite as catalyst was then tested in multicomponent 1,3-dipolar cycloaddition of terminal alkynes and organic azides generated in situ from sodium azide and different organic halides or tosylates. To optimize the reaction conditions, benzyl bromide, sodium azide and phenylacetylene were tested as model substrates in the presence of various solvents (Table 1). The results indicate that both reaction temperature and solvent significantly influence the product yield in the coupling reaction. After several screening experiments with different combinations, the best ones were proved to be NHC-Cu/CL (1 mol% of Cu), benzyl bromide (1 mmol), sodium azide (1.2 mmol), phenylacetylene (1.3 mmol) and  $H_2O$  (3 mL) at 50 °C for 1 h.

Table 1. Screening of the reaction conditions<sup>a</sup>

Entry	Solvent	Temp. (°C)	Yield (%) <sup>b</sup>
1	H <sub>2</sub> O	50	98
2	H <sub>2</sub> O/EtOH (1:1)	50	83
3	EtOH	50	61
4	PhCH <sub>3</sub>	50	20
5	CHCl <sub>3</sub>	50	65
6	CH <sub>3</sub> CN	50	73
7	H <sub>2</sub> O	60	98
8	H <sub>2</sub> O	40	81

<sup>a</sup>benzyl bromide, (1.0 mmol), sodium azide (1.2 mmol), phenylacetylene (1.0 mmol), solvent (3 mL), NHC-Cu/CL (1 mol% of Cu), 1 h <sup>b</sup> Isolated yield

Using the optimized reaction conditions, it was then attempted to expand the scope of organic halides or tosylates and terminal alkynes in water at 50 °C, using 1 mol% NHC-Cu/CL (Table 2). Electron donating substituents like methyl, methoxy (entries 2 and 3), and electron withdrawing substituents such as acetyl, nitro groups at para position of benzyl bromide (entry 4) were equally effective toward the nucleophilic substitution of azide, followed by 1,3-dipolar cycloaddition. However, in case of non-activated alkyl halides like *n*-hexyl bromide as well as *n*-octyl bromide, the reaction required longer reaction time and furnished corresponding triazoles in lower yields (Table 2,

entries 5 and 6). Unfortunately, the catalytic system was less effective for the reaction of benzyl chlorides (Table 2, entries 7-9). Benzyl and allyl tosylate reacted well and giving good yields (Table 2, entries 10 and 11). Furthermore, by using various substituted phenylacetylenes with substituents that have different electronic properties, different yields of the final products were achieved. The aryl acetylene bearing electron-donating group (p-Me) and electron withdrawing group (p-CF<sub>3</sub>) reacted well and giving good yields (Table 2, entries 12 and 13).

Table 2. Multicomponent 1,3-dipolar cycloaddition catalyzed by NHC-Cu/CL<sup>a</sup>

R <sup>1</sup>	-X + NaN <sub>3</sub>	+ R <sup>2</sup>		I=N R <sup>2</sup>
Entry	$\mathbb{R}^1$	Х	$R^2$	Yield <sup>b</sup>
1	Ph	Br	Ph	98%
2	$4\text{-}CH_3C_6H_4$	Br	Ph	94%
3	$4-CH_3OC_6H_4$	Br	Ph	91%
4	$4-NO_2C_6H_4$	Br	Ph	98%
5	$C_5H_{11}$	Br	Ph	82%
6	C7H15	Br	Ph	84%
7°	Ph	Cl	Ph	90%
8°	$4-CH_3OC_6H_4$	Cl	Ph	79%
9°	$4-NO_2C_6H_4$	Cl	Ph	85%
10	Ph	OTs	Ph	98%
11	CH <sub>2</sub> =CH	OTs	Ph	97%
12	Ph	Br	$4\text{-}CH_3C_6H_4$	98%
13	Ph	Br	$4\text{-}CF_3C_6H_4$	90%

aorganic halide or tosylate, (1.0 mmol), sodium azide (1.2 mmol), terminal alkyne (1.0 mmol), H<sub>2</sub>O (3 mL), NHC-Cu/CL (1 mol% of Cu), 1 h <sup>b</sup> Isolated yield. <sup>c</sup> reaction time = 3 h.

The heterogeneous nature of the catalysis was proved using a hot filtration test and AAS analysis. To determine whether the catalyst is actually functioning in a heterogeneous manner or whether it is merely a reservoir for more active soluble copper species, we performed a hot filtration test in the multicomponent 1,3-dipolar cycloaddition of benzyl bromide, sodium azide and phenylacetylene after ~50% of the coupling reaction is completed. The hot filtrates were then transferred to another flask containing H<sub>2</sub>O at 50 °C. Upon the further heating of catalyst-free solution for 6 h, no considerable progress (~3% by GC analysis) was observed. Moreover, using AAS of the same reaction solution at the midpoint of completion indicated that no significant quantities of cooper (~1%) are lost to the reaction liquors during the process.

The recyclability of the NHC-Cu/CL composite was also examined by the multicomponent 1,3-dipolar cycloaddition. It was found that the recovery can be successfully achieved in seven successive reaction runs (Table. 3).

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Reaction cycle	1st	2nd	3rd	4th	5th	6th	7th
Yield <sup>b</sup> (%)	98	98	98	97	97	96	96

 $^a$  benzyl bromide, (1.0 mmol), sodium azide (1.2 mmol), phenylacetylene (1.0 mmol), H2O (3 mL), NHC-Cu/CL (1 mol% of Cu), 1 h, 50 °C. $^b$  Isolated yield

#### Conclusions

We have successfully developed a novel, practical and environmentally friendly method for the multicomponent 1,3dipolar cycloaddition by using NHC-Cu/CL as catalyst. In addition, this methodology offers the competitiveness of recyclability of the catalyst without significant loss of catalytic activity, and the catalyst could be readily recovered and reused for seven cycles, thus making this procedure environmentally more acceptable. Further studies are currently underway in our laboratories and results will be disseminated in due course.

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