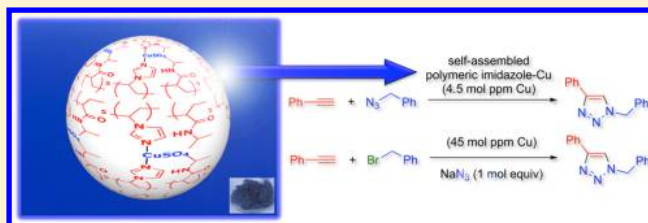


Amphiphilic Self-Assembled Polymeric Copper Catalyst to Parts per Million Levels: Click Chemistry

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S Supporting Information

ABSTRACT: Self-assembly of copper sulfate and a poly-(imidazole–acrylamide) amphiphile provided a highly active, reusable, globular, solid-phase catalyst for click chemistry. The self-assembled polymeric Cu catalyst was readily prepared from poly(*N*-isopropylacrylamide-*co*-*N*-vinylimidazole) and CuSO₄ via coordinative convolution. The surface of the catalyst was covered with globular particles tens of nanometers in diameter, and those sheetlike composites were layered to build an aggregated structure. Moreover, the imidazole units in the polymeric ligand coordinate to CuSO₄ to give a self-assembled, layered, polymeric copper complex. The insoluble amphiphilic polymeric imidazole Cu catalyst with even 4.5–45 mol ppm drove the Huisgen 1,3-dipolar cycloaddition of a variety of alkynes and organic azides, including the three-component cyclization of a variety of alkynes, organic halides, and sodium azide. The catalytic turnover number and frequency were up to 209000 and 6740 h^{−1}, respectively. The catalyst was readily reused without loss of catalytic activity to give the corresponding triazoles quantitatively.



■ INTRODUCTION

Copper metalloenzymes are supramolecular metal–organic hybrids of imidazole-containing polypeptides and copper ions, which are essential proteins in vital activity to promote high-efficiency enzymatic reactions.^{1,2} Complexation of polymeric imidazoles in histidine and copper species provides not only Lewis acidic–Brønsted basic catalytic sites but also a supramolecular tertiary structure. Therefore, to go even further and also ensure high catalytic activity, stability, and reusability, the development of self-assembled polymeric imidazole-supported copper catalysts is one of the most interesting topics in organic, organometallic, and supramolecular chemistry.^{3–5}

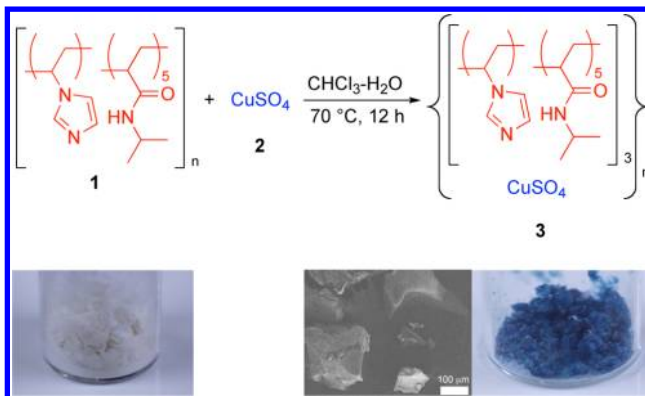
We envisaged that our concept for the preparation of convoluted polymeric imidazole–metal catalysts would offer high catalytic activities with reusability for click reactions.⁶ Amphiphilic polymeric imidazole units coordinate to Cu species through the self-assembly to provide the supramolecular polymeric metal composite with thermodynamic stability and insolubility. Here, we report the development of a novel self-assembled poly[(acrylamide–imidazole)–copper] catalyst. A catalyst in amounts of 0.00045 mol % (4.5 mol ppm) to 0.25 mol % promoted the Huisgen 1,3-dipolar cycloaddition of organic azides and terminal alkynes efficiently with a TON of up to >200000, and it was reused without loss of catalytic activity or leaching of copper species.

■ RESULTS AND DISCUSSION

Preparation of a Self-Assembled Polymeric Imidazole–Copper Catalyst. A novel self-assembled polymeric imidazole–copper catalyst 3 was prepared from a linear amphiphilic polymer

poly(*N*-isopropylacrylamide-*co*-*N*-vinylimidazole) (1) and copper sulfate (2) via a molecular convolution method.⁷ Incorporation of an aqueous solution of 2 into a chloroform solution of 1 drove the self-assembly to provide a polymeric copper composite 3 (Scheme 1). The resulting precipitate 3 was

Scheme 1. Preparation of a Self-Assembled Polymeric Imidazole–Cu Catalyst 3, a Photographic Image of 1 (left) and 3 (right), and a SEM Image of 3 (center)



barely soluble in water, *tert*-butanol, ethyl acetate, toluene, and ether, whereas the starting polymer 1 was soluble in water, methanol, chloroform, tetrahydrofuran, and *N,N*-dimethylfor-

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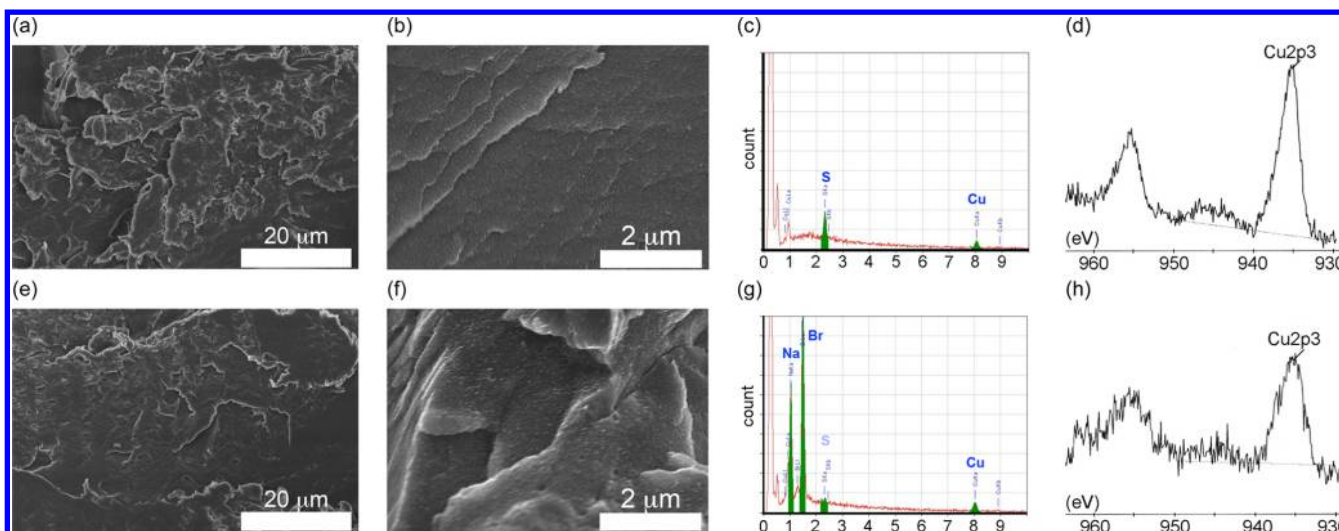


Figure 1. Images of **3** before and after use: SEM images of **3** before (a) and after use (e); HR-SEM images of **3** before (b) and after use (f); EDX/SEM images of **3** before (c) and after use (g); XPS images of **3** before (d) and after use (h).

amide. An SEM image showed that the composite **3** formed a macroaggregated lump several hundreds of micrometers thick (Figure 1). HR-SEM revealed that the surface of **3** was covered with globular particles tens of nanometers in diameter and that sheetlike composites were layered to build an aggregated structure. EDX/SEM analysis of the sheetlike composites showed the existence of copper and sulfur species. XPS analysis of Cu 2p_{3/2} and S 2p_{3/2} showed peaks at 934.8 and 167.9 eV, respectively; these are assigned to Cu(II) and S(IV) (CuSO₄). A UV-vis spectrum of **3** exhibited a new single absorption at 694 nm that was assigned as that of Cu-imidazole.⁸ These results suggest that the imidazole units in **1** coordinate to CuSO₄ to give a self-assembled, layered, polymeric copper complex. Elemental analysis and ICP-AES analysis of copper and sulfur supported the structure of **3**.

Huisgen 1,3-Dipolar Cycloaddition of a Self-Assembled Polymeric Imidazole-Copper Catalyst. The amphiphilic polymeric imidazole-copper composite **3** was used in an investigation of the Huisgen 1,3-dipolar cycloaddition of organic azides and terminal alkynes (Table 1). A copper-catalyzed Huisgen 1,3-dipolar cycloaddition of organic azides and terminal alkynes, also known as a “click reaction”, has become one of the most important reactions for the preparation of 1,2,3-triazoles.^{9,10} High catalytic efficiency of immobilized catalysts for click reactions is important in terms of sustainable and process chemistries as well as in organic syntheses. There have been some pioneering reports on click chemistry with immobilized copper catalysts.³ Recently, Mizuno, Yus, Yamamoto, and Santoyo-Gonzalez developed heterogeneous Cu catalysts for this reaction with TONs of 800, 198, 990, and 746, respectively, as the highest TONs.⁴ The development of heterogeneous immobilized polymeric metal catalysts¹¹ with high efficiencies and reusabilities for this purpose still remains a major challenge.

When the cyclization of phenylacetylene (**4a**) and benzyl azide (**5a**) was carried out with **3** (0.25 mol % Cu) in a *t*-BuOH/H₂O solution of sodium ascorbate (10 mol %) at 50 °C for 1.5 h, **3** drove the reaction smoothly to afford 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (**6a**) in 99% yield (entry 1). All the triazoles **6** were isolated by crystallization. The color of the catalyst changed from blue to green during the reaction. The catalyst was recovered by

Table 1. Huisgen 1,3-Dipolar Cycloaddition of Organic Azides and Terminal Alkynes with **3**

$\text{R}^1\text{C}\equiv\text{C} + \text{N}_3\text{CH}_2\text{R}^2 \xrightarrow[\text{50 } ^\circ\text{C, 1.5 h}]{\text{3 (0.25 mol \%), sodium ascorbate (10 mol \%), } t\text{-BuOH/H}_2\text{O (1:3)}} \text{R}^1\text{C}_3\text{N}_2\text{CH}_2\text{R}^2$			
entry ^a	4 (R ¹)	5 (R ²)	6 yield (%) ^b
1	4a (Ph)	5a (Ph)	6a 99
2 ^c	4a	5a	6a 99
3 ^d	4a	5a	6a 96
4 ^e	4a	5a	6a 99
5 ^f	4a	5a	6a 97
6	4a	5b (4-NO ₂ C ₆ H ₄)	6b 97
7	4a	5c (4-FC ₆ H ₄)	6c 96
8	4a	5d (4-MeC ₆ H ₄)	6d 97
9	4a	5e (4-MeOC ₆ H ₄)	6e 97
10	4a	5f (2-naph)	6f 94
11	4b (4-MeC ₆ H ₄)	5a	6g 97
12	4b	5g (PhCH ₂)	6h 96
13	4b	5h (<i>n</i> -C ₉ H ₁₉)	6i 97
14	4c (HO-(CH ₂) ₄)	5a	6j 97
15	4c	5b	6k 96
16	4c	5c	6l 96
17	4c	5d	6m 96
18	4c	5e	6n 96
19	4c	5f	6o 97
20	4c	5g	6p 95
21	4c	5h	6q 96
22	4d [<i>c</i> -(CH ₂) ₅ C]OH	5a	6r 98
23	4e ((EtO) ₂ CH)	5a	6s 97
24	4f (NMe ₂ CH ₂)	5a	6t 97
25	4g (Cl-(CH ₂) ₃)	5a	6u 96
26	4h (<i>n</i> -C ₄ H ₉)	5a	6v 96

^aConditions: **4** (0.50 mmol), **5** (0.50 mmol), **3** (0.25 mol %), sodium ascorbate (10 mol %), *t*-BuOH (0.5 mL), H₂O (1.5 mL), 50 °C, 1.5 h.

^bIsolated yield by crystallization. ^cFirst reuse. ^dSecond reuse. ^eThird reuse. ^fFourth reuse.

picking it up, and it was reused in the same reaction under similar conditions without loss of catalytic activity (second use 99%,

third use 96%, fourth use 99%, fifth use 97%) (entries 2–5). There was no leaching of Cu species in the reaction mixture in cyclizations with the reused catalyst (ICP-AES analysis) (entry 5). A hot filtration test was conducted to prove that the insoluble catalyst promotes the reaction under heterogeneous conditions and that no copper species were released out in the reaction mixture (Figure 2).¹² SEM observations of fresh and reused 3

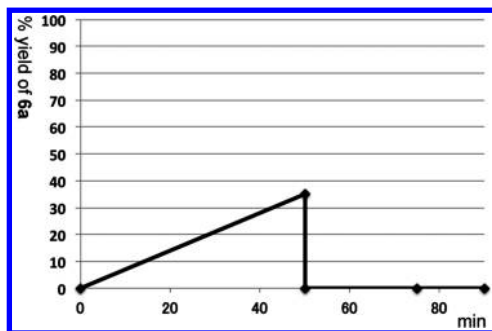


Figure 2. Hot filtration test in the reaction of **4a** and **5a**. The reaction mixture was filtered at 50 °C after 50 min, at which **3** and the precipitated product **6a** were readily removed. The resulting filtrate did not promote the reaction.

indicated that the morphology of the catalyst was undamaged and unchanged under the reaction conditions (Figure 1b, d, f, h). EDX/SEM analysis showed that the sulfur peak disappeared because Cu(II) was reduced by sodium ascorbate to a Cu(I) species. The sulfate should be washed away, and the ascorbate became the counterion of the Cu ions instead. In XPS analysis of Cu 2p_{3/2} of the catalyst before and after use, peaks were observed at 934.8 and 934.6 eV (Figure 1d and h).¹³ The UV–vis spectra of **3** before and after use exhibited a similar single absorption at 694–6 nm that should be assigned as that of Cu-imidazole. These results indicated that the catalyst **3** was intact and stable under the reaction conditions.

Electron-withdrawing- and electron-donating-group-substituted benzyl azides **5b–e** and 2-naphthylmethyl azide (**5f**) reacted efficiently with **4a** under similar conditions to afford the corresponding triazoles **6b–f** in yields of 94–97% (entries 6–10). The reactions of 4-tolylacetylene (**4b**) with benzyl azide (**5a**) and with the alkyl azides 1-azido-2-phenylethane (**5g**) and 1-azidodecane (**5h**) led to complete conversion, giving the cyclized products **6g–i** in yields of 96–97% (entries 11–13). An aliphatic alkynol, hex-5-yn-1-ol (**4c**), readily reacted with a variety of benzylic and aliphatic azides **5a–h** to give the corresponding triazoles **6j–q** in 95–97% yields (entries 14–21). The Cu catalyst **3** also promoted the reaction of alkynes bearing tertiary alcohol, acetal, amine, and chloro moieties (**4d–g**) and an unmodified aliphatic compound 1-pentyne (**4h**) with **5a** to give the corresponding products **6r–v** in 96–98% yields (entries 22–26). In these cyclization reactions, the alcohol, acetal, amine, and chloro groups remained intact and did not affect the reactivity.

Since **3** efficiently drove the click reaction of alkynes and organic azides, the three-component cyclization of alkyl halides, sodium azide, and alkynes was investigated (Table 2). The reaction of phenylacetylene (**4a**), benzyl bromide (**7a**), and sodium azide was carried out under similar conditions to those in Table 1, affording the triazole **6a** in 99% yield (entry 1). The polymeric imidazole Cu catalyst **3** was reused four times without loss of catalytic activity (entries 2–5). The reaction of benzyl chloride (**7b**) was completed within 2.5 h to give **6a** in 97% yield

Table 2. Three-Component Cyclization of Alkyl Halides, Sodium Azide, and Alkynes

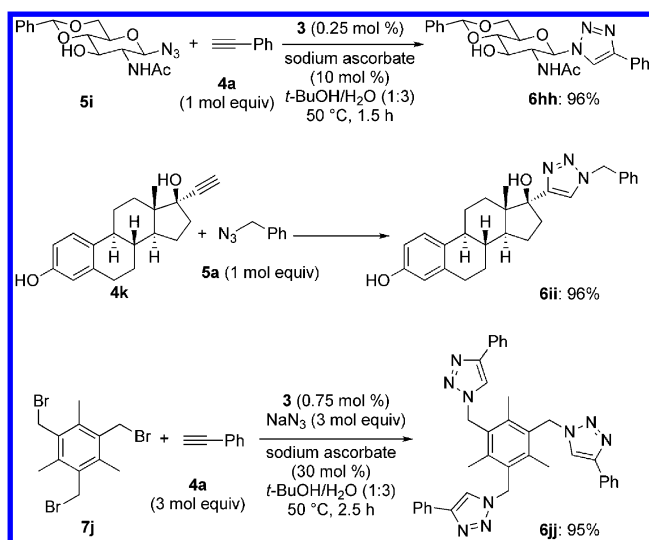
$\text{R}^1\text{—}\text{C}\equiv\text{C—} + \text{X—CH}_2\text{—R}^2 \xrightarrow[\text{50 } ^\circ\text{C, 2.5 h}]{\begin{array}{l} \text{3 (0.25 mol \%)} \\ \text{NaN}_3 \text{ (1 mol equiv)} \\ \text{sodium ascorbate (10 mol \%)} \\ \text{t-BuOH/H}_2\text{O (1:3)} \end{array}} \text{R}^1\text{—C=N—N—CH(R}^2\text{)—} \\ \text{4} \qquad \qquad \qquad \text{7} \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \text{6}$			
entry ^a	4 (R ¹)	7 (R ² , X)	6 yield (%) ^b
1	4a (Ph)	7a (Ph, Br)	6a 99
2 ^c	4a	7a (Ph, Br)	6a 99
3 ^d	4a	7a (Ph, Br)	6a 98
4 ^e	4a	7a (Ph, Br)	6a 97
5 ^f	4a	7a (Ph, Br)	6a 96
6	4a	7b (Ph, Cl)	6a 97
7	4a	7c (4-NO ₂ C ₆ H ₄ , Br)	6b 97
8	4a	7d (4-NO ₂ C ₆ H ₄ , Cl)	6b 94
9	4a	7e (4-FC ₆ H ₄ , Br)	6c 96
10	4a	7f (4-MeC ₆ H ₄ , Br)	6d 98
11	4a	7g (2-naph, Br)	6f 95
12	4a	7h (CO ₂ Et, Br)	6w 97
13	4a	7i (<i>trans</i> -cinnamyl chloride)	6x 97
14	4b (4-MeC ₆ H ₄)	7a	6g 97
15	4b	7c	6y 94
16	4b	7f	6z 97
17	4b	7g	6aa 94
18	4b	7h	6bb 98
19	4i (6-MeO-2-naph)	7c	6cc 81
20	4i	7f	6dd 94
21	4i	7g	6ee 86
22	4i	7h	6ff 96
23	4c (HO-(CH ₂) ₄)	7a	6j 96
24	4c	7c	6k 97
25	4c	7d	6k 96
26	4c	7e	6l 97
27	4c	7f	6m 96
28	4c	7g	6o 95
29	4j (HO-CH ₂)	7a	6gg 96
30	4j	7b	6gg 94

^aConditions: **4** (0.50 mmol), **7** (0.50 mmol), **3** (0.25 mol %), sodium ascorbate (10 mol %), *t*-BuOH (0.5 mL), H₂O (1.5 mL), 50 °C, 2.5 h.

^bIsolated yield by crystallization. ^cFirst reuse. ^dSecond reuse. ^eThird reuse. ^fFourth reuse.

(entry 6). A variety of benzylic halides with substituents were also converted to the corresponding triazoles **6b–d** in yields of 94–98% (entries 7–10). The catalyst **3** promoted the cyclization with 2-naphthylmethyl bromide (**7g**), ethyl bromoacetate (**7h**), and cinnamyl chloride (**7i**) to afford 95–97% yields of the cyclized products **6f**, **6w**, and **6x** (entries 11–13). All the reactions of arylacetylenes, i.e., 4-tolylacetylene (**4b**) and 6-methoxynaphthylacetylene (**4i**), and aliphatic alkynes, i.e., hex-5-yn-1-ol (**4c**) and propargyl alcohol (**4j**), with a variety of halides **7a–h** proceeded smoothly under similar conditions to those above to give the corresponding triazoles **6g–gg** in 81–98% yields (entries 14–30). These results indicate that the catalytic systems can be readily applied to the combinatorial synthesis of triazole compounds.

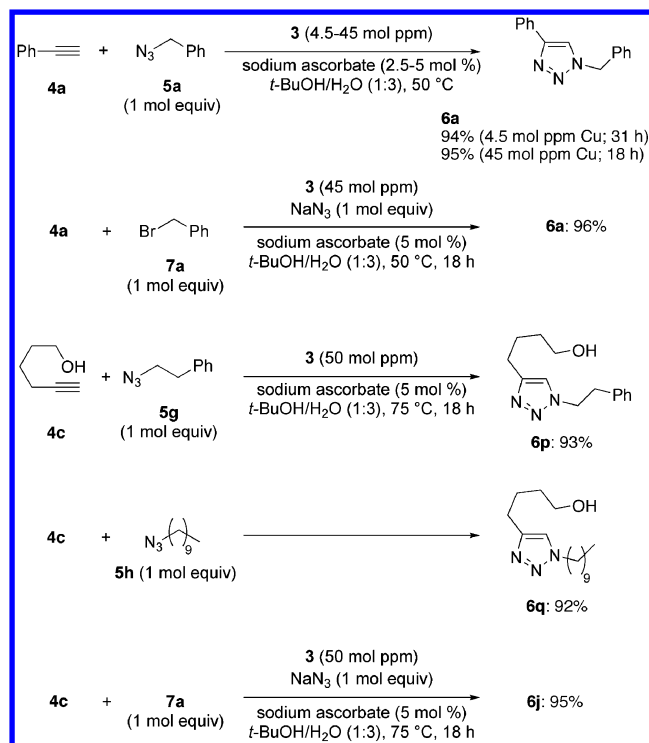
The catalyst **3** was used to prepare functional materials, namely a carbohydrate, a steroid, and a ligand (Scheme 2). The reaction of an *N*-acetylglucosamine derivative bearing an azide moiety **5i** with **4a** was performed with **3** under similar conditions to those previously described to afford the triazole-linked *N*-acetylglucos-

Scheme 2. Application of **3** to the Synthesis of Functional Materials

amine **6hh** in 96% yield. Ethynylestradiol (**4k**) reacted with **5a** to give the triazole-linked estradiol **6ii** in 96% yield. The multicyclization of **7j** with **4a** led to the formation of a tris(triazole) ligand **6jj** in 95% yield.

To investigate the highest catalytic activity obtainable for the cycloaddition, reactions with 4.5–45 mol ppm Cu were performed (Scheme 3). **3** (45 mol ppm Cu) promoted the reaction of **4a** with **5a** to give **6a** in 95% yield. The three-component reaction of **4a**, **7a**, and NaN_3 in the presence of 45 mol ppm, based on Cu, of **3** gave **6a** in 96% yield. We also found that 4.5 mol ppm, based on Cu, of **3** drove the cyclization of **4a** and **5a** to provide **6a** in 94% yield. The TON and the turnover

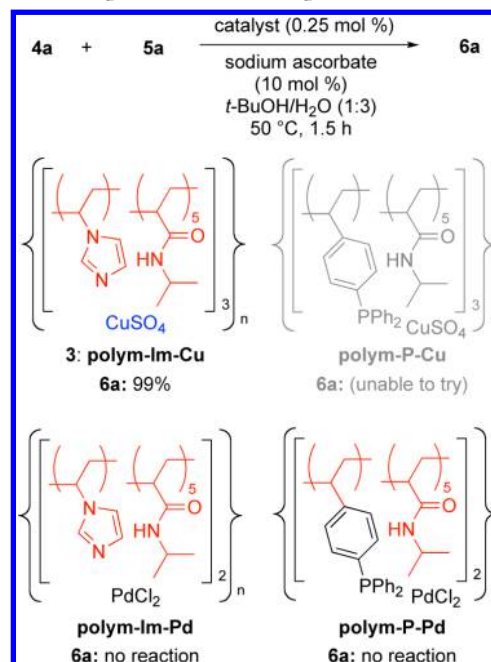
Scheme 3. Lower Catalytic Loadings (4.5–45 ppm) in the Huisgen Reaction



frequency (TOF) of the catalyst reached 209000 and 6740 h^{-1} , respectively; these are, as far as we know, the highest TON and TOF obtained for a heterogeneous-catalyst-promoted Huisgen cycloaddition. This catalytic system was readily applied to the reaction of aliphatic substrates and reactants

Moreover, ligand and metal effects for the Huisgen cycloaddition were evaluated (Scheme 4). Thus, the reaction of **4a** and

Scheme 4. Comparison of the Catalytic Activity of Polymeric Imidazole/Phosphine Cu/Pd Complexes



5a with **3** (0.25 mol %) at 50 °C for 1.5 h gave **6a** in 99% yield. In contrast, poly[(*N*-isopropylacrylamide-*co*-styryldiphenylphosphine)CuSO₄] could not be prepared as an insoluble composite but a soluble one. When the polymeric Pd catalysts polym-Im-Pd and polym-P-Pd were used for the reaction under similar conditions,⁶ no reactions took place. These results indicated that the use of both the polymeric imidazole ligand **1** and Cu species **2** in the catalytic composite was important to prepare a highly active and insoluble catalyst for the efficient Huisgen cycloaddition.

Plausible Catalytic Pathway. The plausible reaction pathway is as follows (Figure 3). The Cu(I) species reacts with an alkyne to give a copper acetylide. The 1,3-dipolar cyclization of the resulting Cu acetylide and an organic azide followed by the protonation provided the formation of a triazole and the regeneration of Cu(I) catalyst.¹⁴ To prove the formation of the Cu acetylide from the catalyst **3** and the alkyne **4** in the presence or absence of sodium ascorbate, the IR observation was conducted (Figures S-1–3 of the Supporting Information). Thus, the reaction of the catalyst **3** and **4a** in the presence of sodium ascorbate afforded a green-colored catalyst. Gratifyingly, the vibrational absorption of Cu—C≡C in the heterogeneous composite was observed at 1936 cm^{-1} . In contrast, a similar reaction in the absence of sodium ascorbate gave an unchanged blue-colored catalyst where no peaks of Cu—C≡C were observed. These results indicate that the heterogeneous Cu(II) catalyst was reduced by sodium ascorbate to give the Cu(I) catalyst. The resulting Cu(I) catalyst reacted with an alkyne **4a** to give the Cu acetylide.

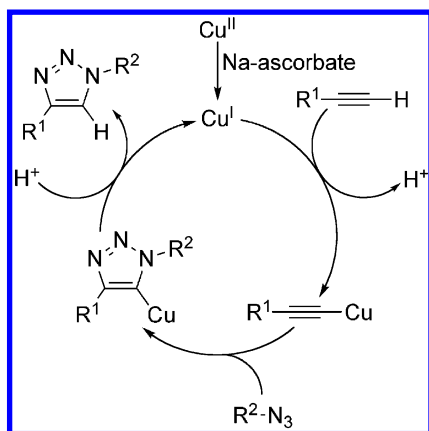


Figure 3. Plausible reaction pathway of the Huisgen cycloaddition.

CONCLUSION

In conclusion, we developed a reusable metalloprotein-inspired polymeric imidazole–copper catalyst, **3**, that formed sheetlike composites with globular polymeric particles. The catalyst **3** efficiently promoted the Huisgen 1,3-dipolar cycloaddition of a variety of alkynes and organic azides, including the three-component cyclization of a variety of alkynes, organic halides, and sodium azide. The catalyst **3** provides the highest TON and TOF so far obtained for a heterogeneous catalyst-promoted Huisgen 1,3-dipolar cycloaddition.

EXPERIMENTAL SECTION

Preparation of Imidazole Polymer 1. A solution of *N*-vinylimidazole (1 g, 10.62 mmol) and *N*-isopropylacrylamide (6.01 g, 53.13 mmol) in toluene (40 mL) was degassed for 30 min under Ar atmosphere. AIBN (16.4 mg, 0.1 mmol) was added to the reaction mixture, which was then degassed for a further 30 min under Ar atmosphere. The solution was then heated at 70 °C for 12 h, during which colorless powders were precipitated out. They were filtered off through a glass filter and washed with toluene. The resulting colorless solid was dried under reduced pressure to give **1** in 83% yield. ¹H NMR (CDCl₃, 500 MHz): δ = 7.18–6.93 (m, 3 H), 4.12–3.81 (m, 5 H), 2.92 (m, 5 H), 2.09 (m, 5 H), 1.30–1.85 (m, 13 H), 1.12 (m, 30 H); ¹³C NMR (CDCl₃, 125 MHz) δ = 174.2, 129.7, 129.0, 128.2, 42.5, 41.3, 27.5, 22.6; IR (KBr) 3294, 2971, 2932, 2878, 1650, 1543, 1458, 1386, 1367, 1228, 1173, 1131, 1079, 915, 816, 667 cm⁻¹; Anal. Calcd for C₃₅H₆₁N₇O₅·2H₂O: C, 60.40; H, 9.41; N, 14.09. Found: C, 60.73; H, 9.38; N, 13.55.

Preparation of 3. To a solution of the imidazole polymer **1** (1 g, 1.51 mmol) in chloroform (10 mL) was slowly added an aqueous solution of CuSO₄·5H₂O (**2**) (189.2 mg, 0.757 mmol; 10 mL) at 25 °C. The resulting blue suspension was heated at 70 °C for 12 h before the precipitates were filtered off through a glass filter. The precipitates were filtered off, washed with chloroform and water on the glass filter, and dried under reduced pressure to give **3** (950 mg, 80%). Anal. Calcd for C₁₀₅H₁₈₃N₂₁O₁₉CuS·2H₂O: C, 57.97; H, 8.66; N, 13.52; Cu, 2.92; S, 1.47. Found: C, 57.75; H, 8.59; N, 13.92; Cu, 2.66; S, 1.32. IR (KBr): 3303, 2971, 2940, 2873, 1645, 1537, 1457, 1387, 1367, 1234, 1172, 1131, 1037, 835, 667 cm⁻¹.

General Procedure for the Two-Component [3 + 2] Cycloaddition Reaction. A 2.5-mL glass vessel was charged with **3** (3 mg, 0.25 mol %), sodium ascorbate (10 mg, 10 mol %), an alkyne **4** (0.5 mmol), and an organic azide **5** (0.5 mmol) in water and *tert*-butyl alcohol (1.5/0.5 mL each). The reaction vessel was shaken using a PetiSzyer (HiPep Laboratories, Japan) at 50 °C for 1.5 h, during which a colorless triazole was precipitated out. The reaction mixture was diluted with water and EtOAc. The Cu catalyst **3** was recovered by picking-up with a pair of tweezers. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic

layers were dried over MgSO₄ and concentrated under reduced pressure to give the corresponding 1,2,3-triazole **6**. Purification of the obtained triazole was accomplished by a recrystallization process (EtOAc/hexane).

General Procedure for the Three-Component [3 + 2] Cycloaddition Reaction. A 2.5-mL glass vessel was charged with **3** (3 mg, 0.25 mol %), sodium ascorbate (10 mg, 10 mol %), an alkyne **4** (0.5 mmol), sodium azide (0.5 mmol), and an alkyl halide **7** (0.5 mmol) in water and *tert*-butyl alcohol (1.5/0.5 mL each). The reaction vessel was shaken using a PetiSzyer (HiPep Laboratories, Japan) at 50 °C for 2.5 h, during which a colorless triazole was precipitated out. The reaction mixture was diluted with water and EtOAc. The polymeric Cu catalyst **3** was recovered by picking-up with a pair of tweezers. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure to give the corresponding 1,2,3-triazole **6**. Purification of the obtained triazole was accomplished by a recrystallization process (EtOAc/hexane).

ASSOCIATED CONTENT

Supporting Information

Experimental details, compound data, and NMR charts. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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