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# HUISGEN CYCLOADDITION WITH ACETYLENE GAS BY USING AN AMPHIPHILIC SELF-ASSEMBLED POLYMERIC COPPER CATALYST

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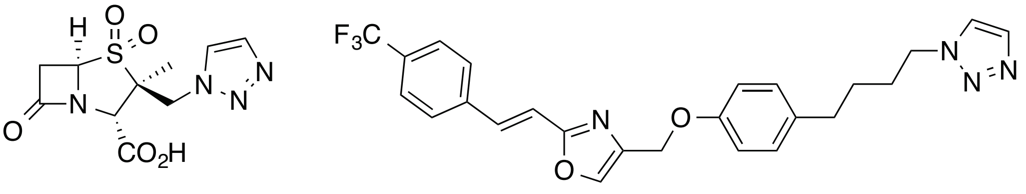
Dedicate this work to Professor Masakatsu Shibasaki on the occasion of his 70th birthday

**Abstract** – A copper-mediated Huisgen cycloaddition, aka the copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC), of flammable acetylene gas and a variety of organic azides proceeded smoothly by using our amphiphilic self-assembled polymeric copper catalyst MPPI-Cu to give the corresponding triazoles in high yield. MPPI-Cu was readily reused without loss of catalytic activity. The XAFS and DFT calculation studies revealed the local structure near Cu atom of an active species MPPI-Cu(I).

A copper-mediated Huisgen cycloaddition, also known as the copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) is among the important reactions for the preparation of triazole compounds that are useful components of bioactive, pharmaceutical, and functional compounds.[1] Although a flammable acetylene gas began to be used for this cycloaddition to synthesize mono-substituted 1*H*-1,2,3-triazoles,[2] potentially biologically active compounds as shown in Figure 1,[3] we seriously worry about naked copper(I) acetylide, generated in the catalytic cycle, that has a potential to be explosive.[4] We have developed a highly active and reusable amphiphilic self-assembled polymeric copper catalyst MPPI-Cu and applied it to the copper(I)-catalyzed alkyne-azide cycloaddition by the use of 4.5 mol ppm to 0.25 mol% of the catalyst.[5] We envisioned that the polymeric moiety in MPPI-Cu could stabilize the resulting copper acetylide as a giant protective polymer matrix, and thus mono-substituted 1,2,3-triazoles should be more readily and safely prepared. Herein, we report Huisgen cycloaddition of acetylene gas and organic azides by using 0.25 mol% of MPPI-Cu, affording a variety of 1-substituted 1*H*-1,2,3-triazoles with high yield. MPPI-Cu was readily reused without loss of catalytic activity. Moreover, the local structure near Cu atom of an active species of MPPI-Cu(I) was also investigated by means of X-ray absorption fine structure (XAFS) spectroscopy as well as DFT calculation.



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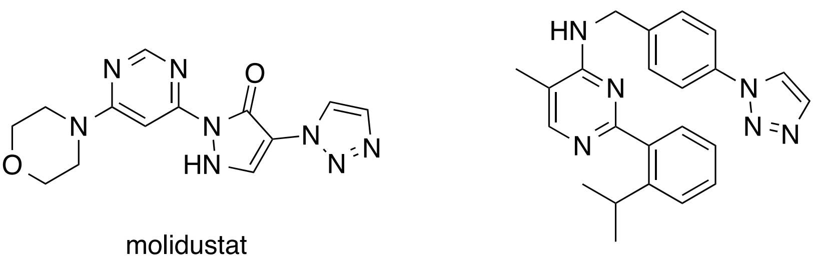

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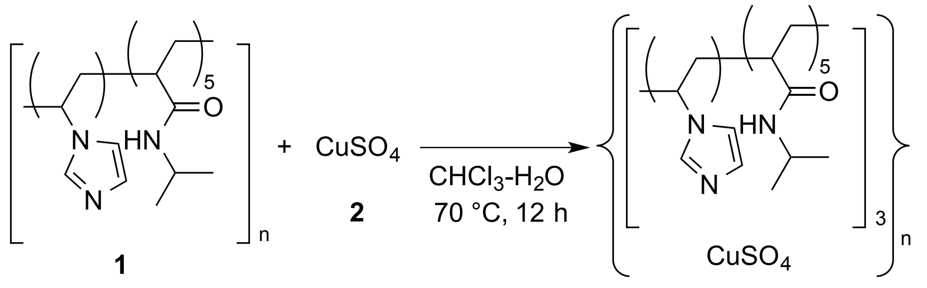
Figure 1. Biologically active 1*H*-1,2,3-triazoles

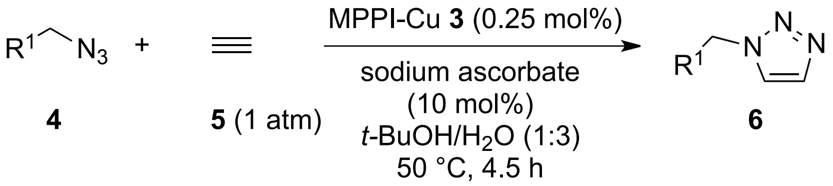


MPPI-Cu **3**

Scheme 1. Preparation of an amphiphilic self-assembled polymeric copper catalyst MPPI-Cu **3**

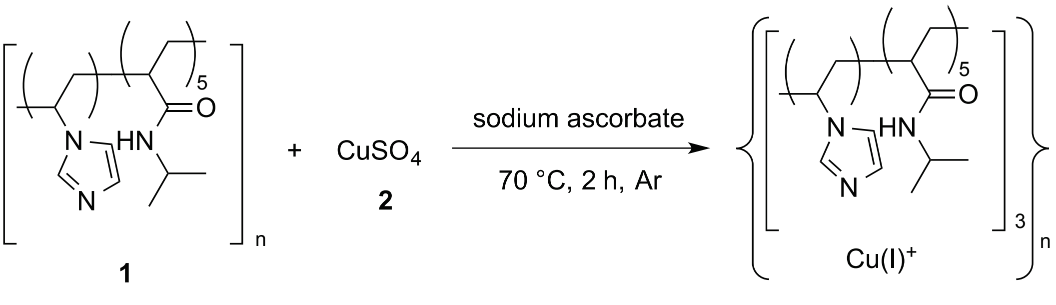
An amphiphilic self-assembled polymeric copper catalyst MPPI-Cu was prepared from poly(vinylimidazole-*co*-*N*-isopropylacrylamide) (**1**) and copper(II) sulfate (**2**) as hardly soluble lumps (Scheme 1).[5] Huisgen cycloaddition was carried out with a variety of organic azides **4** and 1 atm (balloon) of gaseous acetylene **5** in the presence of 0.25 mol% Cu of MPPI-Cu **3** and 10 mol% of sodium ascorbate in *t*-BuOH/$H_2O$ (1:3) at 50 °C for 4.5 h (Table 1). The reaction of benzyl azide (**4a**) and acetylene gas (**5**) proceeded smoothly to give 1-phenylmethyl-1*H*-1,2,3-triazole (**6a**) in 94% yield (Entry 1). The insoluble catalyst was readily recovered and reused to give **6a** with 93% and 91% yield in 2nd and 3rd run, respectively (Entry 1). Substituted benzylic azides are also suitable substrates: The reaction of benzylic azides bearing electron-withdrawing group **4b** and **4c** afforded the corresponding triazoles **6b** and **6c** in 95% and 90% yield, respectively (Entries 2 and 3). Benzylic azides bearing electron-donating groups **4d–g** were readily converted to the corresponding triazoles **6d–g** in 85–96% yield (Entries 4–7). Less reactive aliphatic azides were also utilized: The reaction of 2-phenethyl azide (**4h**), 1-heptyl azide (**4i**) and 1-decyl azide (**4j**) was carried out to give the corresponding triazoles **6h–j** in 76–92% yield (Entries 8–10).

Table 1. Huisgen cycloaddition of organic azides **4** and acetylene gas **5** catalyzed by MPPI-Cu **3**



| Entry[a] | **4** ($R^1$) | **6** Yield (%)[b] |
|---|---|---|
| 1 | **4a** (Ph) | **6a** 94 (1st use), 93 (2nd use), 91 (3rd use) |
| 2 | **4b** ($4\text{-}O_2NC_6H_4$) | **6b** 95 |
| 3 | **4c** ($4\text{-}NCC_6H_4$) | **6c** 90 |
| 4 | **4d** ($4\text{-}MeOC_6H_4$) | **6d** 95 |
| 5 | **4e** ($4\text{-}FC_6H_4$) | **6e** 85 |
| 6 | **4f** ($2\text{-}MeC_6H_4$) | **6f** 96 |
| 7 | **4g** ($4\text{-}MeC_6H_4$) | **6g** 95 |
| 8 | **4h** ($PhCH_2$) | **6h** 83 |
| 9[c] | **4i** ($Me(CH_2)_5$) | **6i** 76 |
| 10[d] | **4j** ($Me(CH_2)_8$) | **6j** 92 |

[a] Conditions: **4** (0.50 mmol), **5** (1 atm; balloon), MPPI-Cu **3** (0.25 mol%), *t*-BuOH (0.50 mL), $H_2O$ (1.5 mL), 50 °C, 4.5 h; [b] isolated yield; [c] **3** (0.50 mol%), 17 h; [d] **3** (1.5 mol%), sodium ascorbate (25 mol%), 15 h.



Scheme 2. Preparation of an active catalytic species MPPI-Cu(I) **7**

To investigate the real catalytic species in the reaction, MPPI-Cu(II) was reduced with sodium ascorbate to give MPPI-Cu(I) **7** (Scheme 2) that was analyzed with XANES, EXAFS as well as DFT calculation.

The oxidation state of the metal centers in MPPI-Cu(II) and -Cu(I) was confirmed by X-ray absorption near-edge structure (XANES) for Cu K-edge (Figure 2). The spectrum of MPPI-Cu(II) exhibited a small pre-edge peak around 8977 eV (feature A), which is a characteristic of $d^9$ Cu complexes (1s-3d(+4p) transition).[6] On the other hand, the position of the absorption edge of MPPI-Cu(I) was obviously shifted toward the lower energy region than that of Cu(II), indicating that the Cu site was reduced to Cu(I). The prominent absorption peak at 8983 eV (feature B) in the spectrum of MPPI-Cu(I) was attributed to the dipole-allowed transition from 1s to 4p orbitals of Cu. The low-energy, intense, and sharp pre-edge feature at 8983 eV (corresponding to 1s-$4p_{x,y}$ transition) strongly implies the two-coordinate linear Cu(I) (coordinated along the z-axis using $4p_z$ orbital).[6] To investigate the details of the coordination structure in MPPI-Cu(I), which was considered the real catalytically active species in the reaction, we analyzed the extended X-ray absorption fine structure (EXAFS) on Cu K-edge. First of all, we performed the geometry optimization of $[Cu^I(1\text{-methylimidazole})_2]^+$, where the two imidazole rings linearly coordinate to the Cu center by N atom at 3-position, as a proposed model for the local structure in MPPI-Cu(I) at the level of B97D/def2-SVP for all atoms (Figure 3).[7] The fitting of $k^3$-weighted EXAFS considering the coordinating 3-N atoms as well as the neighboring 2- and 4-C atoms (1.2–2.9 Å in *R*-space) based on the DFT-optimized geometry showed a good agreement with the experimental data (Figure 4 and Table 2). The statistical errors derived from the analysis are also indicated. The deviations from the theoretical bond length ($\Delta R$) were less than 0.1 Å, and the R-factor was 3.4%. The parameter corresponding to Debye-Waller factor ($\sigma^2$) for C atoms was greater than that of N atoms probably due to the influence of the free rotation along Cu-N single bond.

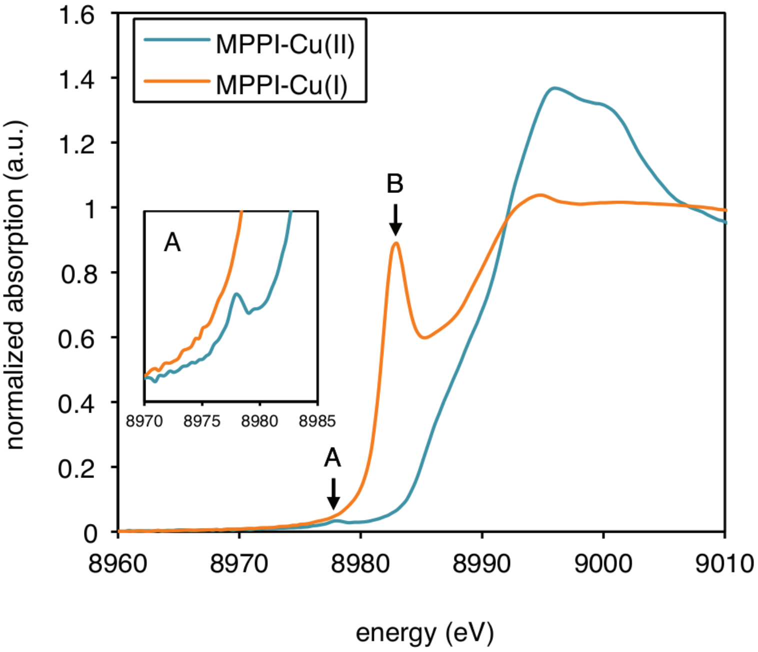


Figure 2. Cu K-edge XANES for MPPI-Cu(II) and -Cu(I)

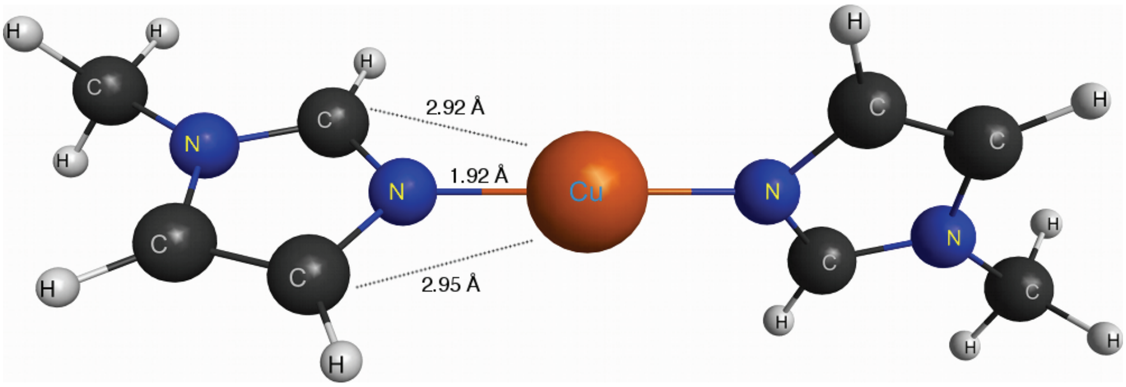


Figure 3. DFT-optimized structure of $[Cu^{I}(1\text{-methylimidazole})_2]^+$ (B97D/def2-SVP). The bond distances between Cu-N and Cu-C (2- and 4-position of imidazole) are 1.92, 2.92, and 2.95 Å, respectively. The dihedral angle between two imidazole rings is 90˚.

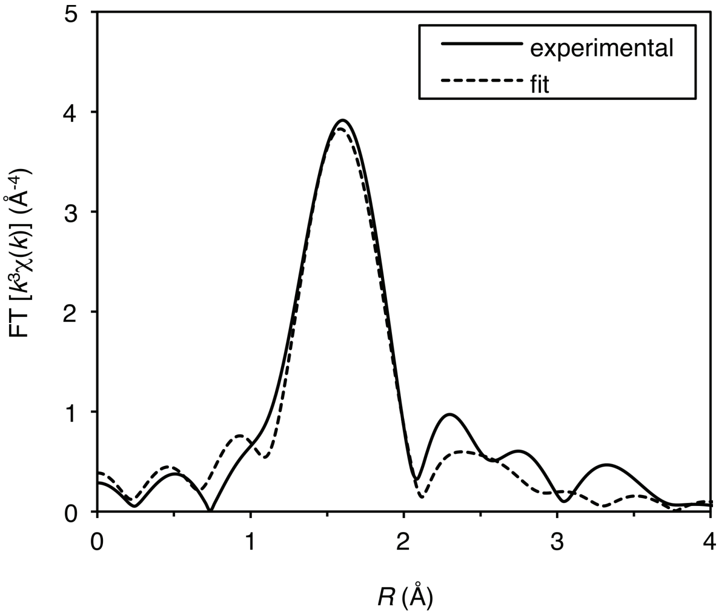


Figure 4. Fourier transform of $k^3$-weighted Cu K-edge EXAFS for MPPI-Cu(I) and the best fit

Table 2. The fitting parameters of EXAFS for MPPI-Cu(I)[a]

| | |
|---|---|
| R-factor | 3.4% |
| $E_0$ (eV) | 8995.6 (65) |
| $\Delta R$(N) (Å) | +0.07 (2) |
| $\Delta R$(C) (Å) | +0.06 (5) |
| $\sigma^2$(N) (Å$^2$) | 0.003 (1) |
| $\sigma^2$(C) (Å$^2$) | 0.012 (6) |

[a] Fitting $k$-range: 4–11 Å$^{-1}$, fitting $R$-range: 1.2–2.9 Å, $S_0{}^2 = 1$ (fixed).

In conclusion, we report Huisgen cycloaddition of organic azides and acetylene gas (1 atm) by using our amphiphilic self-assembled polymeric copper catalyst MPPI-Cu (0.25 mol%), affording the corresponding 1-substituted-1*H*-1,2,3-tiriazoles in high yield. The structure of the active catalytic species of MPPI-Cu was determined by use of XANES, EXAFS, and DFT calculation.

## EXPERIMENTAL

A Schlenk flask was charged with MPPI-Cu (3 mg, 0.25 mol%), an organic azide (0.5 mmol), sodium ascorbate (10 mg, 10 mol%) in water and *t*-BuOH (1.5/0.5 mL each). The Schlenk flask was purged with acetylene gas and the reaction was stirred under a balloon pressure at 50 °C for 4.5 h and monitored by TLC. After the reaction was completed, the reaction mixture was diluted with water and EtOAc. The supernatant was transferred to a separatory funnel, and the recovered catalyst in the Schlenk flask was dried *in vacuo*. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification by column chromatography on silica gel gave the corresponding 1*H*-1,2,3-triazole **6**. The recovered catalyst was reused for further reactions.

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