

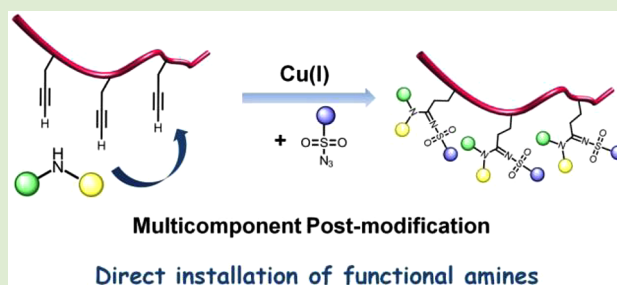
Three-Component Reactions for Post-Polymerization Modifications

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Supporting Information

ABSTRACT: A Cu-catalyzed multi-component reaction (CuMCR) of terminal alkynes, sulfonyl azides, and amines was employed in a post-polymerization modification process. The reaction was conducted on polystyrene bearing 20 mol % alkyne groups with 4-toluenesulfonyl azide and dihexylamine in the presence of a $\text{Cu}(\text{PPh}_3)_3\text{Br}$ /diisopropylethylamine catalyst. The CuMCR on polymer proceeded efficiently, as confirmed by the obvious gas evolution during the reaction, and the conversion of alkyne moiety reached almost 100%, yielding polymeric *N*-sulfonylamidine derivatives, as proven by ^1H NMR measurements. In addition, the precise structural assignment was proven by synthesis and analysis of the model monomeric compound (styrene *N*-sulfonylamidine) and the respective model polymer. We have successfully demonstrated the utilization of this new post-modification reaction by employing various amines including dipeptide and 1-aza-15-crown-5-ether.

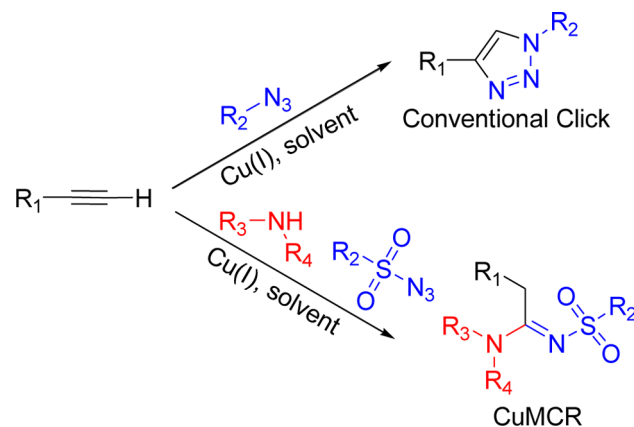


Along with a growing demand on functional polymers in a wide range of interdisciplinary applications, polymers with readily clickable groups received increasing attention because of their robust and reliable ability to yield manifold functional materials.^{1–3} To expand the scope of functional materials obtained by post-polymerization modification,^{4,5} many click-type reactions have been utilized. These include thiol-ene,^{6,7} thiol-maleimide,⁸ nucleophile-isocyanate,^{9,10} activated ester-amine reactions,¹¹ and Cu(I)-catalyzed^{12,13} and metal-free¹⁴ 1,3-dipolar cycloaddition reactions between organo-azides and acetylenes, which all lead practically to quantitative conversions during the post-polymerization modification step.

In spite of a broad window of click reactions, the Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction between organo-azides and acetylenes (CuAAC) has been a dominating reaction in the field of polymer chemistry because of the liability and high tolerance toward coexisting functional groups. However, CuAAC has intrinsic and inevitable drawbacks. The preparation of the organoazide compound is mandatory, which in most cases requires the reaction between alkyl halide with azide anion. This synthetic requirement has been a limitation of CuAAC because reaction processes with metal azides instinctively encounter a possibility of explosions, which is further time-consuming for chemists. Hence, in order to further accelerate click reactions not only in polymer science but also in the material science, direct employment of commercially available functional molecules without further organic synthesis is highly desirable.

The synthesis of multifunctional organic compounds was dramatically enhanced by utilization of multi-component reactions.^{15,16} Recently, Chang et al. reported a new reaction mode of CuAAC employing sulfonyl azides as an azide donating functionality (Scheme 1).^{17–19} To be precise, the

Scheme 1. Schematic Representation of Two Different Reaction Modes of Cu-Catalyzed Click Reactions between Organo-Azides and Acetylenes



Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction between terminal alkynes and sulfonyl azides was found to generate a ketenimine moiety via nitrogen release from corresponding 1,3-triazoles. In addition, the generated ketenimine moiety was then reacted with amines in situ to yield *N*-sulfonylamidines.²⁰ Importantly, both sulfonyl azides and amines are commercially available, which reduces the synthetic difficulties. Accordingly, this three-component reaction among terminal alkynes, sulfonyl azides, and amines was widely utilized in the field of organic chemistry.

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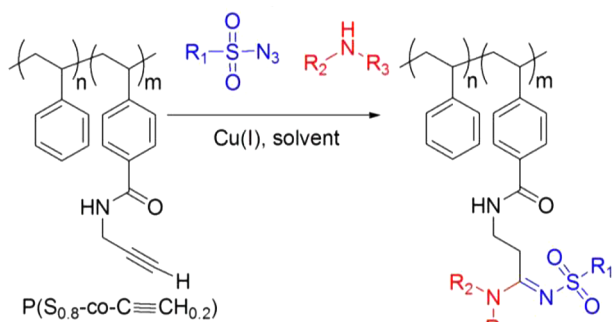
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Selected multi-component reactions have recently been utilized in the synthesis of polymers. For example, the group of Meier validated the use of the Passerini reaction as a possibility to prepare diene monomers suitable for an ADMET polymerization.²¹ In addition, the Passerini reaction was further utilized in the field of polymer chemistry for a step-growth polymerization,^{21–23} dendrimer synthesis,²⁴ and star-shaped polymer synthesis.²⁵ The group of Choi successfully demonstrated a Cu-catalyzed multi-component polymerization.²⁶

Hence, in this letter we describe the first utilization of a multi-component reaction in a post-polymerization modification of alkyne containing polymers. For this purpose, the direct functionalization of the acetylene functionalized polymers will be explored by taking advantage of the Cu-catalyzed multi-component reactions (CuMCR) among acetylene, sulfonyl azides, and amines. We will also compare it to the respective model polymers that were prepared by direct polymerization of corresponding monomers.

To eliminate a possible self-coupling of pendant alkynes via Cu-catalyzed oxidative coupling, alkyne incorporation was adjusted to be 20 mol % in polystyrene. Thus, the CuMCR was conducted by using $P(S_{0.8}\text{-}co\text{-}C\equiv CH_{0.2})$ as a starting polymer (structure is depicted in the Scheme 2), 4-toluenesulfonyl azide (Ts-N₃) as an azide donor, and dihexylamine as an amine donor.

Scheme 2. Schematic Representation of the Post-Modification Process Based on a Cu-Catalyzed Three-Component Reaction



Based on a report by Hawker et al. that showed a very reactive catalyst system for Cu-catalyzed 1,3-dipolar cycloaddition reaction between organo azide and terminal alkyne embedded in polymer structure, the same catalyst system comprised of $Cu(PPh_3)_3Br$ /diisopropylethylamine (DIPEA) was employed in the present study.²⁷ The CuMCR was conducted in THF/toluene mixed solvent system (1/2, v/v) in the presence of 20 mol % $Cu(PPh_3)_3Br$ as a catalyst with 0.06 mol·L⁻¹ alkyne concentration. When the reaction mixture was combined under Ar atmosphere, an obvious gas evolution was observed (Table 1, run 1), suggesting that the CuMCR proceeded smoothly with alkynes attached on a polymer. This clearly indicated the generation of ketenimine species via Cu-mediated reaction between the alkyne and Ts-N₃ and subsequent N₂ release, as demonstrated by Chang et al.¹⁷ In 4 h, the gas evolution was finished, which achieved almost 100% conversion of terminal alkyne group as confirmed by ¹H NMR measurement (run 1). A SEC trace of the polymer after the CuMCR revealed that the reaction system did not involve any detectable decomposition or cross-linking of the polymer

Table 1. Direct Installation of Various Amines onto Polymers via Cu-Catalyzed Three-Component Reactions by Using $P(S_{0.8}\text{-}co\text{-}C\equiv CH_{0.2})^a$

run	$[C\equiv CH]_0/[Ts-N_3]_0/[amine]_0/[Cu]_0/[DIPEA]_0$	amine	conv. of C≡C H ^b (%)
1	1/2/4/0.2/0.4	N,N-dihexylamine	>99.9
2	1/0/4/0.2/0.4	N,N-dihexylamine	~0
3 ^c	1/2/4/0.2/0.4	N,N-dihexylamine	>99.9
4	1/2/4/0.2/0.4	piperidine	>99.9
5	1/2/4/0.2/0.4	N,N-diisopropylamine	>99.9
6	1/2/4/0.2/0.4	anisidine	61.3
7	1/2/4/0.2/0.4	MeO-Leu-Pro-NH	44.2
8	1/2/4/0.2/0.4	1-aza-15-crown-5-ether	87.7

^aThe reaction condition is as follows: $Cu(PPh_3)_3Br$ as a Cu(I) source; THF/toluene (1/2, v/v) as a solvent system; initial acetylene concentration was adjusted to be 0.06 mol·L⁻¹; Ar atmosphere; *p*-toluenesulfonyl azide (Ts-N₃) was employed as an azide donor. The reaction was conducted for 4 h. ^bDetermined by ¹H NMR in CDCl₃. ^cEthyl azidoacetate was employed as an azide donor.

chains (see Supporting Information, Figure S-1). In a clear contrast to the reaction in the presence of Ts-N₃, no detectable reaction was confirmed for the reaction in the absence of Ts-N₃ (Table 1, run 2). In addition, when the reaction was conducted with aliphatic azide (ethyl azidoacetate; Table 1, run 3), the amine component did not participate in the reaction despite the fact that the acetylene moiety was fully consumed. In order to give a direct evidence that the reaction proceeded not via the usual Cu-catalyzed 1,3-dipolar cycloaddition reaction between organo azide and terminal alkyne but via the three component reaction, ¹H NMR measurements of the obtained polymers (run 1) were conducted, as depicted in Figure 1. First, peaks at

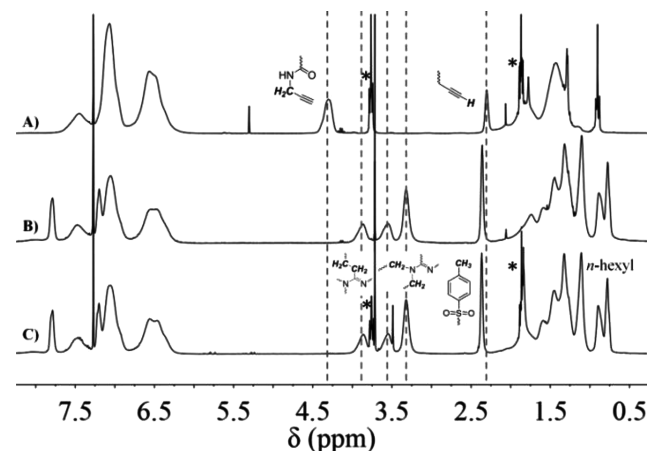


Figure 1. ¹H NMR spectra in CDCl₃ of $P(S_{0.8}\text{-}co\text{-}C\equiv CH_{0.2})$ (A), the obtained polymer by the CuMCR among $P(S_{0.8}\text{-}co\text{-}C\equiv CH_{0.2})$, Ts-N₃, and dihexylamine (B) and $P(S_{0.8}\text{-}co\text{-}St\text{-}NSA_{0.2})$ (C). The symbol (*) refers to peaks owing to residual THF.

2.28 ppm owing to the alkyne disappeared and peaks at 2.35 ppm owing to the methyl group of 4-toluenesulfonyl group appeared (Figure 1B), showing that the alkyne group of the starting polymer was completely consumed and the 4-toluenesulfonyl group was attached via the CuMCR. Furthermore, peaks owing to hexyl groups clearly appeared in the region from 0.7 to 1.2 ppm (Figure 1B), showing that not

only the azide component, namely, Ts-N₃, but also dihexylamine participated in the three-component reaction. To eliminate a possibility of concurrent side reactions, a detailed analysis using model compounds was further carried out. To provide a precise insight into the reaction processes, the CuMCR with low molecular weight model compounds was precisely monitored by using ¹H NMR measurements. The CuMCR among the monomeric structure of the polymer, namely, *N*-(prop-2-ynyl)-4-vinylbenzamide (St-C≡CH), Ts-N₃, and dihexylamine was conducted in the presence of Cu(I) as a catalyst in THF/toluene mixture solvent system to afford a styrenic *N*-sulfonylamidines derivative (St-NSA). As shown in Figure 1B, methylene protons of St-C≡CH adjacent to the acetylene moiety at 4.25 ppm clearly shifted to upfield in the range from 3.2 to 3.9 ppm along with a splitting of the peak because of the generation of a neighboring methylene group.

Furthermore, methylene protons of dihexylamine adjacent to the nitrogen atom appeared in the region from 3.2 to 3.5 ppm (Figure 2B), as proven by ¹H–¹H COSY measurement (Figure

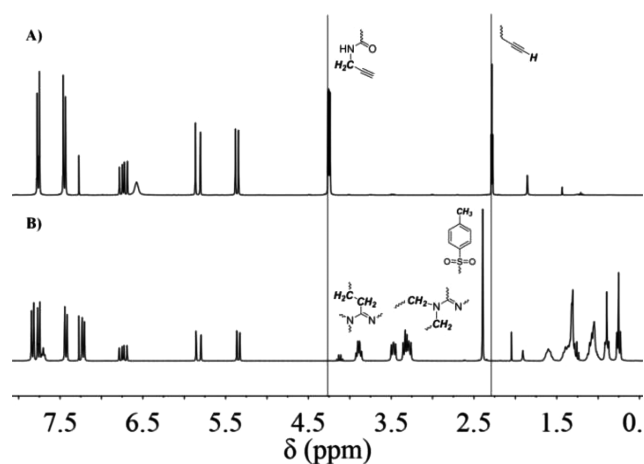


Figure 2. ¹H NMR spectra in CDCl₃ of St-C≡CH before (A) and after (B) the CuMCR with Ts-N₃ and dihexylamine.

S2, see Supporting Information). To give a direct structural proof for the CuMCR based post-polymerization modification reaction, a model polymer was synthesized by a copolymerization of styrene with St-NSA. The ¹H NMR spectrum of the obtained P(S_{0.8-co}-St-NSA_{0.2}) is in agreement with that of the obtained polymer by the CuMCR among P(S_{0.8-co}-C≡CH_{0.2}), Ts-N₃, and dihexylamine, showing that the post-polymerization modification reaction based on CuMCR proceeded without any detectable side reactions. Thus, the facile utilization of CuMCR as a successful post-polymerization modification process was demonstrated by using model reactions and compounds.

To show a direct advantage of CuMCR-based postpolymerization modification reactions, the scope of the employed amine functionality was examined (Table 1). As shown in the Table 1, both aliphatic and aromatic amines were successfully introduced as a facile amine component in the CuMCR to afford corresponding polymers. With taking advantage of the wide window of amine functionality, direct installations of functional amines onto polymer structures via CuMCR were conducted. For this, 1-aza-15-crown-5-ether and MeO-Leu-Pro-NH were selected as multifunctional amines. As shown in Table 1, installation of functional amines was successfully carried out via the CuMCR-based post-polymerization modification process. It is worth noting here that the preparation of

crown-ether derivatives requires a tedious purification step and is sometimes practically impossible because of their strong amphiphilic nature. Thus, this post-polymerization modification route successfully demonstrated the advantage of CuMCR in a post-modification procedure, which would provide a new synthetic possibility for clickable polymers.

■ ASSOCIATED CONTENT

📄 Supporting Information

Detailed experimental procedures, SEC traces, and the ¹H NMR spectra of obtained polymers are listed. 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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