Ionic Polymer Supported Copper(I): A Reusable Catalyst for Huisgen's 1,3-Dipolar Cycloaddition

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Abstract: A series of CuI-immobilized polymeric supports having quaternary ammonium salts were prepared as recyclable heterogeneous catalysts with evaluation of their ability in Cu(I)-catalyzed Huisgen's 1,3-dipolar cycloaddition of azides and terminal alkynes, a 'click reaction'. An ionic polymer possessing an acetate anion was suitable as the solid support for immobilization of CuI and CuI-immobilized compound showed negligible leaching levels of CuI, providing 1,4-disubstituted 1,2,3-triazoles in good yields, regioselectively. The CuI-immobilized compound was also reused not only up to ten times without any loss of yield or catalytic activity, but also for twelve different click reactions.

Key words: Huisgen 1,3-dipolar cycloaddition, click reaction, CuI-immobilized ionic polymer, recyclable solid catalyst

Being one of the most versatile metals for catalysis, copper has been widely used in a variety of organic reactions for several decades,¹ especially the Cu(I)-catalyzed Huisgen's 1,3-dipolar cycloaddition reaction, referred to as a 'click reaction'. This click reaction has become a very useful carbon-heteroatom bond-forming reaction because of i) mild reaction conditions (at room temperature and neutral pH); ii) reaction specificity (reacts only between azide and terminal alkyne); and iii) water tolerance (biomolecular-friendly reaction).² Presently, click reactions are of growing interest in most applied organic chemistry such as small molecule synthesis,³ bioconjugation,⁴ polymerization,⁵ radiolabeling reaction,⁶ and so forth. However, copper metal and some additives such as sodium ascorbate, amine bases, and ligands remain in the mixture after the reaction and must be removed, particularly for an automation system of high-throughput synthesis and biomolecular modifications. Several efforts have been made for an efficient removal and reuse of Cu(I) catalysts by utilizing ionic liquids⁷ or solid supports. Copper iodide was immobilized onto dimethylaminomethyl polystyrene based support by Girard et al., who reported reuse of this heterogeneous CuI over four cycles without a decrease in yield.⁸ However, Smith et al. reported on a modular-flow reactor system composed of three continuous columns containing different polymer resins,⁹ whereby the second column was used to remove CuI slightly leached from the first column filled with CuI-immobilized Amberlyst A-21, indicating that the polymer-bound CuI is somewhat released into the solution during the reaction.

Alternative polymeric supports, ionic polymers having quaternary ammonium salts, are also available as a useful and effective class of solid support for the immobilization of metal catalysts. Since Yb(OTf)₃-immobilized ionic polymer showed good catalytic activity over ten reuses without any loss of yield,¹⁰ it has been extended to other metal catalysts.¹¹

Herein we report the preparation of a series of CuI-immobilized ionic polymers, and their catalytic activities and reusability, for the benefit of Huisgen's 1,3-dipolar cycloaddition reaction, and for the sake of high-throughput synthesis of 1,4-disubstituted 1,2,3-triazoles.

To make a series of ionic polymers having quaternary ammonium salts, high chloromethyl-loaded (2.44 mmol/g) Merrifield resins were prepared by suspension radical polymerization of styrene, vinylbenzyl chloride, and 2% divinylbenzene (DVB), followed by quaternization with



Scheme 1 Preparation of ionic polymers 1a-e

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Table 1 Catalytic Activity of CuI Resins in the Click Reaction^a



^a All reactions were carried out on a 0.20 mmol scale of azide **3** and 1.2 equiv of alkyne **4** using 13 mol% of Cu(I)-catalysts (**2a–e**, 100 mg) in DMF–H₂O (4:1, 1 mL).

^b Determined by HPLC.

excess triethylamine at 60 °C overnight. Consecutively, the corresponding chloride ion (counteranion of the quaternary ammonium salt) was exchanged with three different anions by simple ion-exchange process to afford tetrafluoroborate **1b**, mesylate **1c**, and acetate resins **1d**, respectively. In addition, we purchased commercially available ion-exchange resin, DOWEX[®] 1 × 2-200, a 2% DVB cross-linked polystyrene (PS)-based trimethylben-zylammonium chloride resin (**1e** in Scheme 1). This moisturized, swollen resin was washed with acetone to remove water inside resin and dried under vacuum before use.

These prepared ionic polymers 1a-e were suspended in DMF–MeCN (1:1) with CuI (5 wt% compared to resin), and shaken well for 3 hours (Scheme 2). In all cases, most CuI was immobilized onto the ionic polymers and verified by weight increase of the corresponding resins. Anions of ionic polymers are thought to coordinate with CuI as shown in Scheme 2,^{11b} forming sufficient immobilization of CuI into resins. The color of copper-containing resins varies depending on counteranions; dark green for chloride, light yellow-green for BF₄, dark brown for OMs, and light blue for OAc.

All CuI-immobilized resins except DOWEX[®] chloride **2e** exhibited overall good swelling properties in polar solvents such as DMF, DMSO, MeCN, acetone, and *t*-BuOH for sufficient access to inside resin. Consequently, we obtained 0.25 mmol/g of CuI loaded ionic polymers **2a–e**. An immobilization of CuSO₄ onto DOWEX[®] chloride resins was also attempted using the same procedure with aqueous CuSO₄ solution. However, a very small amount of CuSO₄ was found immobilized onto the polymer.



Scheme 2 Immobilization of CuI onto ionic polymers

To investigate the catalytic ability of these CuI-immobilized ionic polymers **2a–e**, the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of 4-methoxybenzyl azide (**3**) and phenylacetylene (**4**) was performed using 13 mol% of Cu(I)-catalysts in DMF–H₂O (4:1) at room temperature for 3 hours. All catalyst resins were easily separated by simple filtration and washed with THF. The resultant organic filtrates were analyzed by HPLC to determine percent of conversion. In all cases, the 1,4-disubstituted product was regioselectively obtained with no 1,5-disubstituted byproduct. As a result, we observed that the order of catalytic activities of the five solid CuI catalysts was **2c** > **2b** > **2d** > **2a** > **2e**, translating to, OMs >BF₄ > OAc > Cl > DOWEX[®]-Cl (Table 1).

However, two resins having BF_4 (2b) and OMs (2c) showed slight CuI leaching compared to Cl (2a and 2e) and OAc resins (2d). It could be roughly and easily determined by comparing CuI spots on TLC (CuI is visualized on UV lamp at 254 nm and PMA staining). Generally, catalyst leaching is a very critical factor to validate solid catalyst. The CuI leaching indicates that most of the reaction may occur homogeneously, and it may contaminate the product. In contrast to BF_4 (2b) and OMs (2c), there was very small amount of CuI leaching with the Cl (2a and 2e) and OAc (2d) resins, where the OAc resin (2d) provided better conversion. CuI-DOWEX®-Cl gave the worst result with 58% conversion, likely due to less swelling properties than other polystyrene resins made in our lab. From this experiment, we chose the CuI-immobilized OAc resin as a recyclable solid catalyst for further study.

To optimize reaction conditions, several solvents containing 20% water such as MeCN, acetone, DMF, DMSO, and *t*-BuOH were tested in the same standard reaction in the presence of 5 mol% of catalyst **2d** for 12 hours at room temperature (entries 1–5 in Table 2). Thin-layer chromatography was used to monitor the reactions and conversion (%) was determined by HPLC after 12 hours. This experiment revealed that *t*-BuOH–H₂O (4:1) is the best solvent due to the lack of any detectable CuI leaching, whereas tiny leaching was observed in DMF–H₂O (4:1) and DMSO–H₂O (4:1). Better solubility of CuI in MeCN, DMF, and DMSO perhaps makes it easier for CuI to be re-

Table 2	Optimization	of Heterogeneous	Click Reaction	Using 2d
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мео	^N ³ + ≡ −√ −	2d solvent	N=N		
3	4	MeO	5		
Entry	Solvent (4:1)	2d (mol%)	Temp (°C)	Time (h)	Conversion (%) ^b
1	DMF-H ₂ O	5	r.t.	12.0	100
2	MeCN-H ₂ O	5	r.t.	12.0	63
3	DMSO-H ₂ O	5	r.t.	12.0	100
4	acetone-H ₂ O	5	r.t.	12.0	100
5	<i>t</i> -BuOH–H ₂ O	5	r.t.	12.0	100
6	<i>t</i> -BuOH–H ₂ O	5	80	1.0	100
7	<i>t</i> -BuOH–H ₂ O	5	60	1.5	100
8	<i>t</i> -BuOH–H ₂ O	2.5	60	2.0	100
9	<i>t</i> -BuOH–H ₂ O	1.25	60	3.0	100
10	<i>t</i> -BuOH–H ₂ O	0.5	60	5.0	37

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^a All reactions were carried out on a 0.20 mmol scale of azide 3 and 1.2 equiv of alkyne 4.

^b Determined by HPLC.

leased from the resin, whereas CuI leaching in *t*-BuOH or acetone is not allowed due to poor solubility of CuI. However, acetone– H_2O (4:1) gave a mixture of products, including small amounts of undesired 1,5-disubstituted triazole. In addition, for quantitative detection of copper leaching, each filtrate of entries 4 and 5 was analyzed by ICP-AES after dilution with 0.1 M HCl solution. Only negligible amount less than detection limit was observed.

We also repeated the reaction in *t*-BuOH–H₂O (4:1) at two elevated temperatures 60 °C and 80 °C to obtain further information on the effect of reaction temperature and catalyst amount. Copper-free Huisgen 1,3-dipolar cycloaddition has been usually performed at reflux temperature or 100 °C for longer than overnight. However, the reaction proceeded much faster and finished within 1.0 hour and 1.5 hours at 80 °C and 60 °C, respectively, when using 5 mol% of catalyst (entries 6 and 7 in Table 2). Less amount of catalyst also performed sufficiently, allowing the reaction to be completed within 3.0 hours at 60 °C, except the last entry in Table 2, using 0.5 mol%, which showed 37% conversion in 5.0 hours.

Subsequently, resin **2d** was repeatedly used at two different temperatures up to ten times to ensure reliable reusability.

After each reaction, resin 2d was recovered for the next run by filtration, washing with acetone and THF, and drying under vacuum. As shown in Scheme 3, every run was performed under the same reaction conditions, and showed 100% conversion on average. Usually, solid catalyst may lose its inherent activity at high temperature due to physical damage or change to an inactive metal species, such as oxidation of Cu(I) to Cu(II). Interestingly, reiteratively used resin 2d, after the tenth run at 60 °C, maintained initial catalytic activity. It should be also noted that after three months under air contact, 2d showed the same catalytic performance, indicating significant air-stable.

The relative amount of Cu inside resin **2d** before and after the 10th run was analyzed using XRF (X-ray fluores-



Scheme 3 Reusability of 2d in the click reaction. Reaction conditions were the same as entries 5 and 7 in Table 2, respectively.

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Table 3	Various	Heterogeneous	Click R	eactions ^a
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2d (5 mol%)

R ¹ N ₃ +	$= R^{2} \xrightarrow{\text{2d} (5 \text{ mol}\%)}_{t-\text{BuOH}-\text{H}_{2}\text{O} (4:1)} \xrightarrow{\text{R}^{1}-\text{N}}_{\text{N}=\text{N}} R^{2}$			
Entry	R ¹ -N ₃	$\equiv -R_2$	Time (h)	Yield (%) ^b
1	N ₃		2.5	99
2	N ₃		3.0	99
3	N ₃		24.0	99
4	MeO N ₃		4.0	99
5	MeO N ₃		3.0	99
6	MeO N ₃		24.0	85
7	HO O N3		24.0	95
8	HO O N3		5.0	85
9	HO O N3		24.0	82
10	AcO AcO AcO AcO		24.0	94
11	AcO AcO AcO AcO AcO		24.0	91
12	AcO AcO AcO AcO		24.0	36

^a All reactions were carried out on a 1.00 mmol scale of azide using 1.1 equiv of alkyne and 5 mol% of resin 2d in t-BuOH-H₂O (4:1, 3 mL). ^b Isolated yield.

cence) spectroscopy to determine the leaching degree after the 10th run. Figure 1 illustrates that most of the Cu catalyst remained inside the resin 2d, showing constant catalytic activity. In addition, we obtained a TEM image (see Supporting Information for picture) of 2d after the 10th run, revealing an absence of any visual aggregation or nanoparticle formation of the Cu, indicating that the inherent catalyst capabilities of 2d are not changed during reiterate experiments.

After validation of 2d as a recyclable catalyst, we subsequently investigated its general applicability in heterogeneous click reactions with a cross combination of four



Figure 1 An XRF spectrum (Cu) before (blue line) and after (red line) use of 2d

azido compounds and three alkyne compounds (Table 3). All reactions using 5 mol% of **2d** at room temperature successfully yielded the corresponding regioselective product with a high yield after various periods of time (2.5–24 hours). After each reaction was complete, the polymer catalyst was collected by filtration with a plastic syringe equipped with polyethylene frit and washed with acetone and THF three times. Crude products were purified by column chromatography. We also found that the rate of reactions trend to be slow in the case of polar substances. For instance, the reaction of glucosyl azide and *N*-propargyl phthalimide was not complete within 24 hours and only 36% of triazole product was yielded (entry 12 in Table 3).

It is noteworthy that all twelve reactions were performed using the same polymer catalyst **2d** which was recovered and reused from entry 1 to entry 12. To check whether the used polymer catalyst **2d** possessed the same catalytic activity as in the first reaction, it was finally reused in the reaction of benzyl azide and phenylacetylene (entry 1 in Table 3) again after completion of all reactions. Gratifyingly, the same result was obtained.

In conclusion, we developed a novel ionic polymer supported Cu(I) catalyst possessing an OAc anion as a recyclable solid catalyst for click reactions. Robust immobilization of CuI and constantly maintained catalytic activity of **2d** was certified through ICP-AES, XRF spectroscopic analysis, and reusability studies. Polymer catalyst **2d** was reused uneventfully without any bases in twelve click reactions involving four azido and three alkyne compounds in cross manner. Copper iodide immobilized **2d** is also remarkably stable under atmosphere. We expect that it will be applicable to high-throughput syntheses of triazole as well as other Cu(I)-catalyzed reactions. **Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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