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Heterogeneous Copper Catalyst for the Cycloaddition of Azides and Alkynes without Additives under Ambient Conditions

In Soo Park,[†] Min Serk Kwon,[†] Youngkwon Kim,[‡] Jae Sung Lee,[‡] and Jaiwook Park*,[†]

Department of Chemistry and Department of Chemical Engineering,
Pohang University of Science and Technology (POSTECH), San 31 Hyojadong,
Pohang, Kyeongbuk 790-784, Republic of Korea

pjw@postech.ac.kr

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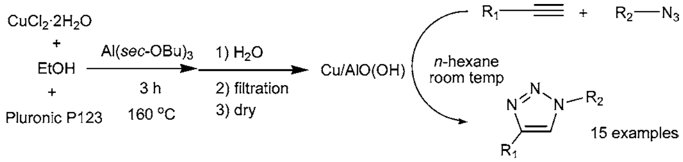
ABSTRACT



A new copper catalyst was developed by immobilizing copper nanoparticles in aluminum oxyhydoxide fiber. The catalyst showed high catalytic activity for the (3 + 2) Huisgen cycloaddition of nonactivated alkynes as well as activated ones with various azides at room temperature. The catalyst was recycled five times without significant loss of activity.

The Huisgen cycloaddition using azides and alkynes is an important method for the synthesis of 1,2,3-triazoles.[1] Its 100% atom economy and simple purification have led to various applications for phamaceuticals, agrochemicals, polymers, biochemicals, and functional materials.[2] In particular, 1,4-disubstituted triazoles have been used as metal-binding compounds, ligand linkers, and triazole-based monophosphine ligands.[3] However, the major limitations of the original reaction are the requirement of high reaction temperatures and low regioselectivity.

Meldal and co-workers have developed the copper(I)-catalyzed Huisgen cycloaddition of terminal alkynes to azides on solid phase in organic solvent.[4a] Sharpless and co-workers have overcome the limitations by employing copper sulfate and sodium ascorbate.[4b] Fokin and co-workers have found $(\eta^5\text{-}C_5Me_5)RuCl(PPh_3)_2$ to be an efficient catalyst to produce 1,5-disubstituted triazoles regioselectively.[5] In addition, many new catalyst systems have been reported in recent years,[6] including *N*-heterocyclic copper carbene complexes[7] and copper nanoclusters.[8] To improve recovery and reuse, copper

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[†] Department of Chemistry.

[‡] Department of Chemical Engineering.

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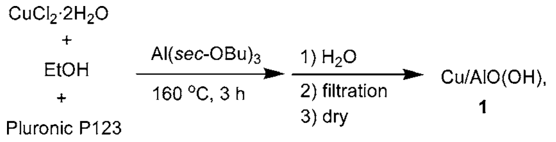
species have been immobilized onto various supports such as activated charcoal,[9] amine-functionalized polymers,[10] and zeolites.[11] However, the immobilized catalysts frequently suffer from low activity and low product yield and require additives[9] and high reaction temperatures.[6,9,11]

We report herein a recyclable copper catalyst (Cu/AlO(OH), (**1**)) which is composed of copper nanoparticles in aluminum oxyhydroxide nanofiber. The catalyst **1** is highly active at room temperature for the Huisgen (3 + 2) cycloaddition of a wide range of azides and nonactivated alkynes without requiring additives. The catalyst **1** can be easily synthesized from readily available reagents by a one-pot procedure similar to those for our Pd,[12b] Ru,[12e] Rh,[12f] and Ir catalysts reported previously (Scheme 1).[12]

Scheme 1. Preparation of Catalyst



Copper nanoparticles were generated by heating a mixture of cupric chloride dihydrate, ethanol, aluminum tri-*sec*-butoxide, and pluronic P123 at 160 °C.[13] After 3 h, water was added for gelation. The resulting bluish powder was filtered, washed with acetone, and dried at 120 °C for 2 h to give a green powder. The green powder was characterized by transmission electron microscopy (TEM), X-ray photoelectron spectroscopy (XPS), inductively coupled plasma (ICP), and nitrogen isotherm experiment.[14] The fibrous morphology, which is a typical feature of aluminum oxyhydroxide, was observed in the low-resolution TEM image (Figure 1).

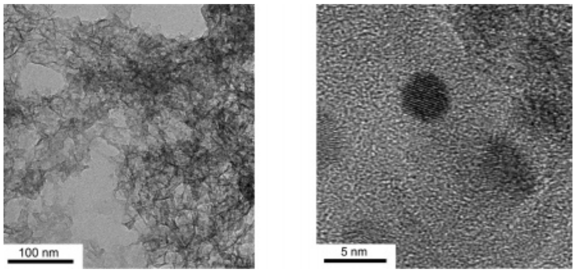


Figure 1. TEM images of **1**: (a) low-resolution (100 nm bar scale); (b) high resolution (5 nm bar scale).

As expected on the basis of previous reports,[15] the XPS analysis revealed that the surface of the Cu nanoparticles is covered with Cu_2O and CuO.[14,15] The surface area, the pore volume, and the pore size of **1** were estimated to be 360 m^2 g^{-1}, 0.65 cm^3 g^{-1}, and 3.2 nm, respectively, by BET nitrogen adsorption analysis. With the ICP data, the copper content of **1** was calculated to be 4.0 wt %; the copper nanoparticles entrapped in the aluminum oxyhydroxide matrix corresponded to 98% of the employed cupric chloride.

We compared the activities of **1** and commercial Cu catalysts in the cycloaddition of phenylacetylene and *n*-octyl azide at room temperature (Table 1). The reaction using **1** (3 mol % of Cu) gave the cyclized product in 95% yield (entry 1). Heating or using triethylamine as an additive increased the rate significantly (entries 2 and 3). Cuprous oxide showed very low activity (entry 4); even with 100 mol % of Cu the yield was only 15% (entry 5). Pure cupric oxide and alumina-supported cupric oxide were inactive (entries 6 and 7). The precursor of **1**, cupric chloride dihydrate, was also inactive (entry 8).

Table 1. Activities of **1** and Commercial Cu Catalysts[a]

entry	catalyst (mol %)	T (°C)	time (h)	yield[b] (%)
1	**1** (3)	25	12	95
2	**1** (5)	60	3	95
3	**1** (5) + Et_3N[c]	60	0.5	94
4	Cu_2O (3)	25	12	trace
5	Cu_2O (100)	25	12	15
6	CuO (100)	25	12	0
7	CuO/Al_2O_3 (6)	25	12	0
8	$CuCl_2 \cdot 2H_2O$ (100)	25	12	0

[a] Phenylacetylene (1.0 mmol) and *n*-octylazide (1.1 mmol) were reacted in *n*-hexane (2.0 mL) for 12 h. [b] Isolated yield of 1-octyl-4-phenyl-1*H*-1,2,3-triazole. [c] Triethylamine (1.0 equiv) was used as an additive.

The scope of the (3 + 2) cycloaddition using **1** was investigated with various alkynes and azides at room temperature (Table 2). *n*-Octyl azide (**2**), 4-azidoanisole (**3**), and benzyl azide (**4**) were employed as aliphatic and aromatic azides and were synthesized by following the reported literature procedures.[16] Various terminal alkynes were readily reacted with the azides to give the corresponding 1,2,3-

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(13) Without pluronic P123, copper nanoparticles were aggregated before gelation.

(14) See the Supporting Information.

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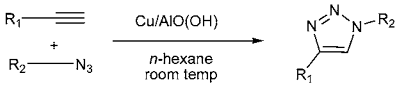
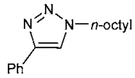
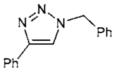
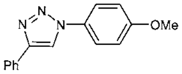
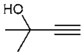
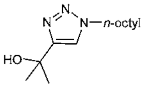
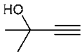
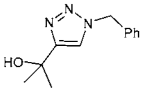
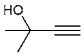
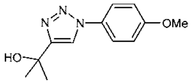
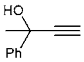
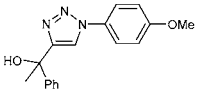
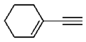
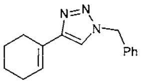
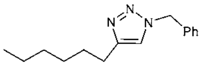
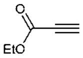
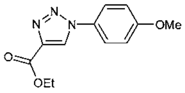
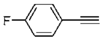
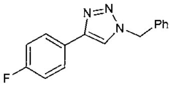
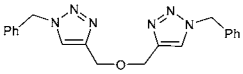
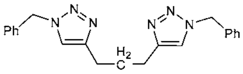
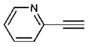
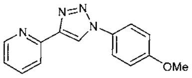
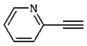
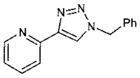
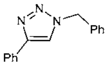
Table 2. Cycloaddition of Various Azides and Alkynes[a]



entry	substrate	azide[b]	time (h)	product (% yield)[c]
1	Ph—≡	**2**	12	 (95)
2	Ph—≡	**4**	6	 (94)
3	Ph—≡	**3**	12	 (97)
4		**2**	20	 (97)
5		**4**	6	 (92)
6		**3**	12	 (97)
7		**3**	12	 (97)
8[d]		**4**	24	 (77)
9[d]	n-Hexyl—≡	**4**	15	 (82)
10		**3**	1	 (97)
11		**4**	3	 (97)
12	propargyl ether	**4**	15	 (85)
13	1,6-heptadiyne	**4**	15	 (85)
14		**3**	3	 (98)
15		**4**	3	 (97)
16	Ph—≡	**4**	8	 (94)[e]

[a] Alkyne (1.0 mmol) and azide (1.1 mmol) were reacted in n-hexane (2.0 mL) at 25 °C in the presence of **1** (3.0 mol %). [b] The azides are n-octylazide (**2**), benzyl azide (**3**), and 4-azidoanisole (**4**). [c] Isolation yield. [d] 6.0 mol % of **1** was used. [e] Benzyl azide (22 mmol) was reacted with 20 mmol of phenylacetylene.

triazoles in over 90% yield in most of the tested reactions. Functional groups such as hydroxy, ethoxycarbonyl, pyridyl group, carbon–carbon double bond, and ether functionality are compatible with the cyclization. The reactions with **4** were faster than those with other azides (entries 2 and 5). It is noticeable that the reaction of 2-methyl-3-butyn-2-ol and **4** was completed within 6 h at room temperature (entry 5), compared to that using Cu/C (10 mol % of Cu), which provided the cyclized product in 65% after 48 h at 23 °C.[9] The reaction with alkynes containing electron-withdrawing substituents such as ethyl propiolate and 4-fluorophenylacetylene were distinctively fast (entries 10 and 11). The reactions with aliphatic alkynes such as 1-octyne, 1-ethynylcyclohex-1-ene, propargyl ether, and 1,6-hexadiyne were relatively sluggish (entries 8, 9, and 13). The cyclization of the dialkynes provided bis(1,2,3-triazole)s, which have been used as metal-binding ligands (entries 12 and 13).[3] The presence of a pyridyl group appeared to enhance the reaction rate; the reactions with 4-azidoanisole and benzyl azide were completed in 3 h (entries 14 and 15).[9,10] A large-scale reaction was tested with phenylacetylene (20 mmol) and benzyl azide (22 mmol); the reaction was completed in 8 h, and the corresponding 1,2,3-triazole was isolated in 94% yield (entry 16).

The recyclability of **1** was tested in the cycloaddition of phenylacetylene and n-octyl azide (Table 3). The catalyst was recovered simply by filtration and reused after washing with ethyl acetate and drying in the air. Although a slight decrease in activity was observed in the reuse, about 95% of the original activity was shown even in the fifth use. Based on ICP analysis, there was no significant leaching of copper species from our catalyst during the recycling test.[17] The observed high activity and recyclability of **1** would result from the fibrous aluminum oxyhydroxide matrix that provides a highly porous structure and stabilizes metal nanoparticles.

Table 3. Recycling Experiment of (3 + 2) Cycloaddition with **1**[a]

cycle	1	2	3	4	5
% yield[b]	95	95	93	91	90

[a] Phenylacetylene (1.0 mmol) and n-octyl azide (1.1 mmol) were reacted in n-hexane (2.0 mL) at 25 °C with **1** (3.0 mol %) for 12 h. [b] Isolation yield.

In conclusion, we have developed a simple and reproducible synthetic method for a recyclable copper catalyst that shows the highest activity among known heterogeneous catalysts in the azide–alkyne cycloaddition without additives. The scope of the cycloaddition using our catalyst is quite broad; various terminal alkynes react readily with aliphatic azides as well as aromatic ones at room temperature.

Acknowledgment. We are grateful for financial support from the Korea Research Foundation (KRF-2006-005-

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[17] The copper content of the catalyst recovered after the fifth use was 3.84 wt %, which is 96% of the original catalyst.

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Supporting Information Available: The synthetic procedure and characterization data for **1** and the triazoles in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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