

A Copper(I) Isonitrile Complex as a Heterogeneous Catalyst for Azide–Alkyne Cycloaddition in Water

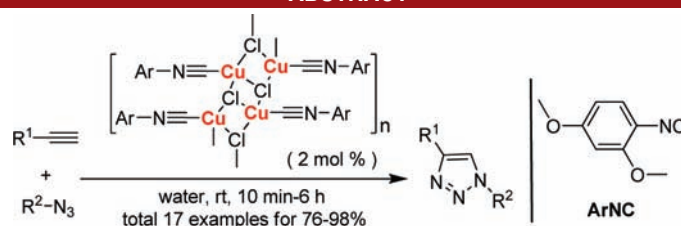
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ABSTRACT



A structurally well-defined copper(I) isonitrile complex is shown to be an efficient, heterogeneous catalyst for the Huisgen azide–alkyne 1,3-dipolar cycloaddition under mild conditions in water. Notably, this catalyst can also be utilized in a three-component reaction of halides, sodium azide and alkynes to form 1,4-disubstituted 1,2,3-triazoles in high yields. Furthermore, it can be readily recovered by precipitation and filtration and recycled for at least five runs without significant loss of activity.

Click chemistry is a chemical philosophy introduced by Sharpless in 2001, emphasizing reactions that generate substances quickly and reliably by joining small units together.¹ The copper(I)-catalyzed Huisgen [3 + 2] dipolar cycloaddition (CuAAC)² between alkynes and azides has arguably become the most popular ligation reaction that has been widely applied in many areas such as polymer and drug discovery, advanced material science, etc.³

Much attention has been paid to the development of copper(I) catalytic systems for CuAAC reactions. Most of the reported copper(I) catalytic species were prepared

in situ by reduction of Cu(II) salts,^{2b} oxidation of Cu(0) metal,⁴ or Cu(II)/Cu(0) comproportionation.⁵ Copper(I) salts are less used because of their general thermodynamic instability,^{2c,6} with copper(I) iodide being a notable exception. The latter, however, requires the employment of amines as additives.⁷ In recent studies, the CuAAC has been proven to be accelerated by Cu(I) species supported by nitrogen,⁸ sulfur,⁹ NHC,¹⁰ and polydentate ligands,¹¹ since those serve both to protect the copper(I) center from oxidation or disproportionation and to enhance its catalytic activity. However, such supported copper(I) catalysts are not always easily prepared. Moreover, reusability of copper catalysts for the CuAAC is scarcely studied¹² because of the generally homogeneous nature of these catalysts,

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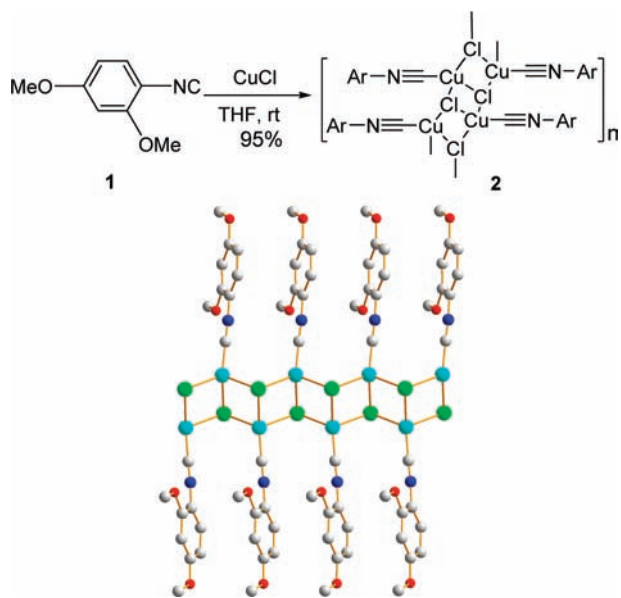
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Scheme 1. Synthesis and X-ray Structure of **2^a**



^a Color code: Cu, cyan; Cl, green; O, red; N, blue; C, grey.

which renders their recovery and recycling difficult. Considering the virtues of ligands and heterogeneous catalysts, we set out to develop a practical, heterogeneous, ligand-supported copper(I) catalyst without the need of immobilization on a polymeric or an inorganic support.

Isonitriles are recognized as valuable synthons in organic synthesis¹³ but have been less frequently applied as ligands for metal catalysts, although they are known to coordinate to a broad variety of transition metal complexes.¹⁴ Owing to their electronic properties, being strong σ -donor ligands comparable to *N*-heterocyclic carbenes, the exploration of metal isonitrile complexes appears to be promising. We recently reported chiral palladium- and iron-bis(isonitrile) complexes as efficient catalyst for

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Table 1. Solvent and Catalyst Optimization Studies^a

entry	catalyst	solvent	yield (%) ^b
1	2	THF	85
2 ^c	2	H ₂ O	98 ^c
3	2	H ₂ O/ <i>t</i> -BuOH (1:1)	94
4	2	<i>i</i> -PrOH	34
5	2	MeOH	42
6	2	DMF	61
7	2	acetone	59
8	2	DMSO	48
9	2	neat	78
10	CuCl	H ₂ O	32
11	CuI	H ₂ O	4
12	CuBr	H ₂ O	15
13	CuCN	H ₂ O	22
14 ^d	CuCl	H ₂ O	50
15 ^{e,f}	[(CuOAc) ₂] _n	H ₂ O	95

^a Reagents and reaction conditions: **3a** (1.05 mmol), **4a** (1.0 mmol), and catalyst (5 mol %) in the given solvent was stirred at room temperature for 1 h unless otherwise stated. ^b Isolated yields as an average of at least two independent experiments. ^c Reaction time (10 min). ^d 50 mol % CuCl, 24 h. ^e Taken from ref 19. ^f Reaction time (11 min).

aerobic Wacker oxidations¹⁵ and asymmetric transfer hydrogenations.¹⁶ As part of our continued interest in copper-catalyzed transformations and click chemistry,¹⁷ we describe here a readily prepared and structurally well-defined copper(I) isonitrile complex **2**, which exhibits excellent activity to CuAAC reaction under mild reaction conditions in water. Notably, **2** is heterogeneously dispersed in most solvents and can therefore be readily recovered and recycled without significant loss of activity.

The isonitrile ligand **1** was prepared following literature procedures.¹⁸ Upon treatment of **1** with CuCl in THF, the off-white complex **2** was obtained in 95% yield, being stable in air or water for several months. Furthermore, **2** is insoluble in water and common organic solvents such as THF, ethanol, acetone, and ethyl acetate but soluble in acetonitrile and DMF. Complex **2** was characterized by NMR spectroscopy as well as X-ray crystallographic analysis. The latter revealed (Scheme 1) that each Cu(I) center is coordinated to an isonitrile ligand and possesses three bridging chloride atoms that coordinate to another Cu(I) center of the next entity. Hence the [CuLCl] units are

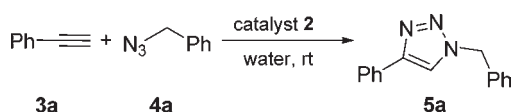
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linked into an extended one-dimensional chain polymer, contrasting an earlier report on copper(CNAr^{Mes})₂ (Mes = 2,4,6-Me₃C₆H₂)¹⁹ for which a bridging dichloro dimer rather than a one-dimensional chain structure was found.

Complex **2** was investigated in the CuAAC of benzyl azide (**4a**) and phenylacetylene (**3a**). A first screening of different solvents revealed exceptional activity of **2** in water, giving rise to the cycloadduct **5a** in virtually quantitative yield within a reaction time of only 10 min. In contrast, other copper(I) salts (CuI, CuCl, CuBr, CuCN) gave far inferior results under the same conditions (Table 1, entries 10–14) with the exception of [(CuOAc)₂]_n (entry 15) that was recently reported to be a highly efficient catalyst for this reaction as well.²⁰

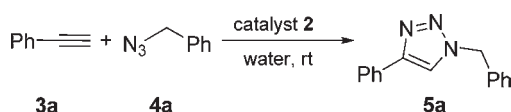
Table 2. CuAAC with Different Loading of Catalyst **2**^a



entry	2 (mol %)	time (min)	yield (%) ^b
1	5	10	98
2	0.5	30	91
3	2	5	94

^a Reagents and reaction conditions: **3a** (1.05 mmol), **4a** (1.0 mmol), and catalyst **2** (0.5–5 mol %), water. ^b Isolated yields after complete conversion of the starting materials as an average of at least two independent experiments.

Table 3. Recyclability Experiments^a



entry	run	time (min)	yield (%) ^b	recovery of catalyst based on the initial amount (%)
1	1	10	98	92
2	2	10	96	83
3	3	10	96	72
4	4	10	97	62
5	5	10	93	50

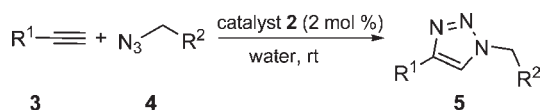
^a Reagents and reaction conditions: **3a** (15.75 mmol), **4a** (15.0 mmol), and catalyst **2** (78 mg, 0.30 mmol, 2 mol %). ^b Isolated yields.

Having identified water as the best solvent for the reaction, we next investigated catalyst loading and recyclability for the title reaction (Table 2). Gratifyingly, upon lowering the catalyst concentration to 0.5 mol % the reaction still proceeded within 30 min in 91% yield (entry 2). A catalyst

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Table 4. Azide–Alkyne Cycloaddition Catalyzed with **2**^a



entry	triazole	5	time (min)	yield (%) ^b
1		5a	5	94
2		5b	10	91
3		5c	60	95
4		5d	50	92
5		5e	30	89
6		5f	10	96
7		5g	45	93
8		5h	30	89
9		5i	90	98
10		5j	240	85
11		5k	45	92
12		5l	360	86
13		5m	30	93
14		5n	45	92
15		5o	180	87
16		5p	360	76
17		5q	30	85

^a Reagents and reaction conditions: **3** (1.05 mmol), **4** (1.0 mmol), and catalyst **2** (5 mg), water. ^b Isolated yields as an average of at least two independent experiments.

loading of 2 mol % appeared to be optimal with respect to yield and short reaction times (entries 3).

Starting with a catalyst loading of 2 mol %, the reaction was performed through 5 cycles on a 15 mmol scale each (Table 3). After each cycle the heterogeneous catalyst was recovered by simple filtration and reused without further purification. High yields (93–98%) were achieved at every run, and after five runs 50% of the initial amount of **2** was still recovered. We attribute the overall loss of the catalyst to transfer operations between the filter and the reaction flask.

Having optimized the reaction conditions, catalyst **2** was applied to the cycloaddition reaction of electron-rich, electron-poor, hindered, and dialkynes at room temperature in water to give the corresponding triazoles **5a–5q** in

Table 5. Azide–Alkyne Cycloaddition Catalyzed with **2**^a

entry	5	time (h)	yield (%)
1	5a	2	95
2	5b	1	93
3	5d	3	84
4	5e	5	88
5	5f	3	94
6	5g	7	91
7	5h	1	92
8	5i	8	95
9	5n	1	90
10	 5r^c 5a^d	3	91
11	5a^d	1	97

^a **3** (1.05 mmol), NaN₃ (1.05 mmol), alkyl halide **6** (1.0 mmol), and catalyst **2** (5 mg, 2 mol %). ^b Isolated yields as an average of at least two independent experiments. ^c Alkyl halide = ethyl 2-iodoethanoate. ^d Alkyl halide = benzyl chloride.

high yields (Table 4, entries 1–17). A broad variety of azides equipped with various functional moieties such as alcohol, ketone, pyridine, nitrile, and fluoride was successfully employed. A dialkyne was also found to be a suitable substrate to afford the triazole **5p** (entry 16), which suggests that catalyst **2** has potential for the synthesis of bidentate ligands.

Inspired by the recent work of Hor et al.,¹¹ we turned our attention toward the three-component (alkyl halide, sodium azide, and alkyne) azide–alkyne cycloaddition reaction (Table 5). Catalyst **2** again performed well in water to give the desired products (entries 1–11) in good to excellent isolated yields (84–97%).

In conclusion, the structurally well-defined copper(I) isonitrile complex **2** was successfully synthesized and developed as a heterogeneous catalyst for the copper-catalyzed azide–alkyne cycloaddition under mild conditions in water. This catalyst shows considerable synthetic advantages in terms of facile and sustainable reaction setup (aerobic conditions in water, no additives are necessary), wide scope, and high reactivity. The catalyst **2** is also efficient in the three-component (alkyl halide, sodium azide, and alkyne) azide–alkyne cycloaddition. Furthermore, it can be readily recovered by filtration and recycled for at least five runs without significant loss of activity.

The reason for the high activity that is conferred by the isonitrile ligands for the CuAAC is under further investigation by us. We reason, however, that these ligands are similar in their electronic properties like nucleophilic carbenes that have shown to give excellent results for the title reaction.¹⁰

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Supporting Information Available. Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.