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Copper(I) Acetate: A Structurally Simple but Highly Efficient Dinuclear Catalyst for Copper-Catalyzed Azide-Alkyne Cycloaddition

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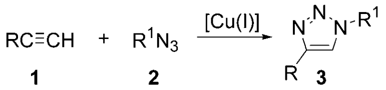
Abstract: In this article, the structurally well-defined dinuclear complex copper(I) acetate was studied in detail and was developed as a highly practical and efficient catalyst for the copper(I)-catalyzed azide-alkyne cycloaddition. The "bare" phenylethynylcopper(I) (i.e., with no exogeneous ligands) was isolated as an intermediate, which can be converted into an active catalytic species by treatment with acetic acid (*in situ* produced in the reaction) to efficiently catalyze the azide-alkyne cycloaddition under mild conditions.

Keywords: acetylides; catalysts; click chemistry; copper; cycloaddition

In 2002, the groups of Sharpless[1] and Meldal[2] discovered independently that the Huisgen 1,3-dipolar cycloaddition[3] of an alkyne (**1**) and an azide (**2**) could be catalyzed by Cu(I) species under mild conditions to regioselectively yield 1,4-disubstituted 1,2,3-triazoles (**3**) (Scheme 1). To date, this copper-catalyzed azide-alkyne cycloaddition (CuAAC) has become the most remarkable example for "click" chemistry[4,5] and has been widely applied in organic syntheses as well as in medicinal and materials research.[6]



Scheme 1. Copper-catalyzed azide-alkyne cycloaddition (CuAAc) reaction.

In the past years, great progress has been made in the development of the efficient catalytic procedures for CuAAC. The first ligand-mediated CuAAC was reported in 2004,[7] in which the ligand was hypothesized to protect the Cu(I) species from oxidation and disproportionation. Later, two mechanistic concepts were developed: (a) a kinetic investigation[8] revealed that the catalytic CuAAC had a strict second-order dependence on Cu(I); (b) two DFT studies[9] indicated that dinuclear and tetranuclear alkynyl–Cu(I) complexes could be intermediates and display both superior stability and high reactivity in CuAAC. The distances between Cu^A and Cu^B (2.54–2.88 Å) in the dinuclear Cu(I) complexes were suggested to be relevant in one of the studies (Figure 1).[9b] Although several efficient ligand-mediated procedures have been reported in the literature,[7,10] they are far from practical because complicated or large amounts of ligands were employed. In spite of the obvious importance of the concept of a "dinuclear alkynyl–Cu(I) intermediate" in the development of highly efficient catalysts for CuAAC, it was rarely applied in the design of catalysts.[11]

During a screen of Cu(I) sources for CuAAC, we found that the commercially available copper(I) ace-

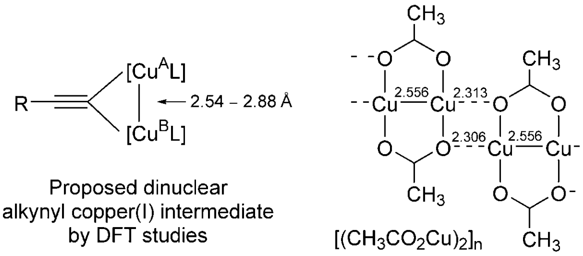
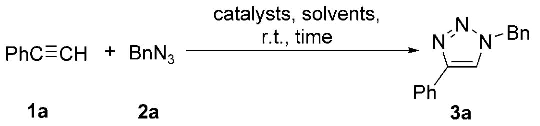


Figure 1. Dinuclear Cu(I) complexes.

tate is a structurally well-defined dinuclear polymer $[(CH_3CO_2Cu)_2]_n$.[12] It has a desirable Cu–Cu distance (2.56 Å, Figure 1), which may serve as a template for the expected "dinuclear alkynyl–Cu(I) intermediate". If the acetate anion is considered as a bidentate ligand, it should be the structurally simplest bidentate ligand to exist in CuAAC. However, the literature search showed that copper(I) acetate was rarely used as a catalyst for CuAAC.[13] In another few articles,[5a,14] the combination of $Cu(OAc)_2$/sodium ascorbate was employed as a catalytic system, in which copper(I) acetate may be generated *in situ*. However, these procedures were usually associated with using a large excess of catalyst, a high temperature or a prolonged reaction time. To our disappointment, no detailed study on the reaction conditions or scope was discussed in those articles.

To explore the catalytic properties of copper(I) acetate for CuAAC, a group of experiments catalyzed by pure $[(CH_3CO_2Cu)_2]_n$ (**Cat-1**) or a combination of $Cu(OAc)_2$/sodium ascorbate (1:5 mol/mol) (**Cat-2**) was undertaken. As shown in Table 1, when the model substrates phenylethyne (**1a**, 1.0 equiv.) and benzyl azide (**2a**, 1.05 equiv.) in *t*-BuOH/H_2O (1:1 v/v) were treated with a high loading of catalyst (10 mol% or 5 mol%), both **Cat-1** and **Cat-2** gave the excellent results (entries 1–4). When 1 mol% of these catalysts was used, the desired product **3a** was obtained in excellent yields, but with prolonged reaction times (entries 5 and 6). Interestingly, by replacement of *t*-BuOH/H_2O with cyclohexane as a solvent, the same reaction catalyzed by **Cat-1** was finished within 8 min to give **3a** in 98% yield (entry 7), while the **Cat-2**-catalyzed reaction gave **3a** in 93% yield after 110 min (entry 8).

Table 1. Effects of catalysts and solvents on CuAAC.[a]

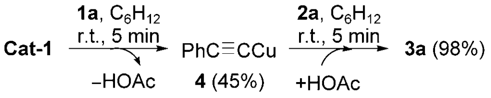


Entry	Catalyst[b] (mol%)	Solvent[c]	Time [min]	Yield of **3a** [%][e]
1	**Cat-1** (10)	*t*-BuOH/H_2O	10	97
2	**Cat-2** (10)	*t*-BuOH/H_2O	10	96
3	**Cat-1** (5)	*t*-BuOH/H_2O	36	95
4	**Cat-2** (5)	*t*-BuOH/H_2O	32	98
5	**Cat-1** (1)	*t*-BuOH/H_2O	270	93
6	**Cat-2** (1)	*t*-BuOH/H_2O	240	92
7	**Cat-1** (1)	cyclohexane	8	98
8	**Cat-2** (1)	cyclohexane	110	93
9	**Cat-1** (1)	CH_2Cl_2	16	92
10	**Cat-1** (1)	$CHCl_3$	15	93
11	**Cat-1** (1)	MeC_6H_5	10	98
12	**Cat-1** (1)	H_2O	11	95
13	**Cat-1** (1)	MeCN	60[d]	65
14	**Cat-1** (1)	EtOH	60[d]	43
15	**Cat-1** (1)	EtOAc	60[d]	20
16	**Cat-1** (1)	THF	60[d]	89

[a] The mixture of **1a** (2.0 mmol), **2a** (2.1 mmol) and Cu(I) catalyst in various solvents (1 mL) was stirred at room temperature without protection by inert gas.
[b] The molecular weight of **Cat-1** was calculated based on CH_3CO_2Cu.
[c] Ratio of *t*-BuOH/H_2O was 1:1 v/v.
[d] Incomplete conversions were observed.
[e] Yields of isolated products.

Further solvent tests proved that the non-polar solvents benefit the reaction rate very much (entries 9–11). However, the polar organic solvents significantly decreased the catalytic activity of **Cat-1** (entries 13–16). It is well known that Cu(I) can be easily oxidized to Cu(II) by air; even so, the reactions of entries 7, 9–11 were performed conveniently open to the air. It was not necessary to use inert gas protection for two reasons: (a) very short reaction time was used; (b) the reaction proceeded in a reductive system, by which Cu(II) can be reduced to Cu(I) by coupling of acetylenes. Although **Cat-1** is sensitive to humidity to decompose into Cu_2O and HOAc as an equilibrium, the reaction in H_2O was finished within 11 min to give a 95% yield (entry 12).

We interestingly observed that a bright yellow color was produced at the beginning of each reaction in entries 7–16 and it disappeared at the end of the reaction in entries 7–12. In the absence of **2a**, a bright yellow solid was isolated from the stoichiometric reaction between **Cat-1** and **1a** (Scheme 2). To our surprise, its structure was assigned as PhC≡CCu (**4**) by elemental analyses and by comparing its IR spectra with that of a commercial sample or samples obtained by reference methods.[15,16] Since **4** when treated with **2a** gave the desired product **3a** in 98% yield, it was proved to be an intermediate in the CuAAC.



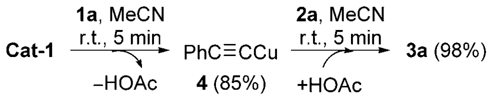
Scheme 2. PhC≡CCu (**4**) was identified as an intermediate.

We also observed that the conversion of **4** and **2a** into **3a** could be influenced by HOAc only, but not by other proton sources, such as *t*-BuOH, H_2O or *t*-BuOH/H_2O. Although the phenomenon[17] that acetate enhances the catalytic activity of Cu(I) in CuAAC has been reported (without sufficient investigation), no acetate enhancement was observed when this conversion was conducted in a solution of NaOAc in *t*-BuOH, H_2O or *t*-BuOH-H_2O. Therefore, these results clearly showed that the acidity of HOAc may play an important role in this conversion.

During the revision of this article, Heaney[11a] reported that **4** could be used as a catalytic species for CuAAC when it was heated at 100 °C with microwave irradiation in MeCN. His reaction conditions and the phenomena we described above together indicate that **4** alone is not an active catalytic species for CuAAC, but it could be converted into an active catalytic species under suitable conditions.

Further investigation showed that **4** is a very stable polymeric dinuclear complex with an extended Cu–Cu ladder structure, in which both Cu atoms adopt the same $\mu,\eta^{1,2}$-C≡C bridging mode.[18] Therefore, we hypothesized that the polymeric structure of **4** may be dissociated initially by HOAc to give monomeric dinuclear complexes. Then, AcO^- coordinates with Cu(I) of monomer to produce an active catalytic species (its structure remains unclear).

Since the coordination ability of MeCN with Cu(I) was emphasized in Heaney's work, the **Cat-1** catalyzed reaction in MeCN was re-tested. As shown in Scheme 3, when a stoichiometric reaction proceeded in MeCN, **4** was formed and converted into **3a** even more efficiently than in cyclohexane.



Scheme 3. The stoichiometric reaction in MeCN.

Thus, MeCN did not have any negative influence on the formation of **4**. The low efficiency of the catalytic reaction in MeCN (see entry 13 in Table 1, 60 min, 65% yield) may be caused by a competitive coordination between MeCN and AcO^- with Cu(I) in the active catalytic species.

Encouraged by the results from **Cat-1**, other structurally well-defined copper(I) benzoate,[19] copper(I) trifluoroacetate[20] and copper(I) pivalate[21] samples were tested under the same conditions (see: entry 7 in Table 1). As shown in Figure 2, each of them represents an amazing polynuclear Cu(I) complex or polynuclear Cu(I) complex polymer, in which the carboxylic acid anions serve as bidentate ligands for Cu(I) ions. As was expected, all of them showed highly catalytic activity for CuAAC and gave **3a** in excellent yields.

Then, the solvent-free CuAAC was tested (the first solvent-free CuAAC was reported by Nolan in 2008).[5b] To our great surprise, when **1a** (1.0 equiv.), **2a** (1.05 equiv.) and **Cat-1** (1 mol%) were mixed at room temperature, **3a** was produced in 98% yield within 3 seconds accompanied by a strong exothermic effect. As shown in Scheme 4, **Cat-1** was so powerful that the same reaction finished within 35 min at 0 °C.

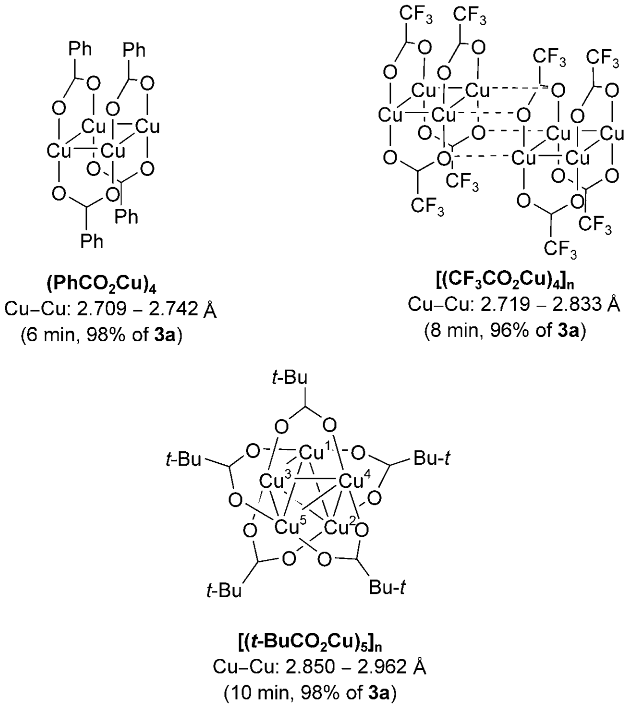


Figure 2. Structurally well-defined copper(I) carboxylates.

$$\textbf{1a} + \textbf{2a} \xrightarrow[\substack{\text{r.t. to ambient temp, 3 sec, 98\%} \\ \text{0 °C, 35 min, 99\%}}]{\textbf{Cat-1}\text{ (1 mol\%), solvent-free}} \textbf{3a}$$

Scheme 4. Cat-1-catalyzed solvent-free CuAAC reaction.

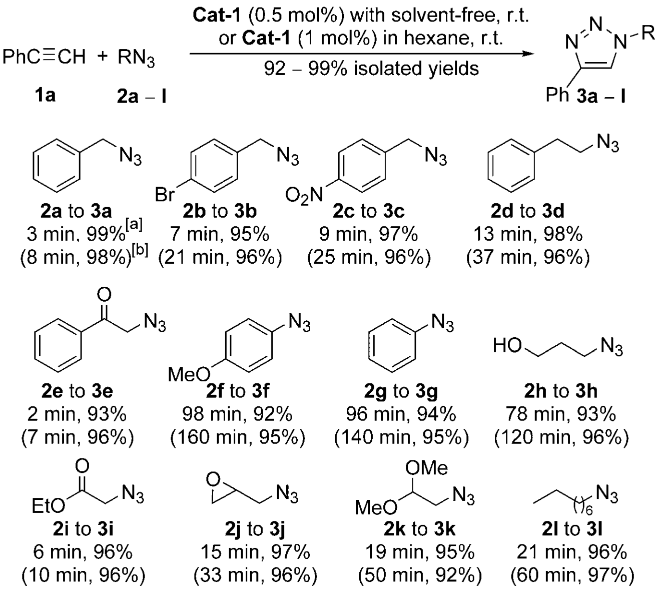
To efficiently control the exothermic effect for safe performance, the reaction with lower loadings of catalyst was tested. As shown in Table 2, when 0.1 mol% of **Cat-1** was used, the product **3a** formed gradually and the reaction finished mildly within 7 min (entry 4). By using 0.05 mol% of **Cat-1**, the reaction finished within 12 min at room temperature (entry 5) or within 4 min at 50 °C (entry 6). Even 0.01 mol% of

Table 2. Effect of the amount of **Cat-1** on CuAAC.[a]

Entry	**Cat-1** (mol%)	Temp. [°C]	Time [min]	Yield of **3a** [%][b]
1	1	0	35	99
2	1	25	0.05	98
3	0.5	25	3	99
4	0.1	25	7	99
5	0.05	25	12	99
6	0.05	50	4	99
7	0.01	50	20	99

[a] The solvent-free mixture of **1a** (2.0 mmol), **2a** (2.1 mmol) and **Cat-1** (0.02–0.0002 mmol, 1–0.01 mol%) was stirred at different temperatures.

[b] Yields of isolated products.



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[a] Reaction yield under the safe solvent-free conditions

[b] Reaction yield in cyclohexane solvent

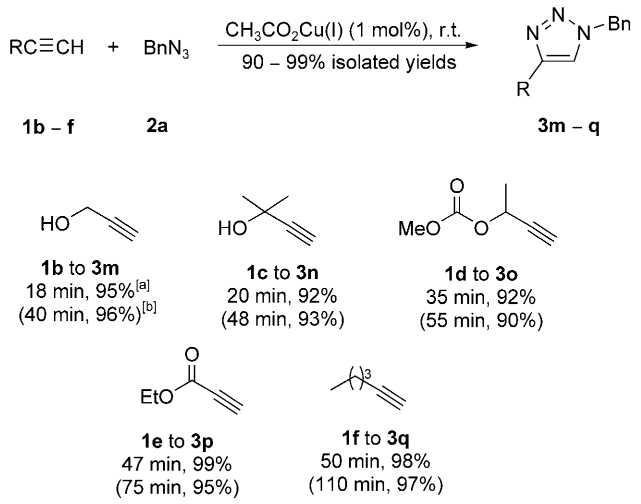
Scheme 5. Cat-1-catalyzed highly efficient CuAAC reaction of **1a** with azides **2a–l**.

Cat-1 was sufficient to give an excellent yield at 50 °C (entry 7).

To generalize this novel procedure, the CuAAC between phenylethyne (**1a**) and different azides (**2a–l**) was tested in cyclohexane solvent or under the safe solvent-free conditions. As shown in Scheme 5, the corresponding products (**3a–l**) were obtained in excellent yields and significant substrate effects were observed. Benzyl azides (**2a–c**) and the azides with functional groups substituted on the β-carbon showed higher reactivity (**2d**, **e** and **2i–k**). As was expected, aromatic azides **2f**, **g** showed lower reactivity due to their resonance stability. The alcohol **2h** needed a prolonged reaction time, possibly because its hydroxy group was involved in the coordination with Cu(I).

As shown in Scheme 6, the CuAAC reactions between different acetylenes (**1b–f**) and benzyl azide (**2a**) were finished smoothly to give the desired products **3m–q** in 92–99% yields.

Finally, the control experiments proved that the unique feature of our highly efficient **Cat-1**-catalyzed CuAAC is that no any additional ligand or additive was required, irrespective of whether the reaction proceeded in hexane or under the solvent-free conditions. As shown in Table 3, the most often used Cu(I) reagents for CuAAC, such as CuCl, CuBr, CuI or Cu_2O, just afforded traces of the desired product in the absence of ligand or additive.



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[a] Reaction yield under the safe solvent-free conditions.

[b] Reaction yield in cyclohexane as solvent.

Scheme 6. Cat-1-catalyzed highly efficient CuAAC of alkynes **1b–f** with **2a**.

Table 3. The results of CuAAC reactions catalyzed by different Cu(I) reagents without ligand or additive.[a]

Entry	Catalyst	Neat[b] (time, yield of **3**)	Cyclohexane[b] (time, yield of **3**)
1	**Cat-1**	0.05 min, 98%	8 min, 98%
2	CuCl	24 h, trace	24 h, trace
3	CuBr	24 h, trace	24 h, trace
4	CuI	24 h, < 10%	24 h, < 10%
5	CuCN	24 h, NR	24 h, NR

[a] The mixture of **1a** (2.0 mmol), **2a** (2.1 mmol) and different catalysts (1 mol%) was stirred at room temperature.

[b] Yields of isolated products.

In conclusion, based on the concept of a "dinuclear alkynyl–Cu(I) intermediate" for CuAAC, the structurally well-defined dinuclear complex $[(CH_3CO_2Cu)_2]_n$ (**Cat-1**) was studied in detail. By using non-polar solvents or under the solvent-free conditions, a highly efficient $[(CH_3CO_2Cu)_2]_n$ (**Cat-1**)-catalyzed CuAAC was developed, which is characterized by extremely low loading of catalyst, short reaction time, excellent yield and simple work-up procedure. The "bare" $[(PhC{\equiv}CCu)_2]_n$ (**4**) (i.e., with no exogeneous ligands) was isolated as an intermediate and proved to be a catalytic species for CuAAC. Since $CH_3CO_2^-$ is one of the structurally simplest bidentate ligands, this method offers an unprecedented easy and atom-economic ligand-mediated CuAAC procedure. Further mechanistic studies on $[(CH_3CO_2Cu)_2]_n$ (**Cat-1**)-catalyzed CuAAC reactions are under way in our laboratory.

Experimental Section

Typical Procedure; Preparation of 1-Benzyl-4-phenyl-*1H*-[1,2,3]triazole (3a) by $[(CH_3CO_2Cu)_2]_n$ (Cat-1)-Catalyzed CuAAC under Solvent-Free Conditions

A solution of $[(CH_3CO_2Cu)_2]_n$ in Et_2O (1 mL) {it was made from $[(CH_3CO_2Cu)_2]_n$ (12.5 mg) in Et_2O (10 mL)} was evaporated under N_2 to yield a powder of $[(CH_3CO_2Cu)_2]_n$ (1.25 mg, 0.01 mmol, 0.5 mol%, MW was calculated based on CH_3CO_2Cu). To this powder was added a mixture of phenylethyne (**1a**, 204 mg, 2 mmol) and benzyl azide (**2a**, 280 mg, 2.1 mmol) at room temperature. The resultant mixture was stirred continuously until the reaction system had solidified completely (*ca.* 3 min). After the crude product had been diluted with CH_2Cl_2 (2 mL), it was purified by a short chromatography (silica gel, EtOAc:PE = 1:3) to give **3a** as an off-white solid; yield: 464 mg (99%).

Typical Procedure; Preparation of 1-Benzyl-4-phenyl-*1H*-[1,2,3]triazole (3a) by $[(CH_3CO_2Cu)_2]_n$ (Cat-1)-Catalyzed CuAAC in Cyclohexane

A solution of $[(CH_3CO_2Cu)_2]_n$ in Et_2O (1 mL) {it was made from $[(CH_3CO_2Cu)_2]_n$ (25 mg) in Et_2O (10 mL)} was evaporated under N_2 to yield a powder of $[(CH_3CO_2Cu)_2]_n$ (2.5 mg, 0.01 mmol, 1 mol%, MW was calculated based on CH_3CO_2Cu). To this powder was added a solution of phenylethyne (**1a**, 204 mg, 2 mmol) and benzyl azide (**2a**, 280 mg, 2.1 mmol) in cyclohexane (1 mL) at room temperature. The resultant mixture was stirred continuously until phenylethyne was exhausted (*ca.* 8 min). After the crude product had been diluted by CH_2Cl_2 (2 mL), it was purified by a short chromatography (silica gel, EtOAc:PE = 1:3) to give **3a** as an off-white solid; yield: 459 mg (98%).

A similar procedure was used in CuAAC for the preparation of triazole products **3b–q** (see Scheme 4 and Scheme 5 in the text).

Supporting Information

The experimental details, characterization data, ^1H NMR and ^{13}C NMR spectra for products **3a–q** are available in the Supporting Information.

Acknowledgements

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