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 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 CuA and CuB (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-
tate is a structurally well-defined dinuclear polymer [(CH₃CO₂Cu)₂]ₙ. 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. In another few articles,[5a,14] the combination of Cu(OAc)₂/sodium ascorbate (1:5 mol/mol) (Cat-2) or a combination of Cu(OAc)₂/sodium ascorbate (1:5 mol/mol) (Cat-2) was used 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 detectable reaction was observed when copper(I) acetate was employed as a catalytic system, in which copper(I) acetate 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/H₂O 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).

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 acetylene. Although Cat-1 is sensitive to humidity to decompose into Cu₂O and HOAc as an equilibrium, the reaction in H₂O 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 sample 3a in 98% yield, it was proved to be an intermediate in the CuAAC.

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, H₂O or t-BuOH/H₂O. 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, H₂O or r-BuOH/H₂O. Therefore, these results clearly showed that the acidity of HOAc may play an important role in this conversion.

### Table 1. Effects of catalysts and solvents on CuAAC

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst(%)</th>
<th>Solvent</th>
<th>Time [min]</th>
<th>Yield of 3a [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cat-1 (10)</td>
<td>t-BuOH/H₂O</td>
<td>10</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>Cat-2 (10)</td>
<td>t-BuOH/H₂O</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>Cat-1 (5)</td>
<td>t-BuOH/H₂O</td>
<td>36</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>Cat-2 (5)</td>
<td>t-BuOH/H₂O</td>
<td>32</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>Cat-1 (1)</td>
<td>t-BuOH/H₂O</td>
<td>270</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>Cat-2 (1)</td>
<td>t-BuOH/H₂O</td>
<td>240</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>Cat-1 (1)</td>
<td>cyclohexane</td>
<td>8</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>Cat-2 (1)</td>
<td>cyclohexane</td>
<td>110</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>Cat-1 (1)</td>
<td>CHCl₃</td>
<td>16</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td>Cat-1 (1)</td>
<td>MeC₆H₄</td>
<td>16</td>
<td>93</td>
</tr>
<tr>
<td>11</td>
<td>Cat-1 (1)</td>
<td>H₂O</td>
<td>11</td>
<td>95</td>
</tr>
<tr>
<td>12</td>
<td>Cat-1 (1)</td>
<td>MeCN</td>
<td>60[^d]</td>
<td>65</td>
</tr>
<tr>
<td>13</td>
<td>Cat-1 (1)</td>
<td>EtOH</td>
<td>60[^d]</td>
<td>43</td>
</tr>
<tr>
<td>14</td>
<td>Cat-1 (1)</td>
<td>EtOAc</td>
<td>60[^d]</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>Cat-1 (1)</td>
<td>THF</td>
<td>60[^d]</td>
<td>89</td>
</tr>
</tbody>
</table>

[^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 CH₃CO₂Cu.

[^c] Ratio of t-BuOH/H₂O was 1:1 v/v.

[^d] Incomplete conversions were observed.

[^e] Yields of isolated products.
During the revision of this article, Heaney\textsuperscript{[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 μ\(_3\)-1,2-C=C bridging mode.\textsuperscript{[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.

```
1a, MeCN
Cat-1
r.t., 5 min
-HOAc
4 (85%)

\[ \text{PhC}=\text{CCu} \]

2a, MeCN
r.t., 5 min
+HOAc
3a (98%)
```

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,\textsuperscript{[19]} copper(I) trifluoroacetate\textsuperscript{[20]} and copper(I) pivalate\textsuperscript{[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).\textsuperscript{[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.

```
1a + 2a
Cat-1 (1 mol%), solvent-free
r.t. to ambient temp., 3 sec, 98% →
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>
<thead>
<tr>
<th>Entry</th>
<th>Cat-1 (mol%)</th>
<th>Temp. [°C]</th>
<th>Time [min]</th>
<th>Yield of 3a [%] \textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>35</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>25</td>
<td>0.05</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>25</td>
<td>3</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>25</td>
<td>7</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>0.05</td>
<td>25</td>
<td>12</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
<td>50</td>
<td>4</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>0.01</td>
<td>50</td>
<td>20</td>
<td>99</td>
</tr>
</tbody>
</table>

\textsuperscript{[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.

\textsuperscript{[b]} Yields of isolated products.
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 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 Cu2O, just afforded traces of the desired product in the absence of ligand or additive.

In conclusion, based on the concept of a “dinuclear alkynyl–Cu(I) intermediate” for CuAAC, the structurally well-defined dinuclear complex [(CH3CO2Cu)2]n (Cat-1) was studied in detail. By using non-polar solvents or under the solvent-free conditions, a highly efficient [(CH3CO2Cu)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=Cu)2]n (4) (i.e., with no exogeneous ligands) was isolated as an intermediate and proved to be a catalytic species for CuAAC. Since CH3CO2− 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 [(CH3CO2Cu)2]n (Cat-1)-catalyzed CuAAC reactions are under way in our laboratory.

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

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]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Neat[b] (time, yield of 3)</th>
<th>Cyclohexane[b] (time, yield of 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cat-1</td>
<td>0.05 min, 98%</td>
<td>8 min, 98%</td>
</tr>
<tr>
<td>2</td>
<td>CuCl</td>
<td>24 h, trace</td>
<td>24 h, trace</td>
</tr>
<tr>
<td>3</td>
<td>CuBr</td>
<td>24 h, trace</td>
<td>24 h, trace</td>
</tr>
<tr>
<td>4</td>
<td>CuI</td>
<td>24 h, &lt;10%</td>
<td>24 h, &lt;10%</td>
</tr>
<tr>
<td>5</td>
<td>CuCN</td>
<td>24 h, NR</td>
<td>24 h, NR</td>
</tr>
</tbody>
</table>

[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.
Experimental Section

Typical Procedure; Preparation of 1-Benzyl-4-phenyl-1H-[1,2,3]triazole (3a) by [(CH₃CO₂Cu)₂]n (Cat-1)-Catalyzed CuAAC under Solvent-Free Conditions

A solution of [(CH₃CO₂Cu)₂]n in Et₂O (1 mL) [it was made from [(CH₃CO₂Cu)₂]n (12.5 mg) in Et₂O (10 mL)] was evaporated under N₂ to yield a powder of [(CH₃CO₂Cu)₂]n (1.25 mg, 0.01 mmol, 0.5 mol%), MW was calculated based on CH₂Cl₂·Cu. To this powder was added a mixture of phenylethyne (1a, 204 mg, 2 mmol) and benzyl azide (2a, 204 mg, 2 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 CH₂Cl₂ (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%).

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 ¹³C NMR spectra for products 3a–q are available in the Supporting Information.

Acknowledgements

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References


[16] The comparison sample was obtained by the method of ref.[15b] The IR spectra for both our sample and the comparison sample are presented in the Supporting Information, in which the vibrational absorption of C≡C–Cu was observed at 1930 cm⁻¹. See: a) Y. Okamoto, S. Kundu, J. Phys. Chem. 1973, 77, 2677–2680; b) V. T. Aleksanyan, I. A. Garbuzova, I. R. Golding, A. M. Sladkov, Spectrochim. Acta 1975, 31A, 517–524.


