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ABSTRACT

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Since copper(I)–catalyzed azide–alkyne cycloaddition (CuAAC) was reported independently by the groups of Sharpless¹ and Meldal² in 2002, great efforts have been made to understand the nature of CuAAC.³ As shown in Scheme 1, a widely accepted three-step catalytic cycle mechanism of CuAAC was proposed by Sharpless in his first CuAAC article.¹

In 2004, Fokin reported first that the efficiency of CuAAC could be enhanced significantly by ligands.⁴ Since then, many efficient ligand-mediated CuAAC procedures were developed,^{5,6} in which the ligands may be useful to dissociate the stable cluster of Cu(I) sources into the active Cu(I) species, or protect Cu(I) species from oxidation and disproportionation. Three years later, Straub⁶ⁱ also proved that the protonation of C–Cu bond in intermediate **5** was inefficient using H₂O or RC=CH as a proton source, but it was highly efficient in MeCO₂H (in few minutes). Although Straub's results clearly indicated that 'step III' in CuAAC mechanism may not be benefited from the most reported ligands because they are all basic or neutral compounds, unfortunately, less attention was paid to the protonation of C–Cu bond in the design of ligands and catalysts in CuAAC studies.

Recently, we reported that copper(I) carboxylates (**6**) were highly efficient catalysts for CuAAC.^{7b} As shown in Scheme 2, by using 0.01 equiv of copper(I) acetate {**6a**, as a polymeric dinuclear complex [(MeCO₂Cu)₂]_n}, the cycloaddition of phenylethyne (**1a**) and benzyl azide (**2a**) gave 1-benzyl-4-phenyl-1,2,3-trizole (**3a**) in 98% yield in 8 min. We also revealed that MeCO₂⁻ plays dual roles^{7a} in this process: (a) it serves as a bidentate ligand to promote the formation of dinuclear alkynyl–copper(I) intermediate **4a** (step I); (b) MeCO₂H (**7a**) in situ generated in the reaction serves as a highly active promoter to cycloaddition (step II) and protonation of C–Cu bond (step III). This is the first example that the ligand could promote all three key steps in CuAAC catalytic cycle.

A simple combination of Cu₂O and PhCO₂H 'on H₂O' has been developed as a highly practical and efficient

catalytic system for copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). It not only provides a fur-

ther evidence for the strategy of carboxylic acids-promoted CuAAC, but also offers significant advantages

to CuAAC because Cu₂O is one of the most stable and cheapest Cu(I) sources; PhCO₂H is one of the struc-

turally simplest bidentate ligands; and water is the most 'green' solvent.

During the further studies on the CuAAC catalyzed by copper(I) carboxylates (**6**), we observed two interesting phenomena as shown in Scheme 3. (a) By using H₂O as a solvent, $[(MeCO_2Cu)_2]_n$ (**6a**) was hydrolyzed quickly to red Cu₂O and MeCO₂H (**7a**).⁸ But, the desired product **3a** was still obtained in 95% yield in 11 min. (b) By using the reference methods, $[(MeCO_2Cu)_2]_n$ (**6a**),⁹ (PhCO₂-Cu)₄ (**6b**),¹⁰ [(CF₃CO₂Cu)₄]_n (**6c**),¹¹ and [(*t*-BuCO₂Cu)₅]_n (**6d**)¹² were prepared from Cu₂O and the corresponding carboxylic acid anhydrides. However, regardless of the purities of **6a**–**d**, they all exhibited similarly excellent catalytic activity. These phenomena strongly implied that the uses of pre-prepared **6a–d** may be not



Scheme 1. A three-step catalytic cycle of CuAAC.







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Scheme 2. Copper(I) acetate-catalyzed highly efficient CuAAC.



Scheme 3. Two interesting phenomena.

necessary and they may be replaced with a simple combination of Cu_2O and RCO_2H (**7**). Since **6a** is a very expensive commercial product and the preparation of **6b–d** suffers from very tedious purifications, plus the fact that all of them are chemically unstable in storage, therefore, studies on the combination of Cu_2O/RCO_2H (**7**) are practically important for the understanding and applications of CuAAC.

In literature, polyvinylpyrrolidone coated nanoparticles of Cu₂O have been reported to catalyze CuAAC efficiently, but the commercial Cu₂O showed very weak catalytic activity.¹³ We also proved that, when the neat mixture of **1a**, **2a** and Cu₂O (0.01 equiv) was stirred at room temperature for 43 h, the substrates were slowly converted into **3a** in 97% yield (Scheme 4). To our delight, when the same mixture was treated with a catalytic amount of MeCO₂H (**7a**, 0.02 equiv), **3a** was obtained in 98% yield within 8 min.

Since copper(I) carboxylates **6a–d** have proved to be excellent catalysts for CuAAC,^{7b} we predicted that the combination of Cu₂O and RCO₂H (**7**) may be a general catalytic system for CuAAC. Thus, different carboxylic acids were tested. As shown in Table 1, the combinations of Cu₂O and aliphatic acids (**7a–g**, entries 1–7) showed highly efficient catalytic activity in neat conditions, but benzoic acid (**7h**, entry 8) had lower activity (38 min). Realizing the solid **7h** could not react efficiently with solid Cu₂O, one drop of H₂O was added and the same reaction finished within 9 min. As was expected, **7i** (entry 9) gave the excellent results because it is a bis(carboxylic acid). However, both **7j** and **k** (entries 10 and 11) gave poor yields of **3a**, even prolonged reaction times were used. Those results may be caused by the fact that they have strong chelating ability to Cu(I) ion, by which the catalytic cycle of Cu(I) ion is retarded.^{7a,14}

As shown in Figure 1, by using a lower loading of Cu₂O (0.005 equiv), the best results (97%, 22 min) were obtained by using 1:2 (by mole) of Cu₂O:**7a**, which may result from the fact that this ratio could generate the maximal catalyst **6a**. However, lower catalytic activity was observed by using large excess of **7a**. For example, reaction time was doubled when 1:8 ratio of Cu₂O:**7a** was used. As was expected, all ratios of Cu₂O:**7a** (1:1–1:8) gave



Scheme 4. Cu₂O and Cu₂O/7a catalyzed CuAAC.

Table 1

	Effects of	the carboxy	vlic acids	7a-k	on	CuAAC
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Entry	RCO ₂ H (7a-k)	Time (min)	Yield of 3a ^b (%)
1	MeCO ₂ H (7a)	8	98
2	HCO ₂ H (85% aq) (7b)	2	97
3	$MeCH_2CH_2CO_2H$ (7c)	8	96
4	$Me_2CHCO_2H(7d)$	6	98
5	<i>t</i> -BuCO ₂ H (7e)	7	98
6	$H_2C = CH(CH_2)_8CO_2H(7f)$	8	95
7	CF ₃ CO ₂ H (7g)	7	93
8	$C_6H_5CO_2H(7h)$	9 ^c	98
9	$HO_2CCH_2CH_2CO_2H(7i)$	10	98
10	HO ₂ CCO ₂ H (7j)	360	35
11	L-Proline (7k)	360	28

^a The neat mixture of **1a** (2 mmol), **2a** (2.1 mmol), Cu_2O (0.01 equiv) and RCO₂H (**7a-k**, 0.02 equiv) was stirred at 25 °C.

^b Isolated yields.

^c The reaction time was obtained by using one drop of H₂O.



Figure 1. Effects of the ratios of Cu₂O:7a on CuAAC.

Table 2Effects of the solvents on the reactivity of Cu₂O/7a^a

Entry	Solvent (2.0 mL)	Time (min)	Yield of $3a^{b}$ (%)
1	H ₂ O	120	98
2	MeCN	120	65
3	CH ₂ Cl ₂	120	56
4	MeCOMe	120	45
5	C ₆ H ₁₂	120	20
6	EtOH	120	18
7	t-BuOH	120	15
8	THF	120	8

 a The mixture of 1a (2 mmol), 2a (2.1 mmol), Cu_2O (0.01 equiv) and 7a (0.02 equiv) in solvent was stirred at 25 $^\circ C.$

^b Isolated yields.

nearly identical excellent results with a higher loading of Cu_2O (0.01 equiv).

Since CuAAC is a highly exothermic reaction, the reaction in a solvent was tested for the safe reason. To our disappointment, the combination of $Cu_2O/7a$ in solvents did not match its highly catalytic activity in neat conditions. As shown in Table 2, low catalytic activities were observed in all testing solvents (entries 1–8). Although H₂O was the best solvent (entry 1), its reaction time was 15 times longer than that in neat conditions.

However, when $MeCO_2H$ (**7a**) was replaced with $PhCO_2H$ (**7h**), the same reaction in H_2O finished in only 8 min to give **3a** in 98% yield. To understand this result, the reaction was monitored care-



Figure 2. Cu₂O powders on the interface between two phases.

fully and two interesting phenomena were observed as shown in Figure 2. (a) After **1a**, **2a** and Cu₂O were added into H₂O, a twophase system formed and the organic layer was surrounded by H₂O. (b) Cu₂O powders were not precipitated in H₂O, but they were spread on the interface between two phases. Thus, the protocol in H₂O actually was still a 'neat condition' for the reactants **1a**, **2a**, and Cu₂O, but not for the carboxylic acids because they have different distributions between H₂O and organic layer. Therefore, the big reactivity difference between **7a** and **h** may simply result from their solubility in H₂O.

According to this opinion, it may be expected that the hydrophilic carboxylic acids lead to lower reactivity and the hydrophobic carboxylic acids lead to higher reactivity. For example, each of **7a**, **b**, **e**, or **h** has high activity in neat conditions (see Table 1). But, the activity of **7a** and **b** was reduced significantly in H₂O (Table 3, entries 1 and 2) because they are miscible with H₂O in all proportions. Both **7e** and **h** still kept high activity (entries 3 and 4) because they have poor solubility in H₂O (2.17 g and 0.34 g/ 100 mL H₂O, respectively). As was expected, **7h** in all testing organic solvents exhibited low activity because all reactants were diluted by organic solvents (entries 5–11).

It is valuable to note that the reaction was not sensitive to the amount of H_2O and the similar results were obtained by using 0.5–2.0 mL of H_2O for 1.0 mmol of **1a**. This result also suggests that the reaction may proceed 'on water' rather than 'in water'. We also observed that the temperature of H_2O increased quickly during the reaction, but it usually was below 40 °C.

Finally, the substrate scopes were tested under our optimized conditions [0.01 equivalent of Cu₂O, 1:2 (by mole) of Cu₂O:**7h**]. As shown in Scheme 5, all cycloadditions of phenylethyne (**1a**) and different azides (**2a**–**I**) proceeded efficiently. Unlike the catalyst **6a**,^{7b}

Table 3

Entry	RCO ₂ H (7a , b , e , h)	Solvent (2.0 mL)	Time (min)	Yield of 3a ^b (%)
1	7a	H ₂ O	120	98
2	7b	H_2O	110	96
3	7e	H_2O	15	98
4	7h	H_2O	8	98
5	7h	MeCN	60	85
6	7h	MeCOMe	60	72
7	7h	CH ₂ Cl ₂	60	65
8	7h	C ₆ H ₁₂	60	58
9	7h	THF	60	46
10	7h	t-BuOH	60	26
11	7h	EtOH	60	22

 a The mixture of 1a (2 mmol), 2a (2.1 mmol), Cu_2O (0.01 equiv) and 7 (0.02 equiv) in solvent was stirred at 25 $^\circ C.$

^b Isolated yields.



Scheme 5. Cu₂O/7h catalyzed CuAAC.

the effects of azide structures on the rates were very small. For example, benzyl azides (**2a**–**d**) and alkyl azides (**2f**–**h**) gave very close rates and yields. It was similar to the catalyst **6a**, the azides (**2i–l**) substituted by electron-withdrawing group at α -carbon gave the excellent results.

As shown in Scheme 6, the structure of alkyne has significant effects on this catalytic system. All hydrophobic alkynes (**1b**–**e**) showed very high efficiency, while the hydrophilic alkynes (**1f**–**i**) showed relatively low efficiency. It was interesting to observe that both propynoic acid (**1f**) and its ester (**1g**) showed similar efficiency. Although the acylated derivatives **1h** and **i** were very good substrates, their parent compounds prop-2-yn-1-ol and prop-2-yn-1-amine just gave moderate results (78% in 14 h and 64% in 16 h, respectively), which may be caused by the coordination between Cu(I) ion with hydroxyl or amine group.

In conclusion, it is well known that the efficiency of CuAAC can be enhanced by ligands, but the protonation of C–Cu bond in CuAAC catalytic cycle could not be benefited from these existing ligands because they are all basic or neutral compounds. Recently, we discovered that copper(I) carboxylates are excellent catalysts for CuAAC, and the carboxylic acids could promote a fast protonation of C–Cu bond in CuAAC intermediate. However, copper(I) carboxylates are chemically unstable and their preparations usually associate with very tedious purifications. In this letter, we found that the pre-prepared copper(I) carboxylates can be replaced with a simple combination of Cu₂O and the corresponding carboxylic acids. Finally, the combination of Cu₂O/PhCO₂H (**7h**) 'on H₂O' was developed as a highly practical and efficient catalytic system for CuAAC. This catalytic system not only provides a further evi-



Scheme 6. Cu₂O/7h catalyzed CuAAC.

dence for the strategy of the carboxylic acid-promoted CuAAC, but also offers significant advantages to CuAAC because Cu_2O is one of the most stable and cheapest Cu(I) sources; PhCO₂H is one of the structurally simplest bidentate ligands; and H₂O is the most 'green' solvent.

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Supplementary data

Supplementary data (Experiments, characterization, ¹H and ¹³C NMR spectra for products **3a**–**t**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.061.

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