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Apparent Copper(II)-Accelerated Azide−Alkyne Cycloaddition

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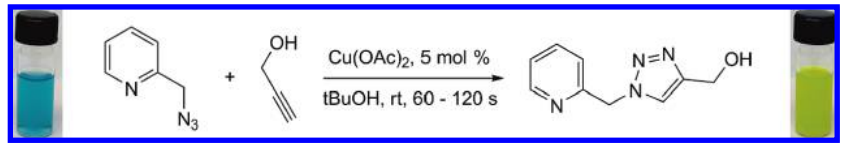
ABSTRACT



Cu(II) salts accelerate azide−alkyne cycloaddition reactions in alcoholic solvents without reductants such as sodium ascorbate. Spectroscopic observations suggest that Cu(II) undergoes reduction to catalytic Cu(I) species via either alcohol oxidation or alkyne homocoupling, or both, during an induction period. The reactions involving 2-picolylazide are likely facilitated by its chelation to Cu(II). The highly exothermic reaction between 2-picolylazide and propargyl alcohol completes within 1−2 min in the presence of as low as 1 mol % $Cu(OAc)_2$.

The discovery of the Cu(I)-catalyzed azide−alkyne cycloaddition (AAC) reaction by groups of Meldal[1] and Sharpless[2] has accelerated advances in areas ranging from drug discovery[3] to material sciences.[4] The most common experimental procedure involves the in situ generation of Cu(I) by reducing $CuSO_4$ with sodium ascorbate in aqueous media.[2] The physiological compatibility of this procedure is imperative for its success in bioconjugation applications. On the other hand, the preparative syntheses of 1,4-substituted-1,2,3-triazoles outside of the bioconjugation realm could be more efficient without additives such as sodium ascorbate. A number of procedures have been developed including the use of (1) Cu turning/$CuSO_4$ combinations,[5] (2) Cu(I) salts[1] directly or as carbene complexes,[6] (3) electrochemically generated Cu(I),[7] (4) Cu(I) on immobile phases,[8] and (5) copper-containing nanoparticles.[9] These methodological advances[10] have addressed challenges posed by specific substrate classes (e.g., reduction-prone biomolecules)[7] or other special needs (e.g., catalyst recycling) involved in respective projects.

In our investigations of triazole-containing metal coordination ligands,[11] we started to develop procedures for the AAC reaction without reducing additives to simplify the isolation of highly polar polyaza compounds. On the basis of the observation by Yamamoto et al. that Cu(II) can be reduced

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(1) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.

(2) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.

(3) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137.

(4) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018–1025.

(5) (a) Brik, A.; Muldoon, J.; Lin, Y.-C.; Elder, J. H.; Goodsell, D. S.; Olson, A. J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *ChemBioChem* **2003**, *4*, 1246–1248. (b) Deiters, A.; Cropp, T. A.; Mukherji, M.; Chin, J. W.; Anderson, J. C.; Schultz, P. G. *J. Am. Chem. Soc.* **2003**, *125*, 11782–11783.

(6) Diéz-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8881–8884.

(7) Hong, V.; Udit, A. K.; Evans, R. A.; Finn, M. G. *ChemBioChem* **2008**, *9*, 1481–1486.

(8) (a) Chassaing, S.; Kumarraja, M.; Sido, A. S. S.; Pale, P.; Sommer, J. *Org. Lett.* **2007**, *9*, 883–886. (b) Girard, C.; önen, E.; Aufort, M.; Beauvière, S.; Samson, E.; Herscovici, J. *Org. Lett.* **2006**, *8*, 1689–1692. (c) Lipshutz, B. H.; Taft, B. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 8235–8238. (d) Chtchigrovsky, M.; Primo, A.; Gonzalez, P.; Molvinger, K.; Robitzer, M.; Quignard, F.; Taran, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5916–5920.

(9) (a) Pachón, L. D.; van Maarseveen, J. H.; Rothenberg, G. *Adv. Synth. Catal.* **2005**, *347*, 811–815. (b) Molteni, G.; Bianchi, C. L.; Marinoni, G.; Santo, N.; Ponti, A. *New J. Chem.* **2006**, *30*, 1137–1139. (c) Park, I. S.; Kwon, M. S.; Kim, Y.; Lee, J. S.; Park, J. *Org. Lett.* **2008**, *10*, 497–500.

(10) For a relatively complete compilation of procedures, see:Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015.

(11) Huang, S.; Clark, R. J.; Zhu, L. *Org. Lett.* **2007**, *9*, 4999–5002.

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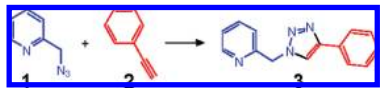
to Cu(I) in iPrOH,[12] we carried out the AAC reaction between 2-picolylazide (**1**) and phenylacetylene (**2**) in tBuOH, iPrOH, EtOH, and MeOH (Table 1, entries 1−4) with 5 mol % $CuCl_2$ loading. The reactions in iPrOH and EtOH proceeded, albeit sluggishly. The isolated yield reached 79% in MeOH after 18 h. In tBuOH, the reaction failed to afford an identifiable amount of **3** by thin-layer chromatography (TLC). The fact that only readily oxidizable alcohols (MeOH, EtOH, and iPrOH) allowed the formation of a detectable amount of the product supported the hypothesis that a catalytic Cu(I) species was generated via the reduction of $CuCl_2$ (Scheme 1A).

Table 1. Effects of Copper Source and Solvent on Reaction Yield After 18 h at rt[a]

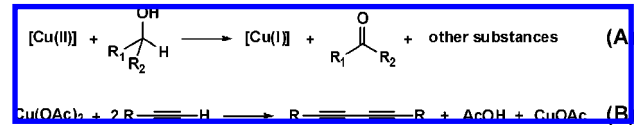


entry	copper source	copper loading	solvent	yield
1	$CuCl_2$	5 mol %	tBuOH	ND[b]
2	$CuCl_2$	5 mol %	iPrOH	4%
3	$CuCl_2$	5 mol %	EtOH	17%
4	$CuCl_2$	5 mol %	MeOH	79%
5	$CuSO_4$	5 mol %	MeOH	81%
6	$CuSO_4$	5 mol %	tBuOH	6%
7	$Cu(OAc)_2$	5 mol %	MeOH	90%
8	$Cu(OAc)_2$	5 mol %	tBuOH	>95%
9	$CuCl_2$ + NaOAc	5 mol %	tBuOH	88%

[a] 0.2−0.25 mmol of **1** and 0.3 mmol of **2** in 0.5 mL of solvent. [b] ND: Not detected by thin-layer chromatography (TLC).

The effect of counterion was studied using three Cu(II) salts, $CuCl_2$ (entry 4), $CuSO_4$ (entry 5), and $Cu(OAc)_2$ (entry 7), in MeOH. All three counterions gave satisfactory yields after 18 h. However, unlike $CuSO_4$ and $CuCl_2$, $Cu(OAc)_2$ enabled a highly efficient reaction in tBuOH (>95%, entry 8). To eliminate the possibility that $Cu(OAc)_2$ may have been contaminated by a miniscule amount of Cu(I) species, the reaction was run using 5 mol % of $CuCl_2$ (99.999% pure), which is inactive in tBuOH (Table 1, entry 1), and NaOAc each in tBuOH (entry 9). An 88% yield was achieved. This observation forced us to formulate an alternative hypothesis accounting for the reaction in tBuOH, which is not prone to oxidation ($CuSO_4$ enabled a 6% yield in tBuOH, entry 6).[13] It is known that terminal alkynes may undergo Cu(II)-catalyzed oxidative homocouping reactions to afford diynes (the Glaser reaction).[14] In the classical Eglinton protocol,[15] $Cu(OAc)_2$ is the most active Cu(II) agent. We hypothesize that a Glaser-type reaction may be taking place to produce the catalytic Cu(I) species that allows the AAC reaction to proceed (Scheme 1B) in tBuOH. The Glaser induction period to generate Cu(I) species was observed by Mizuno et al. in their catalytic AAC processes using silicotungstate- and alumina-supported Cu(II).[16]

Scheme 1. Two Processes by Which Catalytic Cu(I) Species Might Have Been Generated



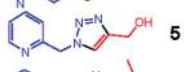
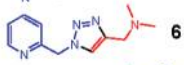
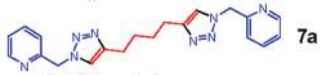
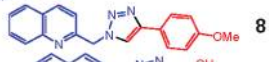
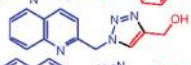
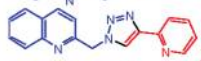
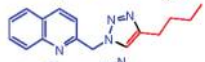
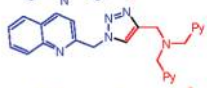
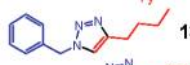
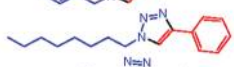
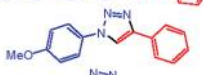
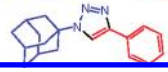
It should be noted that the "catalytic" effect of $Cu(OAc)_2$ on AAC reactions was reported by Kantam et al. in 2006.[17] In their procedure, satisfactory yields were achieved with 20 mol % catalyst loading in aqueous solutions for 20 h. Kantam et al. postulated a direct participation of Cu(II) in the catalysis. We, on the other hand, hypothesize that under the reported conditions at least two processes, alcohol oxidation and homocoupling of terminal alkyne by $Cu(OAc)_2$ (Scheme 1), may generate the needed Cu(I) to complete the catalytic cycle of the AAC reaction proposed and substantiated by Sharpless, Meldal, and others.[10,18] It is conceivable that the efficiencies of these "autoreduction"[19] processes are highly condition-dependent. For instance, in the presence of ligands that favor the +1 oxidation state of copper, the reduction of Cu(II) is known to proceed in a deceptively effortless manner.[20]

On the basis of the postulate that either processes A or B or both may afford the catalytic Cu(I) species, two reaction conditions that favor either process were selected to evaluate various azide and alkyne substrates. Condition A entails 5 mol % $CuSO_4$ in MeOH where Cu(II) reduction by MeOH is presumably the major process to generate the Cu(I) species.

(12) Kirai, N.; Yamamoto, Y. *Eur. J. Org. Chem.* **2009**, 1864–1867.
(13) The same reaction was observed to proceed to a small extent in CH_3CN. A comprehensive solvent scope study is planned in the future.
(14) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632–2657.
(15) Eglinton, G.; Galbraith, A. R. *Chem. Ind. (London)* **1956**, 737–738.
(16) (a) Kamata, K.; Nakagawa, Y.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* **2008**, *130*, 15304–15310. (b) Katayama, T.; Kamata, K.; Yamaguchi, K.; Mizuno, N. *ChemSusChem* **2009**, *2*, 59–62.
(17) Reddy, K. R.; Rajgopal, K.; Kantam, M. L. *Synlett* **2006**, 957–959. For other examples appearing later where Cu(II) was postulated as the catalytic species in AAC reactions, see:(a) Fukuzawa, S.-I.; Shimizu, E.; Kikuchi, S. *Synlett* **2007**, 2436–2438. (b) Reddy, K. R.; Rajgopal, K.; Kantam, M. L. *Catal. Lett.* **2007**, *114*, 36–40. (c) Song, Y.-J.; Yoo, C.; Hong, J.-T.; Kim, S.-J.; Son, S. U.; Jang, H.-Y. *Bull. Korean Chem. Soc.* **2008**, *29*, 1561–1564. (d) Namitharan, K.; Kumaaraja, M.; Pitchumani, K. *Chem.—Eur. J.* **2009**, *15*, 2755–2758.
(18) (a) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210–216. (b) Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2210–2215. (c) Straub, B. F. *Chem. Commun.* **2007**, 3868–3870. (d) Nolte, C.; Mayer, P.; Straub, B. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 2101–2103. (e) Ahlquist, M.; Fokin, V. V. *Organometallics* **2007**, *26*, 4380–4391.
(19) Kitagawa, S.; Munakata, M.; Higashie, A. *Inorg. Chim. Acta* **1984**, *84*, 79–84.
(20) (a) Musker, W. K.; Olmstead, M. M.; Kessler, R. M. *Inorg. Chem.* **1984**, *23*, 1764–1768. (b) Benzekri, A.; Cartier, C.; Latour, J.-M.; Limosin, D.; Rey, P.; Verdaguer, M. *Inorg. Chim. Acta* **1996**, *252*, 413–420. (c) Malachowski, M. R.; Adams, M.; Elia, N.; Rheingold, A. L.; Kelly, R. S. *J. Chem. Soc., Dalton Trans.* **1999**, 2177–2182. (d) Sarkar, S.; Patra, A.; Drew, M. G. B.; Zangrando, E.; Chattopadhyay, P. *Polyhedron* **2009**, *28*, 1–6.

An amount of 5 mol % $Cu(OAc)_2$ in tBuOH completes Condition B where the Glaser reaction may result in the reduction of $Cu(OAc)_2$. The results after 18 h reaction time are summarized in Table 2.

Table 2. Triazole Products Generated under Conditions A and B[a,f]

entry	product	yield %
1	 4	13 (A) >95 (B)
2	 5	56 (A) >95 (B)
3	 6	>95 (A) 92 (B)
4	 7a	10 (A)[b] 85 (B)
5	 8	25 (A) >95 (B)
6	 9	78 (A) 92 (B)
7	 10	82 (A) >95 (B)
8	 11	42 (A) >95 (B)
9[c]	 12	76 (A) 92 (B)
10	 13	68 (A) 87 (B)
11	 14	trace (A) 50 (B)
12	 15	25 (A)[d] 67 (B)[d]
13	 16	ND[e] (A) ND[e] (B)

[a] A: $CuSO_4$, 5 mol % in MeOH, B: $Cu(OAc)_2$, 5 mol % in tBuOH. Other conditions: 0.2 mmol azide (0.6 mmol for entry 4), 0.22−0.3 mmol alkyne, rt, 18 h. [b] 36% of monotriazole product (**7b**) was isolated. [c] py = 2-pyridylmethyl. [d] Reaction was run for 40 h. [e] ND: Not detected. [f] Azide and alkyne components are coded blue and red, respectively.

Overall, the reaction yields were higher under Condition B than those under Condition A, which suggests that $Cu(OAc)_2$ is a very potent catalytic Cu(I) source. 2-Picolylazide (**1**, Table 2, entries 1−4) and 2-azidomethylquinoline (entries 5−9) are superb substrates under these conditions. The facile AAC reactions involving **1** under the normal Cu(I)-catalyzed conditions was also observed by Koǒrlj et al.[21] Other azide substrates are less ideal (entries 10−13). The crystal structure of the complex between **1** and $CuCl_2$ (Figure 1) revealed the association between Cu(II) and the alkylated nitrogen of the azido group. This coordination mode renders the azido group highly electrophilic, which likely enables a facile reaction with the acetylide which is expected to bind at the same copper center in the transition state structure. The other example of a Cu(II) complex with an organic azide that we are aware of also features coordination of the alkylated nitrogen and a $[Cu_2Cl_2]$ core.[22] The in-depth discussion on the structure and bonding of $[Cu_2(\mathbf{1})_2Cl_4]$ will appear in a later report.

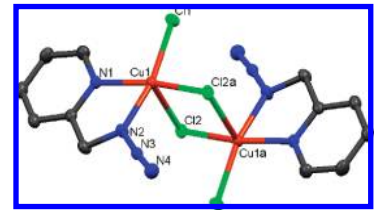
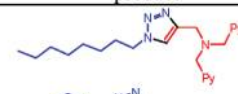
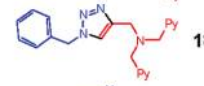
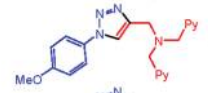
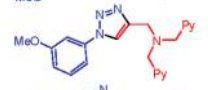
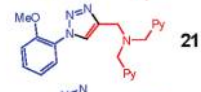
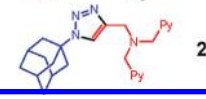


Figure 1. Single-crystal structure of $[Cu_2(\mathbf{1})_2Cl_4]$. Selected bond lengths (Å): Cu1−N1 = 2.027; Cu1−N2 = 2.033; Cu1−Cl1 = 2.232; Cu1−Cl2a = 2.266; Cu1−Cl2 = 2.718; N2−N3 = 1.256; N3−N4 = 1.115.

Table 3. Triazole Products Generated under Condition C[a,d]

entry	product[b]	yield %
1	 17	>95 (C)
2	 18	>95 (C)
3	 19	88 (C)
4	 20	73 (C)
5	 21	89 (C)
6	 22	47 (C)[c]

[a] C: 0.2 mmol azide and alkyne in 0.5 mL of MeOH with 1 mol % $Cu(OAc)_2$ at rt for 18 h. [b] py = 2-pyridylmethyl. [c] Reaction was run for 40 h. [d] Azide and alkyne components are coded blue and red, respectively.

Di(2-picolyl)propargylamine was a relatively poor substrate under Conditions A and B (data not shown). However, when the reactions shown in Table 3 were run in MeOH in the presence of 1 mol % of $Cu(OAc)_2$ (Condition C), high yields were achieved. The isolation of the highly polar triazole products requires merely a short alumina column without aqueous workup. Most compounds listed in Tables 2 and 3 are multidentate ligands for Cu(II), which is evident in the crystal structures of the Cu(II) complexes of **18** (Figure 2A) and **3** (Figure 2B), where N3 and N2 of the 1,2,3-triazole ring are coordinating, respectively. Cu(II) in both structures displays the typical square planar geometry with distant ligand(s) at axial position(s). Despite the affinity to Cu(II), product inhibition in the AAC reactions was not observed.

(21) Urankar, D.; Koǒrlj, J. *J. Comb. Chem.* **2008**, *10*, 981–985.

(22) Barz, M.; Herdtweck, E.; Thiel, W. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 2262–2265.

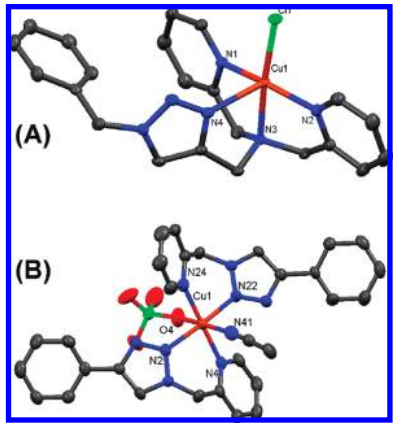


Figure 2. Single crystal structures of (A) [Cu(**18**)Cl]$^+$ and (B) [Cu(**3**)$_2$(CH_3CN)(ClO_4)]$^+$. Selected bond lengths (Å): (A) N1−Cu1 = 1.993; N2−Cu1 = 1.997; N3−Cu1 = 2.067; N4−Cu1 = 2.321; Cl1−Cu1 = 2.238. (B) N2−Cu1 = 2.007; N4−Cu1 = 2.057; N22−Cu1 = 2.003; N24−Cu1 = 2.056; N41−Cu1 = 2.341; O4−Cu1 = 2.675.

All reactions listed in Tables 2 and 3 were analyzed after 18 h reaction time. Some may have taken much less time to complete. For example, the reaction between **1** and propargyl alcohol in the presence of 1−5 mol % $Cu(OAc)_2$ in tBuOH is over within 60−120 s with high exothermicity. The reaction displays dramatic change of color. After initial mixing, the blue tint of the reaction mixture persists until it abruptly disappears. In the ensuing few seconds, the reaction concludes with a spurt of heat release, and the color turns bright yellow. The reaction progress was followed with absorption spectroscopy (Figure 3A). The d−d band of Cu(II) is unaltered until the end of the induction period. The disappearance of the d−d band at the 65th second, which suggests the reduction of Cu(II), accompanies the reaction.

More direct evidence of the reduction of Cu(II) was obtained by the EPR measurements since Cu(II) exhibits a characteristic EPR signal at a *g*-value of about 2.2, while Cu(I) is EPR-inactive and organic radicals have a *g*-value around 2.0. $Cu(OAc)_2$ in tBuOH in the presence and absence of propargyl alcohol yielded similarly strong EPR signals that could be assigned to Cu(II) (black and blue curves in Figure 3B). The spectra are rhombic, with $g_Z = 2.1933$, $g_Y = 2.1306$, and $g_X = 2.0732$ (Figure S3, Supporting Information). After the reaction was completed following the addition of compound **1**, the EPR signal (orange curve) was greatly attenuated, coinciding with the color change. Both the absorption and the EPR data are consistent with the hypothesis that Cu(II) is converted to Cu(I) which enables the rapid reaction between **1** and propargyl alcohol.

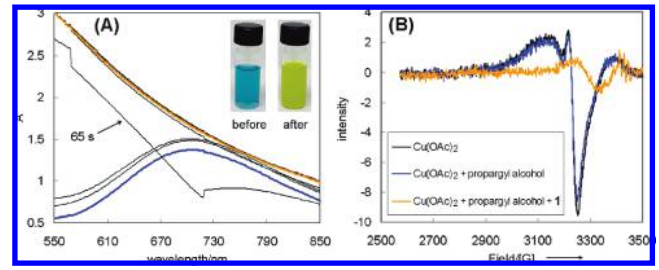


Figure 3. (A) Absorption spectra of the mixture of **1** (1.0 mmol) and propargyl alcohol (1.5 mmol) in the presence of 5 mol % $Cu(OAc)_2$ in tBuOH (2.5 mL) during the course of the reaction over 4 min. Blue and orange traces were collected at the inception of and after the reaction, respectively. Large absorbance values were due to the heterogeneity of the samples. (B) EPR spectra of $Cu(OAc)_2$ in tBuOH at room temperature. Black: $Cu(OAc)_2$ alone. Blue: $Cu(OAc)_2$ and propargyl alcohol. Orange: Mixture of $Cu(OAc)_2$, propargyl alcohol, and **1** after the reaction is completed.

In summary, we find that Cu(II) salts, especially $Cu(OAc)_2$, accelerate the AAC reactions without deliberately adding reducing agents. 2-Picolylazide (**1**) and 2-azidomethylquinoline are superb substrates for the AAC reactions under the discovered conditions. The high reactivity of these two azides is attributed to their abilities to chelate the alkylated azido nitrogen, therefore facilitating the AAC reactions both electronically and sterically. At a low catalyst loading (1 mol %), pyridyl-containing multidentate ligands for Cu(II) were prepared with high yields and no product inhibition. The reaction between **1** and propargyl alcohol in the presence of 1−5 mol % $Cu(OAc)_2$ in tBuOH completes within 60−120 s, which to our knowledge is the fastest AAC reaction under ambient temperature reported thus far. Both absorption and EPR data suggest that catalytic Cu(I) species is generated in an induction period. Further mechanistic studies including solvent and substrate scopes and capture of intermediate species will be carried out in the near future.

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Supporting Information Available: Experimental procedures, characterization of new compounds, photograph of TLC plate for solvent screening, and .cif files for [Cu_2(**1**)$_2Cl_4$], [Cu(**18**)Cl](ClO_4), and [Cu(**3**)$_2$(CH_3CN)(ClO_4)](ClO_4). This material is available free of charge via the Internet at http://pubs.acs.org.

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