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"Click" Chemistry: Application of Copper Metal in Cu-Catalyzed Azomethine Imine−Alkyne Cycloadditions

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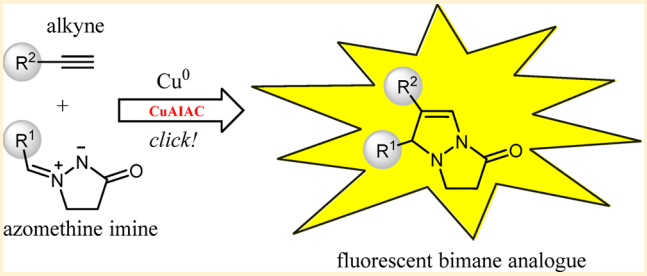
Supporting Information

ABSTRACT: A series of 16 copper-catalyzed azomethine imine−alkyne cycloaddition (CuAIAC) reactions between four pyrazolidinone-1-azomethine imines and four terminal ynones gave the corresponding fluorescent cycloadducts as bimane analogues in very high yields. The applicability of CuAIAC was demonstrated by the fluorescent labeling of functionalized polystyrene and by using Cu−C and Cu−Fe as catalysts. Experimental evidence, kinetic measurements, and correlation between a clean catalyst surface and the reaction rate are in agreement with a homotopic catalytic system with catalytic Cu^{I}−acetylide formed from Cu^{0} by "in situ" oxidation. The availability of azomethine imines, mild reaction conditions, simple workup, and scalability make CuAIAC a viable supplement to the Cu-catalyzed azide−alkyne cycloaddition reaction in "click" chemistry.



1. INTRODUCTION

Since its definition by Sharpless and co-workers in 2001, "click" chemistry has become an important methodology of modern synthetic organic chemistry comprising various highly efficient reactions, such as nucleophilic opening of spring-loaded rings, nonaldol type carbonyl chemistry, additions to C−C multiple bonds, and cycloadditions.[1] Within a variety of "click" reactions, the Cu-catalyzed azide−alkyne cycloaddition (CuAAC), discovered independently by the groups of Meldal[2] and Fokin and Sharpless,[3] has been the first and the most prominent example of the "click" reaction.[1−4] It is no wonder that CuAAC found a widespread use in connecting different types of small as well as macromolecular units. Nowadays, CuAAC is a standard ligation tool in combinatorial synthesis,[4,5] bioconjugation,[6] and material science.[7] A limitation of CuAAC is due to the explosive properties of organic azides; for the safety reasons, CuAAC reactions are usually performed on a small scale.

In their first publication,[1] Sharpless and co-workers already recognized the potential of selective 3 + 2 cycloadditions of azomethine imines for applications in "click" chemistry.[8] In the shade of the successful story of CuAAC that started the next year, cycloadditions of azomethine imines did not make their breakthrough in "click" chemistry. Nevertheless, few yet relevant papers published in the meantime clearly revealed the potential of Cu-catalyzed azomethine imine−alkyne cycloaddition (CuAIAC). In 2003 and 2005, Fu and co-workers reported CuAIAC as a tool for regio- and enantioselective synthesis of bicyclic pyrazolidinones in excellent yields and selectivity using Cu^{I}-based chiral catalysts.[9a,b] Since then, around a dozen examples of highly selective and efficient CuAIAC reactions have been reported.[9c−f,10,11] These results clearly showed the suitability of CuAIAC for connecting azomethine imine- and acetylene-functionalized molecules under conditions compliant with "click" chemistry requirements. In the conventional CuAAC "click" chemistry, the azide- and alkyne-functionalized building blocks (BBs) are reacted in the presence of Cu-catalyst to afford, regioselectively, the 1,2,3-triazole-linked conjugate. In the CuAIAC version, the azide BB is replaced by its azomethine imine equivalent, easily available from a pyrazolidinone and an aldehyde, to give 1-oxo-2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]-pyrazole-linked conjugate. When CuAIAC is carried out with ynones (R^2 = acyl), a yellow fluorescent pyrazolo[1,2-*a*]pyrazole linker (a bimane[12] analogue) is obtained. This implies applicability of CuAIAC, not only as a ligation tool but also in concomitant fluorescent labeling (Figure 1).

Homogeneous chiral Cu^{I} catalysts have been used in asymmetric CuAIAC reactions,[9,11] while achiral, mostly heterogeneous Cu^{I} catalysts have been employed for the preparation of racemic cycloadducts.[10,11] When a "click" connection of two BBs is the primary objective, mild and simple reaction conditions, broad scope, modularity, and ease of preparation become more important than asymmetric induction. Although copper metal (Cu^{0}) should be a suitable catalyst for this purpose, to the best of our knowledge, its use as a catalyst in CuAIAC reaction has not been reported.

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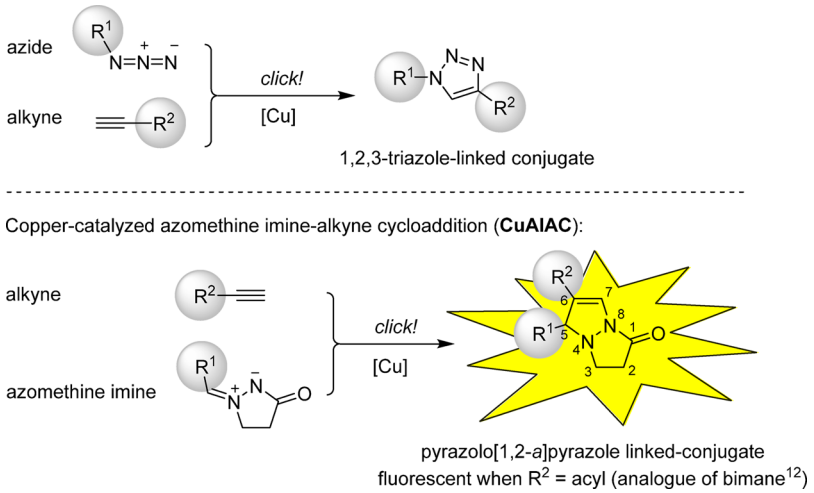


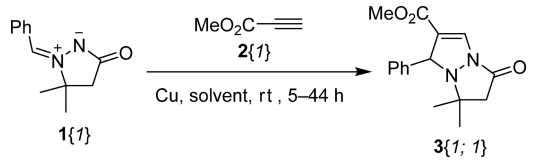
Figure 1. CuAAC and CuAIAC reaction.

In continuation of our work on 3-pyrazolidinone-1-azomethine imines,[10a,h,13] we recently observed that cycloadditions to ynones were catalyzed by copper metal. This triggered our decision to study the copper-metal-catalyzed CuAIAC reaction and its applicability in "click" chemistry (cf. Figure 1). Herein, we report the results of this study showing copper metal as a suitable catalyst and CuAIAC as a viable supplement to CuAAC reaction.

2. RESULTS AND DISCUSSION

2.1. Determination of Optimum Reaction Conditions. Copper-metal-catalyzed reaction of 2-benzylidene-3,3-dimethyl-5-oxopyrazolidin-2-ium-1-ide **1**{*1*}[9a,10b,14a,b] with 1.2 equiv of methyl propiolate **2**{*1*} at rt was used for the optimization of reaction conditions with respect to the solvent, reaction time, and catalyst loading. The results are presented in Table 1. First, reactions were performed in various standard solvents in the presence of 20 wt% of Cu powder for 24 h (Table 1, entries 1–8). The conversion was low in DMF, ethanol, and THF (10–25%). In acetonitrile, 93% conversion was achieved. In the above solvents, formation of small amounts of bright yellow, insoluble CuC≡C−CO_2Me (Cu−**2**{*1*})[10g,15] was observed. Complete conversion was obtained in EtOAc, toluene, $CHCl_3$, and CH_2Cl_2. However, $CHCl_3$ and CH_2Cl_2 were the most suitable solvents due to fast and clean conversion, and those solvents were devoid of byproducts formed in EtOAc and toluene. Consequently, reaction in CH_2Cl_2 was further evaluated (Table 1, entries 9–11). The conversion was slowed down by lower catalyst loading and almost stopped upon addition of Hünig's base (DIPEA). This was surprising, since DIPEA worked well in combination with CuI catalyst.[10h] In the control experiment (Table 1, entry 12), only 5% conversion was achieved upon 19 h.

Table 1. Optimization of Reaction Conditions[a,b]



entry	solvent	Cu (mg)	time (h)	conversion (%)[b]
1	DMF	10	24	10[c]
2	EtOH	10	24	15[c]
3	THF	10	24	25[c]
4	MeCN	10	24	93[c]
5	EtOAc	10	24	100[d]
6	PhMe	10	24	100[d]
7	$CHCl_3$	10	24	100[e]
8	CH_2Cl_2	10	24	100[e]
9	CH_2Cl_2[f]	10	5	<1
10	CH_2Cl_2	5	22	35
11	CH_2Cl_2	5	44	100
12	CH_2Cl_2	0	19	5

[a]All reactions were performed at rt with 0.25 mmol of **1**{*1*} and 0.30 mmol of **2**{*1*} in 1.5 mL of solvent, followed by filtration and evaporation. [b]The conversions were determined from the ^{1}H NMR spectra of the crude products. [c]A small amount of Cu−acetylide precipitated. [d]Byproducts were formed. [e]Conversion of 100% was achieved already after 16 h. [f]In the presence of 0.5 equiv of DIPEA.

2.2. Synthesis of Representative Cycloadducts. Four model azomethine imines **1**{*1*–*4*}[14] were prepared by treatment of 5,5-dimethyl-3-pyrazolidinone (**4**)[16] with benzaldehydes **5**{*1*–*4*} following a general literature procedure.[11,14c] Next, a library of 16 cycloadducts **3**{*1*–*4*;*1*–*4*} was synthesized by reacting the representative dipoles **1**{*1*–*4*} with model terminal alkynes **2**{*1*–*4*} bearing different acyl groups. Reactions were performed under previously determined optimum reaction conditions (cf. Table 1, entry 8). The workup comprised removal of the catalyst by filtration, followed by evaporation. Purification by flash chromatography (FC) was sometimes applied to remove an excess of dipolarophile and to increase the purity (Scheme 1, Table 2). The conversion of starting dipoles **1** was nearly quantitative after 1 day to give cycloadducts **3**{*1*–*4*;*1*–*4*} in 66–99% isolated yields. The experimental data revealed the negligible effect of substituents R^1 and R^2 on the reactivity of dipoles **1** and dipolarophiles **2**. The only exception was a very slow reaction of the bulkiest reactants **1**{*2*} and **2**{*4*} (Table 2, entry 8), which was explainable by the steric hindrance between the 3,4,5-trimethoxybenzylidene residue of **1**{*2*} and the benzoyl group of **2**{*4*}. In summary, neither the structure of dipole **1** nor the structure of ynone **2** affected the reaction time significantly. To test the scalability, cycloaddition of **1**{*4*} to **2**{*1*} was also performed on a 20 times larger scale without any effect on the conversion and yield of **3**{*4*;*1*} (Table 2).

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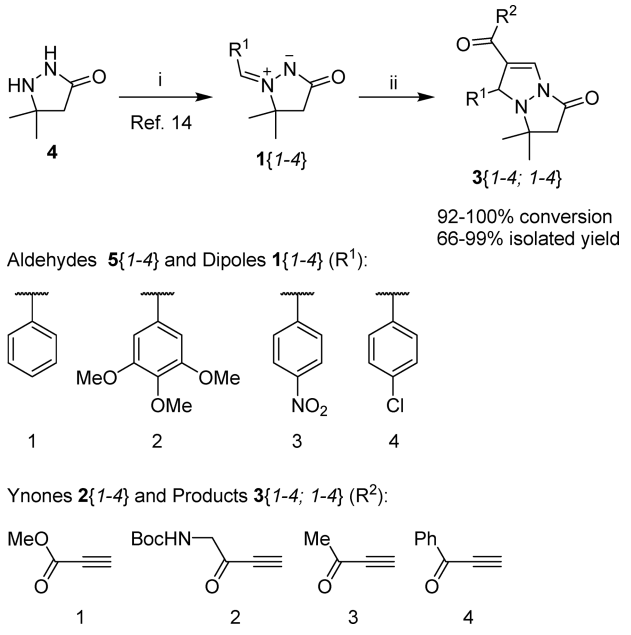
Scheme 1. Synthesis of the Representative Cycloadducts 3{*1–4;1–4*}[a]



[a]Reaction conditions: (i) aldehyde **5**{*1–4*}, EtOH, TFA (cat) rt; (ii) ynone **2**{*1–4*}, CH_2Cl_2, Cu powder (40 mg/mmol), rt, 18–120 h.

Table 2. Experimental Data for a Library of Cycloadducts 3{*1–4;1–4*}[a]

entry	transformation	time (h)	conversion (%)[b]	yield (%)[c]
1	**1**{*1*} + **2**{*1*} → **3**{*1;1*}	18	100	92
2	**1**{*1*} + **2**{*2*} → **3**{*1;2*}	24	95	92
3	**1**{*1*} + **2**{*3*} → **3**{*1;3*}	26	90	75
4	**1**{*1*} + **2**{*4*} → **3**{*1;4*}	24	95	66
5	**1**{*2*} + **2**{*1*} → **3**{*2;1*}	26	100	94
6	**1**{*2*} + **2**{*2*} → **3**{*2;2*}	23	97	96
7	**1**{*2*} + **2**{*3*} → **3**{*2;3*}	18	100	87
8	**1**{*2*} + **2**{*4*} → **3**{*2;4*}	120	97	81
9	**1**{*3*} + **2**{*1*} → **3**{*3;1*}	24	100	93
10	**1**{*3*} + **2**{*2*} → **3**{*3;2*}	24	92	89
11	**1**{*3*} + **2**{*3*} → **3**{*3;3*}	24	100	91
12	**1**{*3*} + **2**{*4*} → **3**{*3;4*}	24	100	92
13	**1**{*4*} + **2**{*1*} → **3**{*4;1*}	24	100[d]	99[d]
14	**1**{*4*} + **2**{*2*} → **3**{*4;2*}	24	97	95
15	**1**{*4*} + **2**{*3*} → **3**{*4;3*}	24	97	89
16	**1**{*4*} + **2**{*4*} → **3**{*4;4*}	24	100	90

[a]All reactions were performed at rt with 0.5 mmol of **1** and 0.6 mmol of **2** in 3 mL of CH_2Cl_2 in the presence of 20 mg of Cu powder, followed by filtration and evaporation. [b]Determined from the ^{1}H NMR spectra of the crude reaction mixtures. [c]Isolated yield. [d]Identical result was obtained on a 10 mmol scale.

2.3. Applicability. To test its applicability as a ligation tool, the CuAIAC reaction was employed for fluorescent labeling of functionalized polymeric materials. Attachment through the ynone component was investigated first. Treatment of chloromethylated polystyrene [Merrifield resin (**6**)] with propiolic acid in the presence of NaI and DIPEA provided the polymer-bound propiolate **2**{*5*},[17] which was reacted with azomethine imine **1**{*1*} in CH_2Cl_2 in the presence of Cu wire for 5 days to give the yellow fluorescent polymer-bound cycloadduct **3**{*1;5*} (Scheme 2, method A, Figure 2). Next, labeling through polymer-bound benzaldehyde was explored. The commercially available benzaldehyde on polystyrene **5**{*5*} was treated with a slight excess of 5,5-dimethyl-3-pyrazolidinone (**4**) in methanol in the presence of catalytic amounts of trifluoroacetic acid to provide the polymer bound dipole **1**{*5*}, which, upon treatment with methyl propiolate **2**{*1*} in the presence of Cu wire, afforded the polymer bound cycloadduct **3**{*5;1*} (Scheme 2, method B). To test some other forms of heterogeneous copper metal catalyst, reactions with 10% Cu–graphite (Cu–C) and with copper-coated iron powder (Cu–Fe) were also performed. Cu–C was prepared following a slightly modified literature procedure.[18] Cycloaddition of **1**{*1*} to methyl propiolate **2**{*1*} was performed on a 0.125 mmol scale in the presence of 25 mg of Cu–C for 24 h. The reaction proceeded similarly as with Cu powder to give **3**{*1;1*} in quantitative yield upon simple filtration workup. The same catalyst was used three more times in the same reaction without the decrease of conversion. Due to higher purity of the product and lower catalyst loading, Cu–C (graphite or charcoal) could be an interesting alternative or even replacement for Cu powder. Another interesting variation of the catalyst was Cu–Fe, which has already found use in CuAAC reaction.[19] It was prepared easily by stirring iron powder with aq $CuSO_4$, followed by filtration, washing, and drying. Cycloaddition of **1**{*2*} to **2**{*1*} was performed on a 0.3 mmol scale in the presence of 80 mg (~100%) of Cu–Fe for 24 h to give **3**{*2;1*} in quantitative yield. The conversion remained 100%, even upon using the same catalyst for three more runs. Easy separation of the catalyst from the reaction mixture by application of a magnetic field is the major advantage of the Cu–Fe-catalyzed reaction (Scheme 2).

2.4. Mechanistic Insight. Like in the closely analogous CuAAC reaction,[4,19] the generally accepted plausible mechanism is based on the catalytic Cu^I–acetylide as the reactive species, which undergoes cycloaddition, followed by protonation of the cuprated cycloadduct.[10,11] This is supported by experiments performed with copper(I) acetylides, deuterated acetylenes, and/or proton sources, such as D_2O and AcOD.[10c,d,f,g] Cu^I was, either used directly or formed "in situ" by reduction of Cu^{II}.[10c,d,f] In contrast to CuAAC, where Cu^I is essential for catalytic activity,[4,20] recently reported Cu^{II}-catalyzed CuAIAC reactions indicate that the mechanism may also involve activation by Cu Lewis acid.[21] However, dipole **1**{*1*} did not react with a nonterminal ynone **2**{*6*} (Table 3, entries 1 and 2), which was in agreement with the acetylide intermediate. Activation by Lewis acid was ruled out, since the acetylide can only be formed from a terminal ynone. To get insight into the catalytic cycle of copper-metal-catalyzed CuAIAC, further experiments were performed using the representative reaction, **1**{*1*} + **2**{*1*} → **3**{*1;1*}. With Cu powder as catalyst under usual conditions and under oxygen or argon, similar conversions were observed (Table 3, entries 3–5). Nevertheless, slightly faster conversion under oxygen suggested that reaction was most probably catalyzed by Cu^I species (Table 3, entry 4). On the other hand, Cu_2O was a poor catalyst, whereas CuO was inactive in this respect (Table 3, entries 6 and 7). Somewhat expectedly,[10g,15] replacement of the dipolarophile **2**{*1*} or Cu catalyst with the acetylide Cu–**2**{*1*}[10g] did not improve the conversion (Table 3, entries 8 and 9). To check the importance of a clean Cu surface devoid of patina, two experiments were carried out with Cu activated with 1 M H_2SO_4 or 50% $N_2H_4{\cdot}H_2O$.[22] Indeed, the conversion

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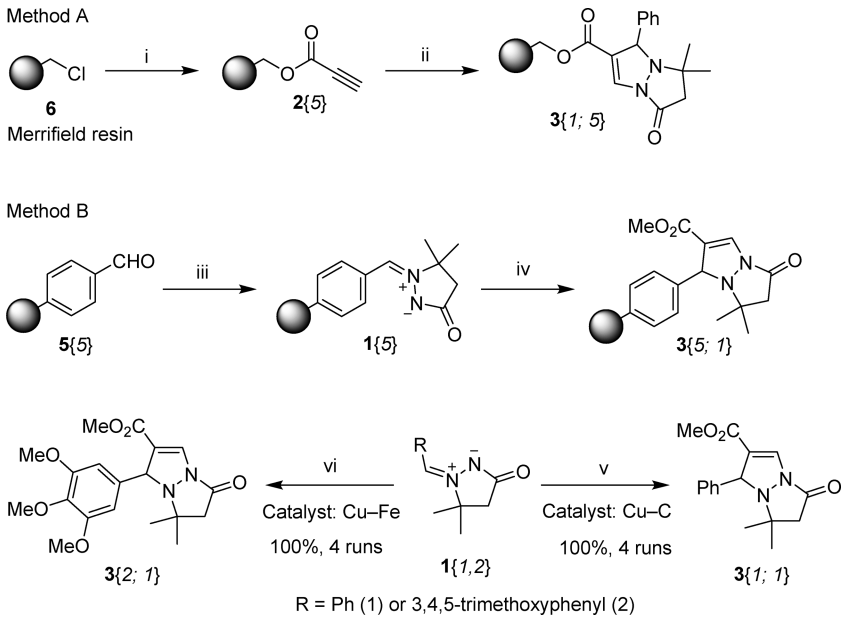
Scheme 2. Synthesis of Fluorescent Polymer-Bound Cycloadducts 3{*1,5*} and 3{*5,1*} and Synthesis of 3{*1,2;1*} with Cu−C and Cu−Fe Catalysts (four runs)[a]



[a]Reaction conditions: (i) propiolic acid, NaI, DIPEA, DMF, rt, 5 days; (ii) dipole **1**{*1*}, CH_2Cl_2, Cu wire, rt, 72 h; (iii) 5,5-dimethyl-3-pyrazolidinone (**4**), MeOH, TFA (cat), rt, 72 h; (iv) methyl propiolate **2**{*1*}, CH_2Cl_2, Cu wire, rt, 72 h; (v) methyl propiolate **2**{*1*}, CH_2Cl_2, 50 wt% Cu−C, rt, 24 h; (vi) methyl propiolate **2**{*1*}, CH_2Cl_2, 100 wt% Cu−Fe, rt, 24 h.

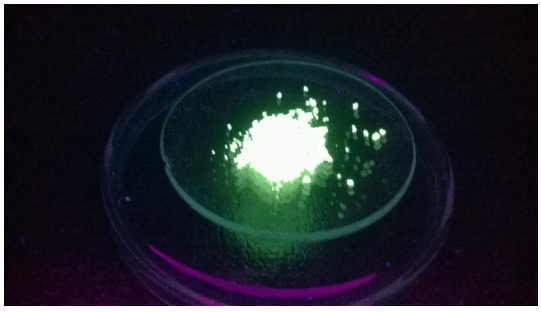


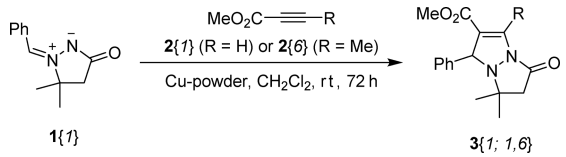
Figure 2. Fluorescent polystyrene resin 3{*1;5*} obtained from Merrifield resin via ynone functionalization followed by CuAIAC reaction. The picture was taken under a UV lamp (375 nm).

increased with both activated catalysts (Table 3, entries 10 and 11). Thus, clean catalyst's surface significantly increased the conversion.

Cycloaddition of **1**{*1*} to deuterium-labeled methyl propiolate (**2**{*1*}-*d*)[23] (D:H = 65:35) afforded cycloadduct 3{*1;1*} with only 8% deuterium incorporation (D:H = 8:92), compliant with analogous results of other groups.[4,10c,d,f,g]

Next, the kinetic profiles of the representative reaction in the presence of various Cu catalysts were determined by ^{1}H NMR. Reactions were performed at 302 K with 0.125 mmol of **1**{*1*} and 0.15 mmol of **2**{*1*} in 0.75 mL of $CDCl_3$ with 5 mg of a catalyst. Kinetic profiles in the presence of Cu, Cu_2O, and CuO are shown in Figure 3. A common feature of reactions was a 45−60 min induction period, similar to that observed in analogous copper-metal-catalyzed CuAAC reactions.[24a] Complete conversion within 12 h was obtained only with Cu (green circles, gray diamonds, and yellow squares); the conversion was lower (92%) in the presence of Cu_2O (blue squares), whereas CuO (red circles) showed no appreciable catalytic activity. The

Table 3. Cu-Catalyzed Cycloadditions of Dipole 1{*1*} to Methyl Propiolate 2{*1*} and Methyl 2-Butynoate 2{*6*}[a]



entry	catalyst	R	loading (mg)	time (h)	conversion (%)[b]
1	Cu	Me	5	72	0
2	[c]	Me	0[c]	72	0
3	Cu	H	5	5	14
4	Cu[d]	H	5	5	17
5	Cu[e]	H	5	5	12
6	Cu_2O	H	8	5	3
7	CuO	H	7	5	<1
8	Cu	Cu[f]	5	17	30
9	Cu-**2**{1}	H	8	22	36[g]
10	Cu[h]	H	5	5	67
11	Cu[i]	H	5	5	76

[a]Reactions were performed at rt with 0.125 mmol of **1**{*1*} and 0.15 mmol of **2**{*1*} in 0.75 mL of CH_2Cl_2, followed by filtration and evaporation. [b]The conversion was determined from the ^{1}H NMR spectra of the crude products. [c]Without Cu catalyst. [d]Under O_2 (balloon). [e]Under argon (balloon). [f]Cu−**2**{*1*} was used as dipolarophile. [g]Conversion of 36% coincides with 36 mol % of Cu−**2**{*1*} used as catalyst. [h]Prewashed with 1 M H_2SO_4. [i]Prewashed with 50% $N_2H_4{\cdot}H_2O$.

shortest induction period and the fastest reaction progress was obtained with activated (washed) Cu (green circles).

The kinetic profiles measured with Cu granules (blue squares) and with Cu powder (green circles, black diamonds) showed dependence of the reaction rate on the specific surface area of Cu metal (blue squares vs green circles and black

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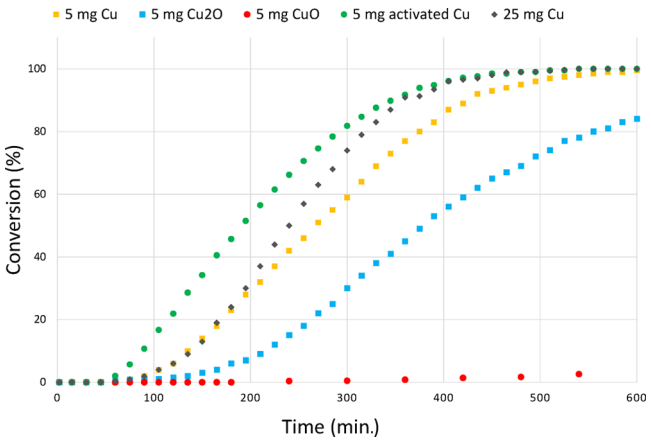

Figure 3. Kinetic profiles of the representative reaction in $CDCl_3$ with activated Cu (green circles), Cu (gray diamonds, yellow squares), Cu_2O (blue squares), and CuO (red circles) as catalysts.

diamonds). On the other hand, five times higher loading of Cu powder had only limited effect on the reaction rate (black diamonds vs green circles), whereas duration of the induction period was very similar for all three catalysts (Figure 4).

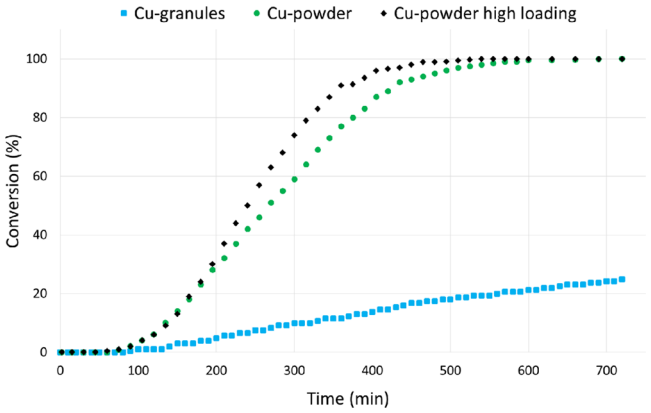

Figure 4. Kinetic profiles of the model reaction in $CDCl_3$ in the presence of Cu granules (blue squares) and Cu powder (green circles, black diamonds).

Catalytic activity of Cu powder was in line with the activity of previously employed Cu^I catalysts.[10] Like in related CuAAC reactions,[4] also the CuAIAC reactions took longer for completion with Cu powder than with conventional Cu^I catalysts, such as CuI[10a,h] and CuOAc.[10g]

The results of the above experiments with heterogeneous copper catalyst strongly suggested that Cu^0 itself was not the heterotopic catalytic species but rather a source of a homogeneous catalytically active Cu^I species. Thus, the catalytic system was most probably homotopic. To check this hypothesis, a mercury poisoning experiment,[25] Cu-removal and readdition experiment, and the control experiment were performed in parallel for the model reaction **1**{*1*} + **2**{*1*} → **3**{*1*;*1*}. Since Hg^0 in the mercury poisoning experiment failed to poison the system, it was safe to conclude that the catalytic system was homotopic.[25,26] Surprisingly, the reaction was accelerated upon addition of Hg^0 and became faster than the control reaction (Figure 5, yellow circles vs green squares). On the other hand, using only Hg^0 as catalyst gave the same conversion as the noncatalyzed reaction. Therefore, the Hg^0-

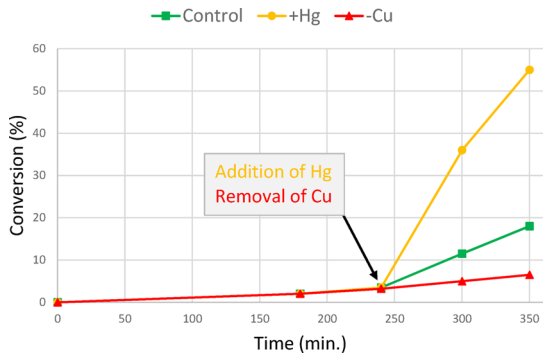

Figure 5. Partial reaction profiles (0−350 min) for the mercury poisoning (yellow circles), Cu removal (red triangles), and the control experiment (green squares).

induced increase of the reaction rate is explainable at best by (partial) amalgamation that activates the catalyst's surface similarly as activation of Cu^0 by acid or hydrazine hydrate (cf. Figure 3).

The Cu removal−addition experiment also confirmed the homotopicity of the catalytic system. The conversion gradually declined after removal of copper and was reboosted upon readdition. The reaction curve was in agreement with the above hypothesis, yet it indicated the reaction taking place also at the surface of the catalyst. Heterogenous catalyst providing a sufficient amount of fresh unexploited homogeneous catalytic species throughout the reaction course, e.g., by slow oxidation of Cu^0, seems a reasonable explanation (Figure 6).

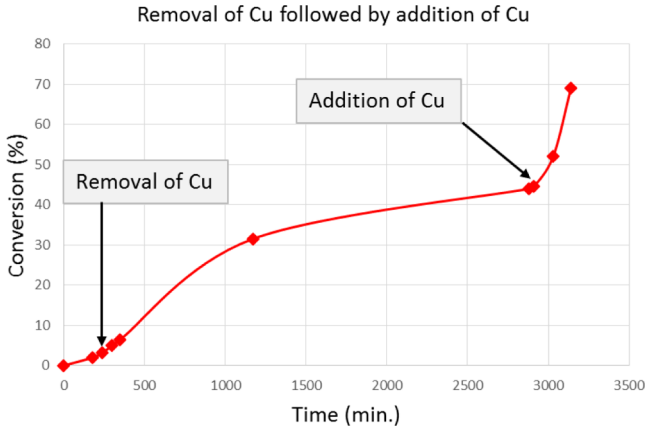

Figure 6. Reaction profile for the Cu removal−addition experiment.

Formation of Cu^I−acetylide on the surface of Cu nanoparticles has been reported, unfortunately without any mechanistic explanation.[24] In this study, small amounts of insoluble Cu−**2**{*1*}[10g] were obtained when the model reaction was performed in polar solvents (cf. Table 1, entries 1−4). To get more information, Cu^0-catalyst was treated with excess propiolate **2**{*1*} in MeCN and CH_2Cl_2 for 7 days. In MeCN, the conversion into Cu−**2**{*1*} was complete under normal (i.e., "aerobic") conditions and only partial under argon. In CH_2Cl_2 no precipitate was formed and the reaction mixture became slightly yellowish.[27] Thus, formation of polynuclear Cu−**2**{*1*} was favored under "aerobic" conditions in MeCN and suppressed in CH_2Cl_2. Thus, slow oxidation of Cu^0 in CH_2Cl_2 provides trace consumable amounts of oligonuclear low molecular weight Cu−**2**{*1*}^{cat} as catalytically active Cu^I

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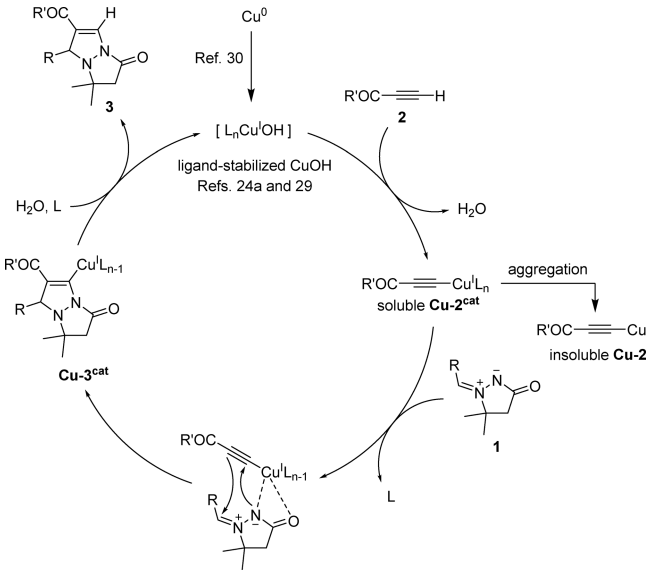
J. Org. Chem. 2016, 81, 5988−5997

species. In contrast, oxidation of Cu^0 in MeCN is faster than consumption of the so-formed catalytic low molecular weight Cu−acetylide, which aggregates into inactive Cu−**2**{*1*} as an insoluble precipitate.

The proposed catalytic cycle, compliant with related literature examples,[4,9,10,24a] is presented in Scheme 3. Oxidation

Scheme 3. Proposed Catalytic Cycle of Copper-Metal-Catalyzed CuAIAC Reaction



of Cu^0 facilitated by traces of oxygen and moisture[28] gives ligand-stabilized L_nCu^IOH[24a] with azomethine imine **1** as plausible ligand. Analogous stable carbene−Cu^IOH complex has recently been reported,[29] while oxidation of Cu^0 with O_2 is known to produce various Cu/O_2 adducts, including oxygenated Cu^I species.[30] This is also in agreement with a slight acceleration of the reaction carried out under oxygen (cf. Table 3, entry 4). Subsequent reaction of L_nCu^IOH with terminal ynone **2** gives the catalytic acetylide Cu−2^{cat}, which then coordinates the dipole **1** (if not coordinated before) and undergoes 3 + 2 cycloaddition to afford the cuprated cycloadduct Cu−3^{cat}. Protonation (S_E) with water and ligand exchange gives the cycloadduct **3** and L_nCu^IOH species (Scheme 3).

3. CONCLUSION

In summary, we have demonstrated, to the best of our knowledge, the first examples of a CuAIAC reaction using copper metal as the source of Cu^I catalyst. In spite of longer reaction times, the major advantages of copper metal over Cu^I-based catalysts are the versatility of (commercially) available forms of copper (e.g., powder, wire, turnings, granules, nanoparticles, etc.) and the simple workup. This makes it easily applicable in most techniques of organic synthesis, including high-throughput synthesis and flow chemistry. Due to ease of access to substrates and substrate tolerance, the reaction is compliant with the requirements of "click" chemistry. Its applicability in fluorescent labeling was also shown; upon modification, the reaction might also be useful in bioconjugation and material functionalization. In this context, CuAIAC has two advantages over the classical CuAAC reaction: (a) the nonexplosive nature of azomethine imines allows large-scale reactions and (b) fluorescent products such as bimane analogues enable direct application in fluorescent labeling. Experimental evidence on the reaction mechanism shows that it is sensitive to the catalyst's particle size and the oxidation state of the catalyst's surface. The correlation between a clean catalyst surface and the reaction rate strongly suggests that the reactive Cu^I species is formed from Cu^0 by "in situ" oxidation rather than from patina on the catalyst's surface. This is in agreement with homotopic low molecular weight catalytic Cu^I−acetylide[9,10] formed from heterogeneous Cu^0 catalyst. The proposed catalytic cycle is compliant with the results of other groups for CuAAC[4,24a] and CuAIAC reactions.[9,10] Further studies on the scope and applications of this reaction are currently in progress.

4. EXPERIMENTAL SECTION

4.1. General Methods. Reaction progress was monitored by TLC and by ^1H NMR analysis of the crude reaction mixture. Melting points were determined on a Kofler micro hot stage and on an automated melting point system. The NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 using TMS as the internal standard on a 300 or 500 MHz instrument at 300 and 500 MHz for ^1H and at 75.5 and 126 MHz for ^{13}C nucleus, respectively. High-resolution mass spectra were recorded on a time-of-flight (TOF) mass spectrometer equipped with a double orthogonal electrospray source at atmospheric pressure ionization (ESI) coupled to an HPLC instrument. IR spectra were recorded on a FTIR ATR spectrophotometer. Microanalyses were performed by combustion analysis on a CHN analyzer. Flash column chromatography (FC) was performed on silica gel (particle size 35−70 μm). Benzaldehyde on polystyrene **5**{*5*} (loading capacity 0.8−1.5 mmol/g resin), benzaldehydes **5**{*1*−*4*}, Cu powder (particle size <10 μm), Cu granules (particle size 100−500 μm), Fe powder (reduced), formylpolystyrene (loading capacity 2.0−3.0 mmol/g resin, 100−200 mesh, cross-linked with 2% DVB), chloromethylated polystyrene (loading capacity 1.1 mmol/g resin, 200−400 mesh, cross-linked with 1% DVB), methyl propiolate **2**{*1*}, but-3-yn-2-one **2**{*3*}, and 1-phenylprop-2-yn-1-one **2**{*4*} are commercially available. 5,5-Dimethyl-3-pyrazolidinone (**4**),[16] azomethine imines **1**{*1,4*},[10b,c] and **1**{*2,3*},[14c] *tert*-butyl (2-oxobut-3-yn-1-yl)carbamate **2**{*2*},[31] and 10% Cu−graphite catalyst[18] were prepared according to the literature procedures.

4.2. Optimization of the Reaction Conditions. General Procedure for the Cu^0-Catalyzed CuAIAC of 1{*1*} to 2{*1*}. A mixture of 2-benzylidene-3,3-dimethyl-5-oxopyrazolidin-2-ium-1-ide **1**{*1*} (50 mg, 0.25 mmol), methyl propiolate **2**{*1*} (25 μL, 0.3 mmol), Cu powder (10 mg), and solvent (1.5 mL, cf. Table 1) was stirred at rt for 5−44 h. The reaction progress was monitored by TLC (EtOAc/hexanes). The catalyst and small amounts of insoluble byproducts were removed by filtration and washed with solvent (2 × 1 mL), and the combined filtrate was evaporated in vacuo. The conversion was determined from the ^1H NMR spectrum of the crude reaction mixture.

4.3. General Procedure for the Synthesis of Cycloadducts 3{*1−4;1−4*}. A mixture of azomethine imine **1** (0.5 mmol), ynone **2** (0.6 mmol), Cu powder (20 mg), and CH_2Cl_2 (3 mL) was stirred at rt for 12−120 h. The catalyst was removed by filtration and washed with CH_2Cl_2 (2 × 1 mL), and the filtrate was evaporated in vacuo to give **3**. The conversion was determined from the ^1H NMR spectrum of the crude reaction mixture. Optionally, the crude product **3** was purified by flash chromatography (FC) over silica gel (EtOAc/hexanes). Fractions containing the product were combined and evaporated in vacuo to give the purified product **3**.

4.3.1. Methyl 7,7-Dimethyl-5-oxo-1-phenyl-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazole-2-carboxylate 3{1;1}. The title compound was prepared from **1**{*1*} (101 mg, 0.5 mmol) and methyl propiolate **2**{*1*} (50 μL, 0.6 mmol), in 18 h. Yield: 131 mg (92%) of a yellow solid. Mp: 154−157 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.23 (s, 3H), 2.39 (d, *J* = 15.5 Hz, 1H), 2.86 (d, *J* = 15.5 Hz, 1H), 3.61 (s, 3H), 5.46 (d, *J* = 1.5 Hz, 1H), 7.25−7.38 (m, 3H), 7.45 (m, 2H), 7.51 (d, *J* = 1.5 Hz, 1H). NMR data are in agreement with the

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literature data.[9d] ATR: ν_{max} 3074, 1734 (C═O), 1687 (C═O), 1598, 1320, 1187, 715 cm^{-1}.

4.3.2. tert-Butyl (2-(7,7-dimethyl-5-oxo-1-phenyl-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-2-oxoethyl)carbamate 3{1;2}. The title compound was prepared from **1**{*1*} (101 mg, 0.5 mmol) and *tert*-butyl (2-oxobut-3-yn-1-yl)carbamate **2**{*2*} (112 mg, 0.6 mmol), in 24 h. FC: EtOAc/hexanes = 1:1. Yield: 179 mg (92%) of a yellow solid. Mp: 147−151 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.22 (s, 3H), 1.40 (s, 9H), 2.43 (d, J = 16.0 Hz, 1H), 2.88 (d, J = 16.0 Hz, 1H), 4.01 (dd, J = 19.0, 4.6 Hz, 1H), 4.19 (dd, J = 19.0, 5.2 Hz, 1H), 5.18−5.20 (m, 1H), 5.55 (s, 1H), 7.25−7.29 (m, 1H), 7.31−7.36 (m, 2H), 7.41−7.45 (m, 2H), 7.60 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.0, 25.1, 28.4, 47.3, 49.4, 64.57, 64.61, 79.9, 123.0, 127.9, 128.1, 128.6, 129.3, 141.8, 155.7, 167.3, 190.1. HRMS: m/z found 386.2075 (MH^+), $C_{21}H_{28}N_3O_4$ requires m/z = 386.2074. ATR: ν_{max} 3445, 2977, 1730 (C═O), 1635, 1570, 1158, 1013 cm^{-1}. Anal. Found: C, 65.15; H, 7.09; N, 10.79. $C_{21}H_{27}N_3O_4$ requires: C, 65.44; H, 7.06; N, 10.90.

4.3.3. 6-Acetyl-3,3-dimethyl-5-phenyl-2,3-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-1-one 3{1;3}. The title compound was prepared from **1**{*1*} (101 mg, 0.5 mmol) and but-3-yn-2-one **2**{*3*} (47 μL, 0.6 mmol), in 26 h. FC: EtOAc/hexanes = 3:5. Yield: 102 mg (75%) of a yellow solid. Mp: 139−142 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.21 (s, 3H), 2.19 (s, 3H), 2.41 (d, J = 16.0 Hz, 1H), 2.88 (d, J = 16.0 Hz, 1H), 5.51 (br s, 1H), 7.23−7.28 (m, 1H), 7.29−7.39 (m, 2H), 7.41−7.45 (m, 2H), 7.52 (d, J = 1.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.8, 24.8, 26.8, 49.2, 64.3, 64.6, 126.4, 127.6, 127.7, 128.3, 129.4, 142.0, 167.5, 192.8. HRMS: m/z found 271.1437 (MH^+), $C_{16}H_{19}N_2O_2$ requires m/z = 271.1441. ATR: ν_{max} 1723 (C═O), 1650 (C═O), 1639, 1577, 1359, 1311, 1254, 1007, 699 cm^{-1}. Anal. Found: C, 70.79; H, 6.64; N, 10.27. $C_{16}H_{18}N_2O_2$ requires: C, 71.09; H, 6.71; N, 10.36.

4.3.4. 6-Benzoyl-3,3-dimethyl-5-phenyl-2,3-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-1-one 3{1;4}. The title compound was prepared from **1**{*1*} (101 mg, 0.5 mmol) and 1-phenylprop-2-yn-1-one **2**{*4*} (79 mg, 0.6 mmol), in 24 h. FC: EtOAc/hexanes = 2:1. Yield: 110 mg (66%) of a yellow solid. Mp: 158−161 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (s, 3H), 1.25 (s, 3H), 2.44 (d, J = 15.5 Hz, 1H), 2.92 (d, J = 15.5 Hz, 1H), 5.79 (br s, 1H), 7.22−7.29 (m, 1H), 7.32−7.37 (m, 3H), 7.39−7.43 (m, 2H), 7.48−7.54 (m, 1H), 7.54−7.60 (m, 2H), 7.64−7.70 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.0, 25.0, 49.4, 64.5, 65.5, 125.6, 127.7, 127.8, 128.3, 128.4, 128.5, 130.3, 132.3, 138.3, 141.7, 167.0, 190.2. HRMS: m/z found 333.1596 (MH^+), $C_{21}H_{21}N_2O_2$ requires m/z = 333.1598. ATR: ν_{max} 1714 (C═O), 1628, 1582, 1574, 1414, 1326, 1219, 1107, 1008, 716 cm^{-1}. Anal. Found: C, 75.69; H, 6.05; N, 8.27. $C_{21}H_{20}N_2O_2$ requires: C, 75.88; H, 6.06; N, 8.43.

4.3.5. Methyl 7,7-Dimethyl-5-oxo-1-(3,4,5-trimethoxyphenyl)-1,5,6,7-tetrahydropyrazolo[1,2-a]pyrazole-2-carboxylate 3{2;1}. The title compound was prepared from **1**{*2*} (146 mg, 0.5 mmol) and methyl propiolate **2**{*1*} (54 μL, 0.6 mmol), in 26 h. FC: first EtOAc/hexanes = 1:1 to elute excess alkyne, and then EtOAc to elute the product. Yield: 177 mg (94%) of a yellow solid. Mp: 106−109 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.145 (s, 3H), 1.153 (s, 3H), 2.40 (d, J = 15.8 Hz, 1H), 2.86 (d, J = 15.8 Hz, 1H), 3.57 (s, 3H), 3.64 (s, 3H), 3.75 (s, 6H), 5.47 (d, J = 1.4 Hz, 1H), 6.70 (s, 2H), 7.75 (d, J = 1.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 17.9, 24.1, 48.1, 51.3, 55.9, 59.9, 63.8, 64.7, 104.8, 114.9, 131.1, 131.2, 136.6, 138.5, 152.7, 163.7, 167.4. HRMS: m/z found 404.2179 (MH^+), $C_{21}H_{30}N_3O_5$ requires m/z = 404.2180. ATR: ν_{max} 2959, 1732 (C═O), 1692 (C═O), 1593, 1319, 1119, 766 cm^{-1}. Physical and spectral data are in agreement with the literature data.[14c]

4.3.6. tert-Butyl (2-(7,7-Dimethyl-5-oxo-1-(3,4,5-trimethoxyphenyl)-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-2-oxoethyl)-carbamate 3{2;2}. The title compound was prepared from **1**{*2*} (150 mg, 0.5 mmol) and *tert*-butyl (2-oxobut-3-yn-1-yl)carbamate **2**{*2*} (112 mg, 0.6 mmol), in 23 h. FC: EtOAc/hexanes = 2:1. Yield: 233 mg (96%) of a yellow solid. Mp: 154−158 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.22 (s, 3H), 1.42 (s, 9H), 2.45 (d, J = 16.0 Hz, 1H), 2.91 (d, J = 16.0 Hz, 1H), 3.83 (s, 3H), 3.87 (s, 6H), 4.05 (dd, J = 18.0, 4.8 Hz, 1H), 4.21 (dd, J = 19.0, 5.2 Hz, 1H), 5.24 (t, J = 4.9 Hz, 1H), 5.51 (s, 1H), 6.67 (s, 2H), 7.62 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 15.4, 18.9, 25.1, 28.4, 47.3, 49.3, 56.2, 60.9, 64.6, 64.7, 65.9, 79.9, 104.7, 122.8, 129.4, 137.3, 137.5, 153.2, 155.7, 167.4, 190.3. HRMS: m/z found 476.2388 (MH^+), $C_{24}H_{34}N_3O_7$ requires m/z = 476.2391. ATR: ν_{max} 3069, 2973, 2932, 1719 (C═O), 1708 (C═O), 1664 (C═O), 1118 cm^{-1}. Anal. Found: C, 60.66; H, 7.01; N, 8.68. $C_{24}H_{33}N_3O_7$ requires: C, 60.62; H, 6.99; N, 8.84.

4.3.7. 6-Acetyl-3,3-dimethyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydropyrazolo[1,2-a]-pyrazol-1(5H)-one 3{2;3}. The title compound was prepared from **1**{*2*} (146 mg, 0.5 mmol) and but-3-yn-2-one **2**{*3*} (48 μL, 0.6 mmol), in 18 h. FC: first EtOAc/hexanes = 2:1 to remove excess alkyne, and then EtOAc to elute the product. Yield: 171 mg (87%) of a yellow solid. Mp: 45−47 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (s, 3H), 1.16 (s, 3H), 2.22 (s, 3H), 2.41 (d, J = 15.8 Hz, 1H), 2.87 (d, J = 15.9 Hz, 1H), 3.64 (s, 3H), 3.75 (s, 6H), 5.46 (d, J = 0.6 Hz, 1H), 6.67 (s, 2H), 8.18 (d, J = 1.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 17.7, 24.1, 26.8, 48.2, 55.8, 59.8, 63.6, 64.5, 104.9, 124.8, 132.4, 136.5, 138.7, 152.5, 167.9, 192.9. HRMS: m/z found 361.1755 (MH^+), $C_{19}H_{25}N_2O_5$ requires m/z = 361.1758. ATR: ν_{max} 2965, 1719 (C═O), 1650 (C═O), 1580, 1228, 1121, 715 cm^{-1}. Anal. Found: C, 63.31; H, 6.91; N, 7.56. $C_{19}H_{24}N_2O_5$ requires: C, 63.32; H, 6.71; N, 7.77.

4.3.8. 6-Benzoyl-3,3-dimethyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydropyrazolo[1,2-a]pyrazol-1(5H)-one 3{2;4}. The title compound was prepared from **1**{*2*} (146 mg, 0.5 mmol) and 1-phenylprop-2-yn-1-one **2**{*4*} (79 mg, 0.6 mmol), in 120 h. FC: EtOAc/hexanes = 1:2). Yield: 171 mg (81%) of a yellow solid. Mp: 190−192 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.26 (s, 3H), 2.46 (d, J = 15.8 Hz, 1H), 2.95 (d, J = 15.8 Hz, 1H), 3.82 (s, 3H), 3.89 (s, 6H), 5.75 (s, 1H), 6.83 (s, 2H), 7.33 (d, J = 1.3 Hz), 7.39−7.46 (m, 2H), 7.50−7.55 (m, 1H), 7.66−7.71 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.0, 25.2, 49.4, 56.2, 56.2, 60.8, 64.7, 65.6, 104.8, 125.5, 128.3, 128.6, 130.6, 132.5, 137.4, 138.4, 153.2, 167.3, 190.5. HRMS: m/z found 423.1911, $C_{24}H_{27}N_2O_5$ requires m/z = 423.1914. ATR: ν_{max} 2936, 1734 (C═O), 1621, 1596, 1565, 1318, 1129, 1001, 725 cm^{-1}. Anal. Found: C, 68.20; H, 6.42; N, 6.64. $C_{24}H_{26}N_2O_5$ requires: C, 68.23; H, 6.20; N, 6.63.

4.3.9. Methyl 7,7-Dimethyl-1-(4-nitrophenyl)-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazole-2-carboxylate 3{3;1}. The title compound was prepared from **1**{*3*} (123 mg, 0.5 mmol) and methyl propiolate **2**{*1*} (50 μL, 0.6 mmol), in 24 h. Yield: 154 mg (93%) of a yellow solid. Mp: 118−120 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (s, 3H), 1.25 (s, 3H), 2.44 (d, J = 16.0 Hz, 1H), 2.89 (d, J = 16.0 Hz, 1H), 3.64 (s, 3H), 5.58 (d, J = 1.5 Hz, 1H), 7.54 (d, J = 1.5 Hz, 1H), 7.69 (d, J = 8.5 Hz, 2H), 8.22 (d, J = 8.5 Hz, 2H). HRMS: m/z found 332.1238 (MH^+), $C_{16}H_{18}N_3O_5$ requires: m/z = 332.1241. Physical and spectral data are consistent with the literature data.[14c]

4.3.10. tert-Butyl (2-(7,7-Dimethyl-1-(4-nitrophenyl)-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-2-oxoethyl)carbamate 3{3;2}. The title compound was prepared from **1**{*3*} (123 mg, 0.5 mmol) and *tert*-butyl (2-oxobut-3-yn-1-yl)carbamate **2**{*2*} (112 mg, 0.6 mmol), in 24 h. FC: EtOAc/hexanes = 1:1. Yield: 190 mg (89%) of a yellow solid. Mp: 160−166 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.23 (s, 3H), 1.41 (s, 9H), 2.49 (d, J = 16.0 Hz, 1H), 2.92 (d, J = 16.0 Hz, 1H), 4.01 (dd, J = 18.0, 4.8 Hz, 1H), 4.25 (dd, J = 18.0, 5.5 Hz, 1H), 5.12−5.14 (m, 1H), 5.67 (s, 1H), 7.64 (s, 1H), 7.68−7.70 (m, 2H), 8.19−8.21 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.1, 25.1, 28.4, 47.1, 49.2, 64.0, 64.8, 80.1, 122.0, 123.8, 129.0, 129.7, 147.7, 148.9, 155.7, 167.1, 190.2. HRMS: m/z found 431.1920 (MH^+), $C_{21}H_{27}N_4O_6$ requires m/z = 431.1925. ATR: ν_{max} 2971, 1702 (C═O), 1660 (C═O), 1516, 1347, 1158 cm^{-1}. Anal. Found: C, 57.69; H, 6.20; N, 12.69. $C_{21}H_{26}N_4O_6 \cdot {}^1/_2H_2O$ requires: C, 57.39; H, 6.19; N, 12.75.

4.3.11. 6-Acetyl-3,3-dimethyl-5-(4-nitrophenyl)-2,3-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-1-one 3{3;3}. The title compound was prepared from **1**{*3*} (123 mg, 0.5 mmol) and but-3-yn-2-one **2**{*3*} (48 μL, 0.6 mmol), in 24 h. Yield: 115 mg (91%) of a yellow solid. Mp: 136−140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.22 (s, 3H), 2.21 (s, 3H), 2.46 (d, J = 16.0 Hz, 1H), 2.91 (d, J = 16.0

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J. Org. Chem. 2016, 81, 5988−5997

Hz, 1H), 5.62 (d, J = 1.5 Hz, 1H), 7.54 (d, J = 1.5 Hz, 1H), 7.69 (d, J = 8.5 Hz, 2H), 8.19 (d, J = 8.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.9, 24.9, 26.7, 49.0, 63.7, 64.7, 123.5, 125.4, 128.8, 129.8, 147.4, 149.1, 167.3, 192.5. HRMS: m/z found 316.1292 (MH^+), $C_{16}H_{18}N_3O_4$ requires m/z = 316.1292. ATR: ν_{max} 3077, 1722 (C═O), 1644, 1573, 1514, 1428, 1347, 1211, 823, 702 cm^{-1}. Anal. Found: C, 60.80; H, 5.48; N, 13.16. $C_{16}H_{17}N_3O_4$ requires: C, 60.94; H, 5.43; N, 13.33.

4.3.12. 6-Benzoyl-3,3-dimethyl-5-(4-nitrophenyl)-2,3-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-1-one ***3****{3;4}*. The title compound was prepared from **1**{3} (123 mg, 0.5 mmol) and 1-phenylprop-2-yn-1-one **2**{4} (79 mg, 0.6 mmol), in 24 h. Yield: 173 mg (92%) of a yellow solid. Mp: 199−203 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (s, 3H), 1.27 (s, 3H), 2.49 (d, J = 15.9 Hz, 1H), 2.95 (d, J = 15.9 Hz, 1H), 5.90 (s, 1H), 7.40−7.43 (m, 3H), 7.51−7.54 (m, 1H), 7.62−7.64 (m, 2H), 7.82−7.84 (m, 2H), 8.20−8.22 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.1, 25.1, 49.3, 64.8, 65.0, 123.8, 124.5, 128.3, 128.7, 129.0, 131.0, 132.7, 138.1, 147.6, 149.0, 167.0, 190.1. HRMS: m/z found 378.1445 (MH^+), $C_{21}H_{20}N_3O_4$ requires m/z = 378.1448. ATR: ν_{max} 3101, 2973, 1749 (C═O), 1611, 1570, 1514, 1322, 1201, 1003, 718, 695 cm^{-1}. Anal. Found: C, 66.01; H, 4.98; N, 10.89. $C_{21}H_{19}N_3O_4 \cdot {}^1/_4H_2O$ requires: C, 66.05; H, 5.15; N, 11.00.

4.3.13. Methyl 1-(4-Chlorophenyl)-7,7-dimethyl-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazole-2-carboxylate ***3****{4;1}*. The title compound was prepared from **1**{4} (116 mg, 0.5 mmol) and methyl propiolate **2**{1} (54 μL, 0.6 mmol), in 24 h. Yield: 134 mg (99%) of a yellow solid. Mp: 110−116 °C (with previous softening). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (s, 3H), 1.23 (s, 3H), 2.41 (d, J = 15.8 Hz, 1H), 2.87 (d, J = 15.8 Hz, 1H), 3.63 (s, 3H), 5.45 (d, J = 1.5 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 1.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.1, 25.1, 49.5, 51.7, 64.0, 64.6, 116.6, 128.7, 129.4, 129.6, 133.8, 140.7, 164.1, 166.5. HRMS: m/z found 321.0997 (MH^+), $C_{16}H_{18}ClN_2O_3$ requires m/z = 321.1000. ATR: ν_{max} 3075, 2946, 1740 (C═O), 1685 (C═O), 1598, 1378, 1322, 1192, 1087, 841 cm^{-1}. Anal. Found: C, 59.37; H, 5.33; N, 8.46. $C_{16}H_{17}ClN_2O_3$ requires: C, 59.91; H, 5.34; N, 8.73.

4.3.14. tert-Butyl (2-(1-(4-Chlorophenyl)-7,7-dimethyl-5-oxo-6,7-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl)-2-oxoethyl)carbamate ***3****{4;2}*. The title compound was prepared from **1**{4} (117 mg, 0.5 mmol) and *tert*-butyl (2-oxobut-3-yn-1-yl)carbamate **2**{2} (112 mg, 0.6 mmol), in 24 h. FC: EtOAc/hexanes = 1:1. Yield: 199 mg (95%) of a yellow solid. Mp: 150−155 °C (with previous softening). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.21 (s, 3H), 1.41 (s, 9H), 2.45 (d, J = 16.0 Hz, 1H), 2.89 (d, J = 16.0 Hz, 1H), 4.01 (dd, J = 18.0, 4.6 Hz, 1H), 4.22 (dd, J = 18.0, 5.4 Hz, 1H), 5.18−5.20 (m, 1H), 5.54 (s, 1H), 7.29−7.32 (m, 2H), 7.39−7.42 (m, 2H), 7.61 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.1, 25.1, 28.4, 47.2, 49.4, 63.9, 64.6, 80.0, 122.7, 128.7, 129.3, 133.8, 140.4, 155.7, 167.1, 190.2. HRMS: m/z found 420.1681 (MH^+), $C_{21}H_{27}ClN_3O_4$ requires m/z = 420.1685. ATR: ν_{max} 3070, 1735 (C═O), 1721 (C═O), 1633, 1361, 1161, 1014 cm^{-1}. Anal. Found: C, 59.93; H, 6.46; N, 9.94. $C_{21}H_{26}ClN_3O_4$ requires: C, 60.07; H, 6.24; N, 10.01.

4.3.15. 6-Acetyl-5-(4-chlorophenyl)-3,3-dimethyl-2,3-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-1-one ***3****{4;3}*. The title compound was prepared from **1**{4} (117 mg, 0.5 mmol) and but-3-yn-2-one **2**{3} (48 μL, 0.6 mmol), in 24 h. Yield: 114 mg (89%) of a yellow solid. Mp: 137−141 °C (with previous softening). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.19 (s, 3H), 2.20 (s, 3H), 2.42 (d, J = 16.0 Hz, 1H), 2.89 (d, J = 16.0 Hz, 1H), 5.49 (d, J = 1.5 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 1.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.0, 25.1, 26.9, 49.4, 63.9, 64.7, 126.3, 128.9, 129.3, 129.5, 133.6, 140.8, 167.5, 192.9. HRMS: m/z found 305.1058 (MH^+), $C_{16}H_{18}ClN_2O_2$ requires m/z = 305.1057. ATR: ν_{max} 2980, 1726 (C═O), 1655 (C═O), 1631, 1397, 1197, 1088, 830, 678 cm^{-1}. Anal. Found: C, 59.96; H, 5.49; N, 8.59. $C_{16}H_{17}ClN_2O_2$ requires: C, 63.06; H, 5.62; N, 9.19.

4.3.16. 6-Benzoyl-5-(4-chlorophenyl)-3,3-dimethyl-2,3-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-1-one ***3****{4;4}*. The title compound was prepared from **1**{4} (117 mg, 0.5 mmol) and 1-phenylprop-2-yn-1-one **2**{4} (79 mg, 0.6 mmol), in 24 h. Yield: 140 mg (90%) of a yellow solid. Mp: 181−184 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (s, 3H), 1.24 (s, 3H), 2.45 (d, J = 16.0 Hz, 1H), 2.92 (d, J = 16.0 Hz, 1H), 5.77 (d, J = 1.5 Hz, 1H), 7.29−7.34 (m, 3H), 7.40−7.43 (m, 2H), 7.51−7.55 (m, 3H), 7.64−7.65 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.2, 25.2, 49.5, 64.6, 65.0, 125.4, 128.4, 128.68, 128.73, 129.4, 130.5, 132.6, 133.7, 138.3, 140.5, 167.0, 190.3. HRMS: m/z found 367.1205 (MH^+), $C_{21}H_{20}ClN_2O_2$ requires m/z = 367.1208. ATR: ν_{max} 2982, 1725 (C═O), 1622, 1571, 1313, 1201, 1007, 722, 697 cm^{-1}. Anal. Found: C, 68.53; H, 5.48; N, 7.56. $C_{21}H_{19}ClN_2O_2$ requires: C, 68.76; H, 5.22; N, 7.64.

4.4. Procedure for the Cu−C-Catalyzed CuAIAC Reaction. Synthesis of Compound 3*{1;1}*. A mixture of dipole **1**{1} (25 mg, 0.125 mmol), methyl propiolate **2**{1} (12.5 μL, 0.15 mmol), 10% Cu−C (25 mg), and CH_2Cl_2 (2 mL) was stirred at rt for 24 h. The catalyst was removed by filtration and washed with CH_2Cl_2 (2 × 3 mL), and the combined filtrate was evaporated in vacuo to give **3**{1;1}. The Cu−C catalyst was reused three more times following the above procedure without a decrease of conversion. When being reused, the catalyst was air-dried before each run. ^{1}H NMR data were in agreement with the literature data.[9d] For physical, analytical, and spectral data see also section 4.3.1.

4.5. Procedure for the Cu−Fe-Catalyzed CuAIAC Reaction. *4.5.1. Preparation of Cu−Fe Catalyst.* Fe powder (0.554 g, 9.92 mmol) was added to a solution of $CuSO_4 \cdot 5H_2O$ (0.50 g, 2 mmol) in water (20 mL) and the mixture was stirred on orbital shaker at rt for 20 min. The so-formed Cu-coated iron powder was collected by filtration, washed with water (3 × 20 mL) and acetone (3 × 20 mL), and dried on air to give the Cu−Fe catalyst (∼0.52 g).

4.5.2. Synthesis of Compound ***3****{2;1}*. A mixture of dipole **1**{2} (88 mg, 0.3 mmol), methyl propiolate **2**{1} (36 μL, 0.36 mmol), Cu−Fe catalyst (82 mg), and CH_2Cl_2 (3 mL) was stirred at rt for 24 h. Then a magnetic field was applied with a strong permanent magnet from the outside of the flask to hold the Cu−Fe catalyst inside. The reaction mixture was removed by decantation and the catalyst was washed twice with CH_2Cl_2 (2 × 3 mL). The combined fractions were filtered through a glass frit, and the filtrate was evaporated in vacuo to give **3**{2;1} in quantitative yield. The Cu−Fe catalyst was reused three more times following the above procedure without a decrease of conversion and yield. When being reused, the catalyst was air-dried before each run. Physical, analytical, and spectral data for compound **3**{2;1} are given in section 4.3.5. Physical and spectral data are in agreement with the literature data.[14c]

4.6. Cu-Catalyzed CuAIAC Reaction on Functionalized Polystyrene. *4.6.1. Preparation of Polystyrene-Bound Propiolic Acid* ***2****{5}*.[17] A mixture of chloromethyl polystyrene **6** (1.1 mmol/g, 1.24 g, 1.36 mmol), sodium iodide (215 mg, 1.44 mmol), propiolic acid (150 μL, 132 mg, 1.89 mmol), DMF (5 mL), and DIPEA (450 μL, 600 mg, 4.62 mmol) was stirred on an orbital shaker (300 s^{-1}) at rt for 5 days. The resin was collected by filtration; washed with DMF (2 × 5 mL), DMF−H_2O (2 × 5 mL), EtOH (2 × 5 mL), EtOH−CH_2Cl_2 (2 × 5 mL), and CH_2Cl_2 (3 × 5 mL); and air-dried to give **4**{5}. Yield: 1.333 g (100%). ATR: ν_{max} 3271 (H−C≡C), 2093 (C≡C), 1716 cm^{-1} (C═O).

4.6.2. Cu-Catalyzed Cycloaddition to Polystyrene-Bound Propiolic Acid ***4****{5}. Preparation of Polystyrene-Bound Cycloadduct* ***3****{1;5}*. A cluster of Cu wires (N = 30, l = ∼8 cm, d = 0.3 mm, ∼1.5 g) was added to a mixture of polystyrene-bound propiolic acid **2**{5} (1.1 mmol/g, 543 mg, 0.6 mmol), CH_2Cl_2 (10 mL), and azomethine imine **1**{1} (160 mg, 0.8 mmol), and the mixture was stirred on an orbital shaker (300 s^{-1}) at rt for 3 days. The cluster of Cu wires was removed from the flask, and the resin was collected by filtration; washed with CH_2Cl_2 (5 mL), CH_2Cl_2−DMF (5 mL), DMF (5 mL), CH_2Cl_2−DMF (5 mL), and CH_2Cl_2 (2 × 5 mL); and dried in vacuo at rt for 12 h to give **3**{1;5}. Yield: 595 mg (100%) of a yellow-fluorescent resin. ATR: ν_{max} 1701 cm^{-1} (C═O).

4.6.3. Preparation of Polystyrene-Bound Azomethine Imine ***1****{5}*. A mixture of benzaldehyde on polystyrene **5**{5} (0.8−1.5 mmol/g, 100 mg, ∼ 0.115 mmol), 5,5-dimethyl-3-pyrazolidinone (**4**) (34 mg, 0.30 mmol), CH_2Cl_2 (2 mL), and TFA (one drop) was stirred on an orbital shaker (300 s^{-1}) for 72 h. The polymer was collected by

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J. Org. Chem. 2016, 81, 5988−5997

filtration, washed with CH_2Cl_2 (5 × 2 mL), and dried in vacuo at rt for 12 h to give **1**{*5*}. Yield: 113 mg (100%). ATR: ν_{max} 1654 cm^{-1} (C═O of dipole), a strong formyl band at 1700 cm^{-1} is absent that is present in the starting polymer **5**{*5*}.

*4.6.4. Cu-Catalyzed Cycloaddition to Polystyrene-Bound Azomethine Imine **1**{5}. Preparation of Polystyrene-Bound Cycloadduct **3**{5;1}.* A cluster of Cu wires (N = 5, l = ∼8 cm, d = 0.3 mm, ∼0.25 g) was added to a mixture of polystyrene-bound dipole **1**{*5*} (1.1 mmol/g, 112 mg, 0.11 mmol), CH_2Cl_2 (5 mL), and methyl propiolate **2**{*1*} (20 μL, 0.22 mmol), and the mixture was stirred on an orbital shaker (300 s^{-1}) at rt for 72 h. The cluster of Cu wires was removed from the flask, and the resin was collected by filtration; washed with CH_2Cl_2 (2 × 3 mL), DMF (2 × 3 mL), and CH_2Cl_2 (3 × 3 mL); and dried in vacuo at rt for 12 h to give **3**{*5;1*}. Yield: 121 mg (100%) of a yellow-fluorescent resin. ATR: ν_{max} 1686 and 1646 cm^{-1} (C═O).

4.7. Synthesis of Polynuclear Cu−acetylide Cu−2{*1*}.[10g] A mixture of Cu powder (16 mg, 0.25 mmol), acetonitrile (5 mL), and methyl propiolate **2**{*1*} (50 μL, 0.6 mmol) was stirred in a 10 mL flask stopped with a glass stopper for 7 days until the Cu was completely consumed. A bright yellow suspension was formed. The precipitate was collected by filtration to give Cu−**2**{*1*} in quantitative yield. ATR: ν_{max} 1928, 1692 (C═O), 1430, 1211, 1181, 986, 865, 747, 641 cm^{-1}. Anal. Found: C, 32.90; H, 2.05. $C_4H_3CuO_2$ requires: C, 32.77; H, 2.06.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00945.

Copies of the NMR spectra of compounds **3**{*1−4;1−4*} and figures regarding the recyclability of Cu−C and Cu−Fe catalysts (PDF)

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Notes

The authors declare no competing financial interest.

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