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Mechanistic Insights into Copper(I)-Catalyzed Azide-Alkyne Cycloadditions using Continuous Flow Conditions

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Abstract: The copper-catalyzed azide-alkyne cycloaddition (CuAAC, "click chemistry") was studied employing copper-in-charcoal (Cu/C) and a variety of copper metal sources as "heterogeneous" catalysts. The type and pretreatment conditions of the different copper sources on the CuAAC were investigated. In addition, the effect of copper leaching from the catalyst over time and in dependence on the reaction mixture composition was studied by ICP-MS analysis in the continuous flow mode. These investigations confirm a "homogeneous" mechanism and suggest surface layer copper(I) oxide as the catalytically active species in CuAAC chemistry involving zerovalent copper metal.

Keywords: 1,3-dipolar cycloaddition; click chemistry; copper catalysis; flow chemistry; microwave chemistry; 1,2,3-triazoles

Since the development of the Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) independently by the groups of Medal and Sharpless in 2002, this transformation has attracted a significant amount of attention within the scientific community.[1,2] The reasons for the popularity of CuAAC are related to the generated 1,4-substituted-1,2,3-triazole scaffold and its chemical and biological properties, as well as to the robustness of the cycloaddition process, the high stereoselectivity and wide substrate scope.[2] Modern applications of the CuAAC are today not only widely used in classical organic/combinatorial synthesis and medicinal chemistry/drug discovery programs, but have also made a major impact in polymer/material science, and the field of chemical biology.[2]

Recent preparative synthetic advances in the field of the CuAAC include the generation of the required azides *in situ*,[3,4] or alternatively the use of continuous flow processing.[5] Performing chemical reactions under flow conditions in micro- or mesofluidic devices is of growing interest since these conditions offer a variety of advantages over macroscopic batch reactors, such as reduced consumption of reagents, high surface-to-volume ratios, and improved control over mass and heat transfer.[5] For the CuAAC, the safety aspects in combination with the inherent scalability of continuous flow processing are particularly appealing since both types of starting materials can – in principle – be generated in-line using flow chemistry.[6–9] In this communication we report new mechanistic insights into CuAAC chemistry performed both in batch and under continuous flow conditions using immobilized Cu catalysts in combination with leaching studies using ICP-MS Cu analysis.

Our initial experiments were concerned with investigating the suitability of copper-in-charcoal (Cu/C) as a catalyst for the CuAAC under continuous flow conditions. The Cu/C system was introduced by Lipshutz and Taft in 2006 as a heterogeneous, inexpensive and shelf-stable catalyst for CuAAC chemistry, with Cu_2O dispersed within the charcoal matrix implicated as the most likely catalytically active species.[10] Applying microwave heating, near quantitative yields of 1,2,3-triazole products were obtained after 3 min at 150 °C using dioxane as solvent in the absence of any additives such as base or a reducing agents.[10] Based on our recent experience with Mizoroki–Heck coupling chemistry performed with Pd/C in a dedicated high-temperature/pressure flow reactor,[11] we speculated that Cu/C would be a very suitable catalyst for CuAAC reactions under continuous flow conditions.

Using the cycloaddition of benzyl azide (**1**) and phenylacetylene (**2**) as a model reaction we initially repeated the CuAAC using the microwave conditions reported by Lipshutz and Taft.[10] We were pleased to find that full conversion to the 1,2,3-triazole **3** (Scheme 1) was obtained under a variety of experimental conditions, using different solvents and concentrations of starting material. Having continuous flow processing in mind, we noted that using acetone as a solvent the reaction not only provided complete conversion but also remained completely homogeneous – apart from the Cu/C catalyst – throughout the course of the cycloaddition process. Ultimately, suitable processing conditions involved an equimolar mixture of cycloaddition partners in 0.25 M concentration, 10 mol% Cu/C catalyst, acetone as solvent and 150 °C controlled microwave heating for 3 min. These experimental conditions provided a 94% isolated yield of pure 1,2,3-triazole product **3** by simple filtration from the catalyst and evaporation of solvent. In addition, we have studied the Cu/C catalyst system in a one-pot, three-component modification of the CuAAC process, whereby azide **1** was generated *in situ* from benzyl chloride and sodium azide in a 1:1 *t*-BuOH/H_2O mixture. This protocol, originally introduced by Van der Eycken using Cu(I) generated by comproportionation from Cu(0) and Cu(II) (Cu turnings/$CuSO_4$),[4] worked equally well and provided high yields of the desired triazole **3** (MW, 150 °C, 10 min, 93% yield).

While our work was in progress, an elegant study by Bogdan and Sach was published in the literature, where the authors have performed a variety of CuAAC transformations in the continuous-flow mode using a 0.75 mm i.d. Cu coil as a reactor.[9] Notably, without any additives [i.e., a Cu(II) source] successful cycloadditions were performed at temperatures ~150 °C using DMF/H_2O mixtures as solvent system. With this in mind, we have evaluated the catalytic activity of various sources of Cu metal in the CuAAC reaction. Applying our standard set of conditions (MW, 160 °C, 10 min) the data shown in Table 1 clearly reveal a strong dependence on surface area (powder being more effective than turnings or wire), and on the commercial supplier. In agreement with the generally accepted mechanistic hypotheses concerning the CuAAC reaction,[2] we speculated that the genuine catalytically active species in the cycloadditions using Cu(0) metal is in fact surface Cu(I). In fact, it is well known that Cu metal itself is oxidized continuously in the air even at room temperature forming non-self-protecting layers of Cu oxides of different oxidation states.[12]

In order to obtain more detailed information about the catalytically active species in CuAAC reactions involving zerovalent Cu metal catalysts, samples of Cu turnings were pretreated before being subjected to the CuAAC reaction (Table 2). For the purpose of eliminating the Cu_2O/CuO layers, the Cu turnings were first stirred in concentrated HCl prior to use, followed by a careful wash with acetone.[13] Indeed the conversion in the CuAAC was significantly reduced (Table 2, entry 2) compared to untreated Cu turnings (Table 2, entry 1). The opposite effect was achieved by pretreatment with 35% H_2O_2, a known effective oxidizing agent for Cu metal (Table 2, entry 3).[14] To further corroborate our hypothesis we additionally executed the reversed cycle of washings, i.e., previously oxidized ("activated") Cu turnings were deactivated with HCl, and HCl-cleaned ("deactivated") Cu turnings were activated with H_2O_2. The results were as expected (Table 2, entries 4 and 5) and confirmed that the catalytically active species in CuAAC chemistry involving zerovalent Cu metal is most likely connected to a surface layer of Cu_2O.[12] Thus, employing suitable reaction conditions, it may

Table 1. Cu-catalyzed cycloaddition of benzyl azide and phenylacetylene using different Cu(0) sources (Scheme 1).[a]

Entry	Cu source[b]	Conversion [%][c]
1	turnings (Strem #29-0090)	6
2	wire (Strem #93-2972)	4
3	powder (−100 mesh, Strem #93-2999)	47
4	powder (−140 mesh, Acros #196570250)	98 (92)
5	powder (−200 mesh, Aldrich #20778-0)	97 (92)

[a] *General conditions:* 0.5 mmol benzyl azide (**1**), 0.55 mmol phenylacetylene (**2**), 0.5 mequiv. Cu in 2 mL of acetone, MW, 160 °C, 10 min.

[b] Fresh bottles, used as received.

[c] Calibrated HPLC conversions. Isolated yield in parenthesis.

Table 2. Cu-catalyzed cycloaddition of benzyl azide and phenylacetylene using differently treated sources of Cu turnings (Scheme 1).[a]

Entry	Cu Treatment[b]	Conversion [%][c]
1	–	35
2	conc. HCl	11
3	35% H_2O_2	48
4[d]	conc. HCl	9
5[e]	35% H_2O_2	36

[a] *General conditions:* 0.5 mmol benzyl azide (**1**), 0.55 mmol phenylacetylene (**2**), 2.0 mequiv Cu turnings (Strem #29-0090) in 2 mL of acetone, MW, 160 °C, 10 min.

[b] Treatment involves 15 min stirring in conc. HCl or 35% aq. H_2O_2 solution, followed by acetone washes (2 × 5 mL).

[c] Calibrated HPLC conversions.

[d] Cu turnings used for the experiment described in entry 3 were dried and reused.

[e] Cu turnings used for the experiment described in entry 2 were dried and reused.

not be necessary to use a Cu(II) source for comproportionation purposes in conjunction with the use of Cu turnings, powders or coils.[1,2]

Because of the significantly higher activity and better reproducibility of Cu/C compared to the Cu metal catalysts we decided to perform our continuous-flow experiments with this catalyst. Before starting flow experimentation a control experiment involving a silicon carbide (SiC) reaction vessel and microwave heating confirmed that the rapid reaction rates achieved under microwave batch conditions were only related to a bulk temperature effect, and not to a specific interaction of the electromagnetic field with the Cu/C catalyst (see the Supporting Information for details).[15] These results ensured that the reaction times could be translated to residence times in a conventionally heated flow instrument. Flow experiments were subsequently performed in a dedicated high-pressure flow reactor (X-Cube, ThalesNano Inc.)[11] where the heterogeneous Cu/C catalyst is immobilized in a pre-packed, replaceable stainless steel cartridge (60×4 mm i.d., ~250 mg Cu/C). The catalyst cartridge can be heated to 200 °C and the reaction mixture is pumped through the cartridge using HPLC pumps at flow rates of 0.1 to 3.0 mL min^{-1} and pressures of up to 150 bar.[11] Since complete reaction homogeneity is generally required for performing flow synthesis,[5] the optimized protocol starting from isolated benzyl azide (**1**) and phenylacetylene (**2**) shown in Scheme 1 was used for the experiments described herein.

Optimization of the CuAAC reaction shown in Scheme 1 demonstrated that full conversion and a >99% isolated triazole yield were readily obtained at 170 °C and a 1.5 mL min^{-1} flow rate (20 bar set pressure) using a 0.25 M concentration of azide **1** in acetone (1.1 equivalents of acetylene **2**). Lower reaction temperatures led to incomplete conversions. Based on the measured dead volume of ~300 μL of the filled catalyst cartridge (60×4 mm i.d., 250 mg of Cu/C), a residence time over the catalyst of ~12 s can be calculated applying a 1.5 mL min^{-1} flow rate (the residence time in the complete X-Cube system is ~3 min at this flow rate). An initial evaluation of the influence of the flow rate appeared to indicate that higher flow rates would lead to increased isolated product yields. More detailed investigations of this effect, however, revealed that the higher flow rates did not influence the conversion in the CuAAC reaction, but instead led to an enhanced desorption/washing-off of the triazole product from the charcoal support. This kind of "chromatography" or "adsorption" effect has previously been observed in the context of Pd/C-catalyzed Mizoroki–Heck coupling chemistry utilizing the same flow reactor system.[11]

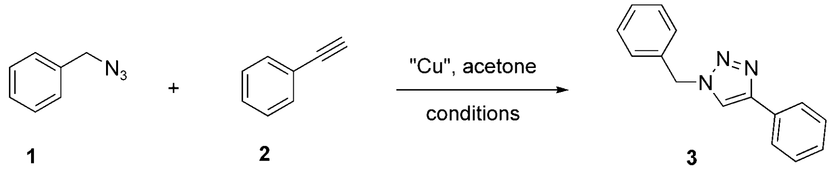
In the next phase of our experiments the leaching of Cu from the charcoal support was investigated utilizing ICP-MS. Performing reactions with "heterogeneous" transition metal catalysts under continuous flow conditions provides a unique opportunity to gain mechanistic insights otherwise not easily available.[11] In contrast to standard batch processing, leached metal will not simply be readsorbed onto the support after the catalytic cycle is completed, but is removed from the support by the flow process. In the experiments described in Table 3 we have determined the leaching of Cu from a standard X-Cube catalyst cartridge [250 mg, 8.7% (w/w) Cu/C, 22 mg Cu] during the CuAAC reaction of benzyl azide (**1**) and phenylacetylene (**2**) under optimized flow conditions (Scheme 1). Keeping temperature, pressure, and flow rate constant, the only changes made were related to the composition of the reaction mixture processed through the catalyst cartridge. The results summarized in Table 3 clearly indicate a homogeneous catalysis for the CuAAC reaction with the charcoal acting as a

Table 3. Leaching of Cu from Cu/C catalyst for the cycloaddition of benzyl azide (**1**) and phenylacetylene (**2**) under X-Cube flow conditions (Scheme 1).[a]

Entry	Reaction mixture composition	Leaching [μg Cu][b]
1	acetone	2.1
2	acetone/**2**	3.6
3	acetone/**1**	59
4	acetone/**2**/**1**	30
5	acetone/Et_3N	38.6
6	acetone/Et_3N/**2**	18.7
7	acetone/**3**	71

[a] Complete reaction mixture composition: 0.25 mmol benzyl azide (**1**), 0.27 mmol phenylacetylene (**2**), acetone (1 mL), Cu/C catalyst in cartridge (8.7% Cu/C, 250 mg, 22 mg Cu). *Conditions:* 170 °C, 20 bar, 1.5 mL min^{-1} flow rate. A fresh cartridge was used for every run. See the Supporting Information for details.

[b] Determined by ICPMS analysis of the product contained in a 7.5 mL fraction.



Scheme 1. Cu-catalyzed cycloaddition of benzyl azide and phenylacetylene.

reservoir for Cu involving a release-recapture mechanism.[16] Significant leaching of Cu metal was observed when the full reaction mixture was passed through the Cu/C cartridge (Table 3, entry 4). Interestingly, it was established that the leaching of Cu was minimal when a solution of the terminal alkyne **2** was passed through the Cu/C catalyst cartridge (entry 2), comparable to the background leaching observed with pure solvent (entry 1). In contrast, leaching for the azide cycloaddition partner **1** was 20 times higher, indicating a strong complexation of the organic azide with the Cu(I) or Cu(II) species present in the Cu/C matrix (entry 3). These results seem to contradict the generally accepted mechanistic hypothesis for the CuAAC reaction involving a distinct Cu-alkyne complex as the key intermediate,[2,17] and may here be related to the base- and ligand-free conditions, the solvent system, or the comparatively high temperatures used in our studies. Clearly, quite stable complexes between organic azides and Cu(I/II) ions have been reported in the literature providing support for the observed leaching of Cu by azide **1** in our flow experiments.[18] In addition, we have performed leaching experiments using Et_3N which is frequently used as base in the CuAAC to gain information about a potential base-catalyzed pathway.[1,2] Indeed, Et_3N enhances the leaching of Cu from the solid support under our reaction conditions (entry 5). The leaching of a mixture of alkyne **2** and Et_3N is in the same magnitude, although a slightly lower value was obtained (entry 6).

For the reaction mixture itself (entry 4) processed on a 0.25-mmol scale (1 mL of reaction mixture in acetone) 0.14% of the Cu were leached from the Cu/C catalyst, resulting in a Cu contamination of the triazole product **3** of ~600 $\mu g\,g^{-1}$, far above the maximum allowed Cu contamination in pharmaceuticals of 15 $mg\,kg^{-1}$.[19] In order to scavenge the leached Cu from the reaction mixture, in-line scavenging protocols using either Quadrapure™ TU (thiourea) resin[20] or activated charcoal (Norite type A) were evaluated. For this purpose both scavengers were packed into empty stainless steel cartridges (60 × 4 mm i.d., ~350 mg) and the cartridges placed into the X-Cube reactor in sequence to the Cu/C catalyst cartridge. Quadrapure™ TU is a functionalized polystyrol resin, frequently used for metal scavenging *via* thiol complexation and has been successfully applied previously in CuAAC reactions to remove Cu impurities.[7,9] Activated charcoal represents a less costly alternative and possesses substantial metal scavenging properties,[20] although in the case of charcoal the scavenging originates from adsorption of the metal on the surface, thus the interaction is a lot weaker compared to the thiol complexation of Quadrapure™ TU.[20] We were pleased to see that on applying the CuAAC flow reaction conditions given in Table 3 (entry 4) both scavenging methods decreased the Cu contamination from 600 $mg\,kg^{-1}$ to acceptable levels (6 $mg\,kg^{-1}$ for charcoal, <1 $mg\,kg^{-1}$ for Quadrapure™ TU).

In order to obtain information on the lifetime of the Cu/C catalyst cartridge for larger scale preparations, and on the capacity of the charcoal scavenging cartridge we have performed a scale-up experiment using the X-Cube flow reactor. In the event, ~1 L of reaction mixture (0.25 M azide **1** + 0.27 M alkyne **2** in acetone) were processed through the flow reactor fitted with both a catalyst and a scavenging cartridge over a period of 11 h. Each hour a sample was taken, which was analyzed for conversion (HPLC-UV), Cu contamination (ICP-MS) and isolated yield. The results are summarized in Table 4. During the first 6 h nearly full conversion to 1,2,3-triazole **3** was observed and we were able to isolate 32 g of pure triazole product (>99% yield, 98% HPLC purity). After this period conversion dropped significantly and the isolated crude products were contaminated with substantial amounts of both azide and alkyne starting materials. Disappointingly, all product fractions contained substantial amounts of Cu metal despite the presence of the Norite scavenging cartridge. Apparently, the scavenging capacity of the Norite charcoal for Cu is too low to cope with the amounts of Cu released from the Cu/C catalyst cartridge in a large-scale experiment.[20] Cu analysis by ICP-MS of the spent Cu/C catalyst cartridge after 11 h of processing revealed that >60% of the originally impregnated Cu had been leached (the Cu loading decreased from 8.7 to

Table 4. Conversion/yield and leaching of Cu from Cu/C catalyst for the cycloaddition of benzyl azide (**1**) and phenylacetylene (**2**) under X-Cube flow conditions (Scheme 1).[a]

Entry	*t* [h]	Yield [%]	Conversion [%][b]	Cu [$mg\,kg^{-1}$][c]
1	1	93	>99	297 ± 6
2	2	100	>99	260 ± 50
3	3	100	>99	199 ± 40
4	4	100	>99	179 ± 14
5	5	100	>99	156 ± 11
6	6	100	92	162 ± 12
7	7	99[d]	65	87 ± 2
8	8	99[d]	59	74 ± 1
9	9	96[d]	40	62 ± 2
10	10	92[d]	39	76 ± 1
11	11	95[d]	29	47 ± 1

[a] *Conditions:* 0.248 mol benzyl azide (**1**), 0.267 mol phenylacetylene (**2**), acetone (990 mL), Cu/C catalyst cartridge (8.7% Cu/C, 250 mg, 22 mg Cu), Norite A scavenging cartridge (350 mg). Conditions: 170 °C, 20 bar, 1.5 $mL\,min^{-1}$ flow rate. See the Supporting Information for details.

[b] Calibrated HPLC conversion.

[c] Determined by ICP-MS analysis of the product. Mean value of three measurements.

[d] Crude product contaminated with starting materials.

3.3%). At this point we performed an additional control experiment investigating the complexation properties of the 1,2,3-triazole product **3** for Cu. As demonstrated in Table 3 (entry 7), the triazole product itself is capable of coordinating to Cu and leaches Cu metal from the Cu/C catalyst in substantial amounts. Therefore, the ineffectiveness of the charcoal-based scavenging cartridge is not surprising, since the formed triazole product will constantly remove Cu metal from the charcoal support. It is therefore also not practical to use the scavenger cartridge containing adsorbed Cu as a "catalyst cartridge" by reversing the flow direction. Notably, 1,2,3-triazoles are known to form strong complexes with Cu(I) salts.[21] Although the scavenging capacity of Quadrapure™ TU is three times higher (Norite A: 0.06 mequiv. g^{-1}, Quadrapure™ TU: 0.17 mequiv. g^{-1})[20] for large-scale CuAAC reactions both methods are clearly unsuitable.

Ultimately, we decided to remove Cu impurities off-line by a simple washing step with ethylenediaminetetraacetic acid (EDTA), a strong complexation agent for Cu species (stability constant = 18.80 L mol^{-1}).[22] For this purpose, the product with the highest Cu contamination from the scale-up experiment described above (Table 4, entry 1, 297 mg kg^{-1}) was dissolved in CH_2Cl_2 and extracted 3 times with an aqueous EDTA solution. This simple aqueous washing step reduced the Cu levels to 2 mg kg^{-1}, thus being almost as efficient as the Quadrapure scavenger.

In conclusion, we have investigated continuous-flow methods for the Cu(I)-catalyzed cycloaddition of organic azides and terminal alkynes (CuAAC reaction) that rely on the use of copper-in-charcoal (Cu/C) as an immobilized source of Cu catalyst. By studying different Cu sources and pretreatment methods it has become clear that the catalytically active species in CuAAC chemistry involving zerovalent Cu metal is most likely connected to a surface layer of Cu_2O. By performing leaching experiments it was demonstrated that a homogeneous mechanism is in operation using Cu/C as a catalyst. Under flow conditions, this leads to leaching of Cu from the heterogeneous catalyst. On a small scale efficient in-line scavenging can be performed using activated charcoal or Quadrapure™ TU resin, while for large-scale experiments an extractive work-up with EDTA is the method of choice.

Experimental Section

Cu-Catalyzed Cycloaddition of Benzyl Azide (1) and Phenylacetylene (2) in Continuous Flow Mode (Scheme 1)

A CatCartridge packed with Cu/C [60 × 4 mm i.d., ~250 mg Cu/C, 8.7% (w/w) loading, 0.34 mmol] was placed in the cartridge holder of the X-Cube flow reactor.[11] The cartridge was primed with acetone for 10 min at a flow rate of 1.5 mL min^{-1}, then the instrument was turned on: $T = 170$ °C, 1.5 mL min^{-1} flow rate and $p = 20$ bar. When the set parameters were reached (3–4 min) the reaction mixture, containing benzyl azide (**1**) (32 μL, 34 mg, 0.25 mmol) and phenylacetylene (**2**) (30 μL, 28 mg, 0.27 mmol) in acetone (1 mL), was introduced into the flow system. Subsequent to the introduction of the reaction mixture, the inlet tube was placed back into the solvent reservoir. After 20 min of collection the experiment was stopped and the obtained solution was concentrated under reduced pressure to give pure 1,2,3-triazole **3** as a pale yellow solid; yield: 59 mg (99%); mp 132 °C (lit. mp[23] 132–133 °C); ^{1}H NMR (300 MHz, DMSO): $\delta = 8.67$ (s, 1 H), 7.86 (m, 2 H), 7.52 (m, 8 H), 5.65 (s, 2 H); ^{13}C NMR (75 MHz, DMSO): $\delta = 147.1$, 136.5, 131.1, 129.4, 129.3, 128.6, 128.4, 125.6, 122.0, 53.5.

For the large-scale run (Table 4), the X-Cube flow reactor was prepared as for the small-scale experiments (*vide supra*), but with a scavenging cartridge in the second cartridge holder containing activated charcoal Norite type A (350 mg). When the settings were reached the tube was changed to the reaction mixture, containing benzyl azide (**1**) (32 mL, 34 g, 250 mmol) and phenylacetylene (**2**) (30 mL, 28 g, 270 mmol) in acetone (990 mL). For a period of 11 h each hour the collection flask was changed and 100 μL of the obtained solution were taken to determine the conversion. The solvent was evaporated to determine the isolated yield and the product was subjected to ICP-MS analysis. The product fractions isolated from entries 1–6 (Table 4) were combined to provide 32 g of triazole **3**. The analytical and spectral data of this material were as described for the small-scale experiments.

Supporting Information

General experimental details and further description of experimental procedures are available as Supporting Information.

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