

Aminopropyl-silica supported Cu nanoparticles: an efficient catalyst for continuous-flow Huisgen azide-alkyne cycloaddition (CuAAC)

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Abstract

Cu nanoparticles prepared by metal vapor synthesis (MVS) were immobilized on 3-aminopropyl functionalized silica at room temperature. HRTEM analysis of the catalyst showed that the copper nanoparticles are present with mean diameters limited in the range 1.0 – 4.5 nm. TPR analysis were performed in order to study the oxidation state of the supported copper nanoparticles. The supported catalyst was used both in batch and in a packed-bed reactor for continuous-flow CuAAC reaction. The activation of the copper catalyst by reduction using phenyl hydrazine in continuous flow conditions was demonstrated. Along with the high catalytic activity (productivity up to 1689 mol/mol), the catalyst can be used several times with negligible Cu leaching in the product (< 9 ppm), less than allowed Cu contaminant in pharmaceuticals. The applicability of packed-bed flow reactor was showed by sequentially converting different substrates in their corresponding products using same column.

Keywords:

Catalysed Azide-alkyne cycloaddition, supported copper nanoparticles, flow-chemistry, metal vapor synthesis

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1. Introduction

The regioselective Cu(I) catalyzed 1,3-dipolar azide-alkyne cycloaddition leading to 1,4-disubstituted-1,2,3-triazoles (CuAAC) was independently introduced by the groups of Meldal and Sharpless.[1-3] Since then, the broad applicability, ease reliability and high efficiency of this reaction stimulated an increasing interest for a wide range of synthetic applications, from drug discovery to material science and chemical biology.[4-12] Different copper sources have been described for the CuAAC, including simple halide salts and coordination complexes in homogeneous or heterogeneous form.[13-22] From the last decade nanostructured Cu systems are being explored in both homogeneous and heterogeneous form in CuAAC reactions.[13,14,23-30] The combination of supported Cu-based catalysts and flow reactor technologies represent a step forward in terms of reliability, time, safety, and costs over traditional batch reaction conditions. Recently, considerable efforts in this direction have been devoted to the preparation of innovative Cu-based catalysts by using different strategies to perform CuAAC in flow.[31-38] However, the development of highly recyclable heterogeneous systems with a copper contamination content into the final product at the acceptable levels, still remains a challenge.[35]

Here we report the preparation of Cu nanoparticles supported on 3-aminopropyl functionalized silica (APSiO₂) by metal vapor synthesis (MVS) technique and their use as catalyst both in batch and in continuous-flow Huisgen azide-alkyne cycloaddition (CuAAC). Supported Cu catalyst showed remarkable activity and stability in continuous-flow CuAAC with a very low Cu leaching in the product. In addition, the activation and re-generation of the catalyst by flowing phenyl hydrazine as a reducing agent for copper, was demonstrated. In order to better understand the morphology and the active phase of the supported copper nanoparticles, high resolution electron microscopy and temperature programmed reduction (TPR) analysis, both in the pristine state and after use in catalysis, were performed.

2. Experimental

2.1. General

All the reactions involving sensitive compounds were carried out under dry argon by using conventional Schlenk technique. All anhydrous solvents were either purchased in Sure/Seal™ bottles or dried by standard procedure. Cu shots, 2-8 mm, 99.999 % trace metals basis, were purchased from Strem Chemicals. Acetone (Aldrich product) was dried over molecular sieves and stored under dry argon. 3-Aminopropyl functionalized silica gel (40 – 63 μm, extent of labelling: ~1 mmol/g NH₂) was purchased from Silicycle. If not noted otherwise, the other compounds were used as received. TLC analyses were carried out with Macherey-Nagel ALOX-25 UV254 plates (0.25 mm) and chromatography purifications with Merck 9385 flash grade silica-gel (230-400 mesh). Unless noted otherwise, ¹H and ¹³C NMR spectra were recorded as CDCl₃ solutions on a Varian INOVA-600 spectrometer operating at 600 MHz and 150 MHz for ¹H and ¹³C, respectively. Chemical shifts are reported in ppm relative to TMS (¹H) or to the solvent (¹³C, CDCl₃ at 77.16 ppm). Data are summarized as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, td = triplet of doublets and br = broad), coupling constants, and integration. Electrospray mass analyses were carried out in the positive [MS(ESI+)] or negative [MS(ESI-)] ion mode on methanolic solutions, with a Perkin-Elmer-Sciex Api 3000 spectrometer. Inductively Coupled Plasma-Optical Emission Spectrometer (ICP-OES; iCAP 6200 Duo upgrade, Thermofisher). For ICP-OES, a sample (1 mL) of solution was heated over a heating plate in a porcelain crucible in the presence of aqua regia (2 mL) for four times, dissolving the solid residue in 0.5 M aqueous HCl. The limit of detection (lod) calculated for copper was 0.01 ppm. Electron micrographs were obtained with a Zeiss LIBRA 200FE, equipped with: 200 kV FEG, in column second-generation omega filter for energy selective spectroscopy (EELS) and imaging (ESI), HAADF STEM facility, EDS probe for chemical analysis, integrated tomographic HW and SW. Before introduction in the instrument, the samples were ultrasonically dispersed in isopropyl alcohol and a drop of the suspension was deposited on a holey carbon gold grid (300 mesh). The

histograms of the metal particle size distribution for the Cu samples were obtained by counting at least 500 particles onto the micrographs. The mean particle diameter (d_m) was calculated by using the formula $d_m = \sum d_i n_i / \sum n_i$, where n_i is the number of particles with diameter d_i . Temperature Programmed Reductions (TPR) profiles were recorded with a modified version of the Micromeritics Pulse Chemisorb 2700 apparatus. The catalysts (50 mg) were diluted with quartz, pre-treated under Ar at 150 °C and reduced at 8 °C/min with a 8% H₂/Ar mixture at 15 mL/min.

2.2. Preparation of Cu nanoparticles supported on 3-aminopropyl-silica (Cu/APSiO₂)

The synthesis of Cu/acetone solvated metal atoms (SMA) was carried out in a static MVS reactor, similar to those previously described.[39,40] In a typical experiment, copper vapors, generated by resistive heating of an tungsten-alumina crucible filled with ca. 500 mg of copper shots, were co-condensed at liquid nitrogen temperature with acetone (100 mL) in the glass reactor chamber of the MVS apparatus in ca. 2 hours ($P = 5 \times 10^{-4}$ mBar). The reactor chamber was warmed to the melting point of the solid matrix (ca.-80 °C) and the resulting brown solution was siphoned at low temperature in a Schlenk tube and kept in a refrigerator at -40 °C. The content of the copper in SMA was 0.4 mg / mL, as determined ICP-OES analysis. A portion of 50 mL (20 mg of Cu) was added to a suspension of 3-aminopropyl functionalized silica support (2 g, previously degassed for three times at 25°C and kept under dry argon atmosphere) in acetone (20 mL). The mixture was stirred for 12 h at room temperature. The colourless solution was removed and the light-brown solid, containing 1 wt. % of Cu, was washed 3 times with n-pentane (20 mL) and dried under reduced pressure. The same procedure was used to prepare Cu/APSiO₂ system containing 0.55 wt.% of Cu. The catalysts were stored under dry argon atmosphere by using standard Schlenk techniques.

2.3. CuAAC reaction in batch conditions: general procedure

A 25-mL Schlenk tube fitted with a glass frit and stopcock side arm, was charged under argon with Cu/APSiO₂ (65 mg, 1 wt.% of Cu, 0.01 mmol, 0.02 equiv.), and dry THF (2 mL), followed by benzyl azide (62.5 μL, 0.5 mmol, 1 equiv.) and phenyl acetylene (65.9 μL, 0.6 mmol, 1.2 equiv.). The flask was closed under argon and kept stirring at 25°C, for the time t (Table 1). Then the mixture was filtered through the enclosed frit, collecting the filtrate and catalyst rinses with THF (2 × 2 mL). For the regeneration, the catalyst was treated with the solution of PhNHNH₂ (34 μL, 0.35 mmol) in THF (5 mL) for 15 h at room temperature. Then catalyst was washed with THF (2 × 5 mL), dried under argon flow and used in next run.

2.4. Control experiments for catalytic activity in solution.

Each of two 25 mL Schlenk tubes (A and B) fitted with a medium porosity glass frit and stopcock side arm, was charged under argon with Cu/APSiO₂ (65 mg, 1 wt.% of Cu, 0.01 mmol, 0.02 equiv.). The catalyst in Schlenk-A was pre-activated with PhNHNH₂ (9.8 μL, 0.1 mmol), washed with THF, and dried as above, while the catalyst in Schlenk-B was used in its pristine form. Each tube was charged with THF (2 mL), benzyl azide (0.5 mmol, 1 equiv.) and phenyl acetylene (0.6 mmol, 1.2 equiv.), sealed under argon and kept stirring at 25°C, for 2 h. Then the mixtures were filtered through the enclosed frit under argon into another Schlenk tube. NMR analysis of small amount of mixture from Schlenk-A and Schlenk-B at this stage showed 50 and 35 % conversion, respectively. Keeping reaction mixture at 25°C under argon for additional 4 h showed only slight increase in conversion of benzyl azide to 1,2,3-triazol product (See Figure 2S).

2.5 Preparation of Cu/APSiO₂ packed-bed reactor

Packed-bed reactor was prepared in a commercially available PTFE tubing with Luer-lock fitting (Figure. 1S, 161 × 1 mm i.d.). As shown in Fig. 1, glass wool and a piece of smaller PTFE tube (o.d. 1/16") were used as a frit at the tubing end devoid of the Luer-lock fitting. Catalyst was packed by sucking Cu/APSiO₂ from Schlenk tube with the help of vacuum. In

order to keep the catalyst bed in place, glass wool and a short piece of 1/16" o.d. PTFE tubing was also placed at the other end of the reactor.

2.6 CuAAC reaction under continuous-flow conditions: general procedure

The Luer-lock PTFE tubing packed with Cu/APSiO₂ (190 mg Cu/APSiO₂, 1 wt.% or 230 mg 0.55 wt% Cu loading, respectively) was connected to a 5 mL SGE Gas-Tight syringe and flushed with dry THF for 30 min at 50 $\mu\text{L}\cdot\text{min}^{-1}$ flow rate. The CuAAC reaction was then carried out at 25°C, by flushing the solution of reagents (benzyl azide (**1**), 3.75 mmol, 1 equiv.; phenyl acetylene (**2**), 4.5 mmol, 1.2 equiv.; solvent = THF, 15 mL) through the reactor at 50 $\mu\text{L}\cdot\text{min}^{-1}$ flow rate. For regeneration, the reactor was flushed with PhNHNH₂ (103 μL , 1.05 mmol) in THF (5 mL) at 50 $\mu\text{L}\cdot\text{min}^{-1}$ flow rate. For the runs carried out in presence of reducing agent, PhNHNH₂ (30 μL , 0.30 mmol) was used in the feed mixture. The catalyst was washed with anhydrous THF (2 x 5 mL) after each run as well as after regeneration. The copper content in the crude product was determined at this stage, by ICP-OES analysis of the combined eluates from each run. For purification purposes, the reaction mixture was treated with water (20 mL) and extracted with CH₂Cl₂ (2 x 15 mL). The combined organic layers were dried over Na₂SO₄, the volatiles were removed with a rotary evaporator and the residue was purified by flash chromatography (SiO₂, *n*-hexane:AcOEt = 3:1).

3. Results and Discussion

3.1 Preparation and characterization of Cu nanoparticles supported on 3-aminopropyl functionalized silica (Cu/APSiO₂)

Cu nanoparticles were prepared by MVS technique [41,42] and supported on APSiO₂ (See 2.2). The MVS approach allowed to deposit very small copper nanoparticles (< 5 nm) at room temperature directly in its reduced form, so that, calcination and activation processes, which can eventually

modify the structure of hybrid organic/inorganic support, was avoided. The choice of amino-functionalized silica was dictated by the ability of primary alkyl amines to stabilize Cu nanoparticles,[43] and the strong tendency of amino functionalized silica to bind copper species.[44-48]

Transmission electron microscopy (TEM) analysis was performed in order to study the metal particle size distribution of the Cu/APSiO₂ samples. Copper nanoparticles turned out to be highly dispersed on the functionalized silica support and mainly present in a narrow size distribution (ranging 1.0 - 4.5 nm), with an average diameter close to 2.5 nm (Figure 1). A very low amount of larger particles ranging from 10-15 nm in diameter, were also detected.

[Figure 1, near here]

In order to investigate the crystalline phase of starting Cu (0) nanoparticles obtained by MVS approach, high resolution TEM analysis were performed on the Cu/APSiO₂ catalyst (Figure 2).[49] Lattice planes extend to the whole particle without any stacking faults or twins, indicating their single crystalline nature. Lattice fringe analysis recorded on larger Cu particles (> 10 nm, Figure 2A) exhibited spots in the FFT pattern at 2.1 Å that are ascribed to the spacing of (1 1 1) planes of the face centered cubic (fcc) structure of metallic Cu.[50] Besides, the FFT pattern of smaller Cu nanoparticles (< 5 nm) showed spots at 2.5 Å which can be attributed to the (002) lattice spacing of Cu(II) oxide (Figure 2B).[51] Moreover, high resolution micrographs revealed an amorphous phase bonded to the surface of the Cu particles that can be due to the presence of the residual APSiO₂ support. The data showed that the starting small Cu nanoparticles prepared in their reduced form are readily oxidised after exposition in air.

[Figure 2, near here]

Temperature Programmed Reduction (TPR) was carried out in order to get detailed information about the nature, oxidation state and reducibility of supported Cu catalyst.[52] The analysis consists in a reductive treatment of the catalyst under controlled temperature program and hydrogen concentration conditions. The reducibility of the supported phase strongly depends on the particles dimension, the metal oxidation state and the interaction with the matrix used as the support. The TPR of the Cu/APSiO₂ (Figure 3a) shows a narrow peak with a maximum at 260 °C, that further confirms the presence of very uniform and small particles that easy reduce under H₂ flow. The reduction temperature is in agreement with the presence of a Cu(II) oxide, as detected by HRTEM.[52]

[Figure 3, near here]

3.2 Catalytic behaviour of Cu/APSiO₂ catalyst.

In order to evaluate the catalytic efficiency of the supported Cu-nanoparticles, the Cu/APSiO₂ system was first employed under batch reaction conditions (Table 1).

[Table 1, near here]

We were pleased to find that full conversion of **1** to the 1,2,3-triazole product **3** was achieved in 6 h by using 2 mol. % of Cu catalyst at room temperature. Remarkably, the reaction proceeded in the absence of any basic additive, suggesting that the primary amine groups on the support could play a dual role, as a stabilizer of Cu particles and as a heterogeneous base. The recovered catalyst could be reused in next 3-runs (entries 1-4, Table 1), albeit at the expense of a steady decrease of the specific activity (*SA*). The ICP-OES analysis showed a very low amount of Cu species leached in the reaction mixture after each catalytic run (< 0.05 wt.% of the total available Cu content, corresponding to 0.39 ppm in solution, entries 1-4, Table 1). Given the negligible metal leaching, oxidation of the Cu particles to less active Cu(II) oxide, as also evidenced

by HRTEM and TPR analysis, was therefore considered as the most likely explanation of the loss of catalytic activity on recycling.[53]

In order to test this hypothesis, the effect of the treatment of the Cu/APSiO₂ catalyst with phenyl hydrazine (PhNHNH₂) was evaluated. The use of this reducing agent for selectively obtaining Cu(I) species has been reported in different reactions.[54,55] Interestingly, the SA of the PhNHNH₂-treated system was almost doubled with respect to the non-activated catalyst (entry 5 vs. entry 1). TPR analysis of the PhNHNH₂-treated system (Figure 3b) exhibited a shift of the reduction peak at higher temperature (500 °C) and a shoulder at around 400 °C. This change in the TPR profile confirms that a new copper phase appears after the treatment with phenyl hydrazine, which can be attributed to formation of Cu₂O phase.[56] Recycling this catalyst showed similar decreasing trend of activity as that of first set of reaction; nonetheless pre-activation allowed a more effective use of supported catalyst, as higher SA values were noticed (entries 5-7 vs. entries 1-4). These results agree with the previously reported evidences on the role of Cu(I) as catalytically active species in CuAAC reaction. Indeed, as demonstrated by theoretical and experimental studies, the reaction mechanism involves the initial formation of Cu(I)-acetylide species followed by the azide attack.[41,57-68] On the other hand, the ICP-OES data showed comparatively larger amounts of copper species released in the reaction mixture under these conditions. From the above results it was clear that PhNHNH₂ is able to reduce the oxidized surface layer of copper particles and keep it in the active state, but at the same time it favors to some extent the release of the metal in the reaction mixture.[69] In order to establish the nature of the catalytic systems we monitored two test reactions performed in batch conditions with the Cu/APSiO₂ system untreated and pre-treated with phenyl hydrazine, respectively (Figure 2S). After conducting the reaction of phenylacetylene and benzyl azide for 2 h, 1,2,3-triazole was produced in a yield of 35 % (untreated Cu/APSiO₂) and 50 % (pre-activated Cu/APSiO₂), respectively. After that the catalysts were removed from the reaction vessels and the reaction were stirred for further 4 h at 25°C in absence of the catalysts a further conversion of less than 5% was observed. The results point out the significant heterogeneous

contribution of the copper-based catalyst confirming that the click reaction can occur at the surface of the supported copper particle, as recently reported. [70]

The catalytic behavior of MVS-derived Cu catalyst was compared with that of previously reported CuI immobilized on APSiO₂ (CuI/APSiO₂). [71] For this purpose CuI/APSiO₂ catalyst was prepared following the reported procedure. [70] Despite its easy preparation and high SA (entry 8), freshly prepared CuI/APSiO₂ turned out to suffer from a nearly one order of magnitude larger metal leaching (16% of total Cu content) than the MVS catalyst. Not surprisingly this led to a significant drop of catalytic activity upon recycling CuI/APSiO₂ (entry 9) and the inability to recover the initial performance by treatment with PhNHNH₂ (entry 10).

With these promising results in hand we set out to evaluate the performance of this system under continuous flow conditions. The flow experiments were carried out using a home-made reactor packed with Cu/APSiO₂. [72] Given the findings in the batch runs, the catalyst was subjected to pre-activation in flow, by flushing the reactor with PhNHNH₂ in THF. After brief initial optimization of flow rate, 3.75 mmol of **1** was quantitatively converted in 5 h into the corresponding 1,2,3-triazole product **3** at 50 μL min⁻¹ (Table 2, entry 1).

[Table 2, near here]

The same flow reactor was employed next in two additional runs, without any intermediate regeneration of the catalyst (entries 2-3). Even though the recorded SA values were higher than obtained in batch (Table 2, entries 1-3 vs. Table 1, entries 5-7), a steady reduction of the conversion was noted in the course of the successive cycles. Reasoning that the activity decrease could be due to the partial oxidation of the catalyst by adventitious oxygen, TPR analysis was performed on a sample of Cu/APSiO₂ pre-reduced with PhNHNH₂ and then exposed to air (Figure 3c).

Interestingly, the reduction profile of the air-exposed sample showed a relatively small peak with a maximum at around 250 °C, which can be traced back to the formation of the CuO phase. At the same time, the broad peak with shoulder at higher temperature, related to Cu₂O nanoparticles, was

still present, thus showing that only partial re-oxidation of the metal occurs when the phenylhydrazine-treated catalyst is handled in air in the dry state. Moreover, comparatively lower copper leaching was observed in continuous-flow runs than in batch. This could be explained by the reduced mechanical stress on the catalyst with respect to the stirred-flask conditions where, indeed, some grinding of silica particles by magnetic stirring was noticed. Furthermore, the catalytic activity was increased significantly if the flow reactor was regenerated before next use by flushing with PhNHNH₂ (1.05 mmol, 0.21 M in THF) (entry 4) and restored completely when the reducing agent (0.3 mmol, 0.02 M) was included in the reaction feed (entry 5). With this latter modification the catalyst provided rather constant SA values in subsequent runs (entries 6 and 7) albeit, as already noticed in batch, at the expense of a some increase in the copper leaching (entries 4-7 vs. 1-3).

Overall the packed-bed reactor could be used effectively for seven times (entries 1-7), thus obtaining higher total productivity of catalyst ($P_n = 727$)[73] than in batch ($P_n = 200$ and 150 for the two sets of reactions, Table 1 entries 1-4 and 5-7, respectively). The amount of copper present in the combined products from all the flow reactions (53 ppm) was much less than reported for other supported Cu-systems.[31-38] Nonetheless, the leaching level in these initial experiments was still above the generally accepted Cu contamination in pharmaceuticals (15 mg kg⁻¹).[35] In order to solve this problem we speculated that lowering the amount of Cu on APSiO₂ could increase the stability of supported nanoparticles, due to the availability of comparatively more amino groups on the silica surface. Moreover, decreasing the reducing agent to the minimum amount required for keeping the catalyst in the active form could help to limit the metal dissolution.

To investigate the assumptions made above, a new batch of catalyst with lower Cu loading (0.55 wt.%) was prepared and second set of flow experiments were carried out (Figure 4). Despite the comparatively lower amount of Cu immobilized in the device, the reactor was still able to quantitatively convert **1** to the 1,2,3-triazole product **3** at 50 μL min⁻¹ flow-rate (run 1, Figure 2). After the initial activation, a minute amount of PhNHNH₂ in the feed (0.10 mmol, 0.007 M) was

able to keep the catalyst active for the next five-runs. Afterwards a clear decrease in activity was noticed from Run 6 to 8. Regeneration at this stage with PhNHNH₂ in THF permitted restoring the activity of catalyst to a large extent (Runs 9 and 10), while almost the initial conversion could be attained by decreasing the flow-rate to 25 μ L/min and adding a larger amount of reducing agent (0.05 M) to the feed (Runs 11 and 12). Comparison of the results of Figure 4 with those obtained in the initial set of flow experiments (Table 1, entries 11-17) confirmed the anticipated advantages of using Cu/APSiO₂ (0.55 wt.%) instead of Cu/APSiO₂ (1.0 wt.%). Indeed, with proper modification of the reaction conditions the former could be used very effectively for 12 times and provided notably higher and stable SA values than the latter. As a consequence, the total productivity obtained with Cu/APSiO₂ (0.55 wt.%) in flow ($P_n = 1689$) was more than two times larger of that achieved with Cu/APSiO₂ (1.0 wt.%) under comparable conditions (vide supra).[74] Most importantly, ICP-OES data for all the flow reactions showed now very low copper leaching in the reaction mixture (8.1 ppm)[75], which is below the maximum allowed limit for pharmaceuticals and demonstrates the unique features of the nanostructured MVS system described in this work with respect to bulk copper catalysts and devices reported to date.[31,34-37]

[Figure 4, near here]

In order to further demonstrate the applicability of our packed-bed flow reactor, the substrate scope was briefly examined (Table 3). A new device containing Cu/APSiO₂ (0.55 wt. %) was prepared and employed to sequentially promote in continuo the CuAAC reaction of different substituted azides (**1a-d**) with phenylacetylene. Functional groups on the azide partner seems not to have a decisive effect on the catalytic activity, as benzyl azides with substituents at *meta* and *para* position reacted to give the corresponding 1,2,3-triazole products **3a-d** in essentially quantitative yields. Remarkably, the same packed-bed reactor was used for running CuAAC reaction of the four different substrates, by intermediate washing of catalyst bed with THF and treatment with

PhNHNH₂.

[Table 3, near here]

Conclusions

New 3-aminopropylsilica supported copper catalysts have been developed, which showed remarkable activity and recyclability in continuous-flow CuAAC. With respect to other immobilized Cu catalysts reported to date, including nanostructured ones, [35,36,76-81] these novel systems displayed improved performances especially for what it concerns the low metal leaching and extended re-use under optimized conditions. Arguably, these unique properties can be traced back to the use of MVS-derived Cu nanoparticles and the possibility to prepare, by this technique, supported metal catalyst containing particles in the low nanometer range and without contamination by foreign substances. Moreover, the results confirmed that the 3-aminopropylsilica support is able to stabilize Cu particles without compromising the catalytic activity. As a matter of facts, the flow-reactions positively compete with the batch ones, thus affording larger quantity of product (i.e. greater P_n of catalyst) and simplified separation procedures. Careful tailoring of reaction conditions and Cu loading on APSiO₂ allowed exploiting the supported catalyst more effectively and for longer time and also to diminish the metal leaching in the reaction medium. In this context the feasibility of extending the catalyst' life-time by reduction in continuo of phenylhydrazine was also demonstrated for the first time. The versatility of the flow-system was also proven by sequentially converting different substrates to 1,2,3-triazole products with the same column.

Acknowledgement

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Figure 1. Transmission electron microscopy (TEM) image of a freshly prepared Cu/APSiO₂ sample.

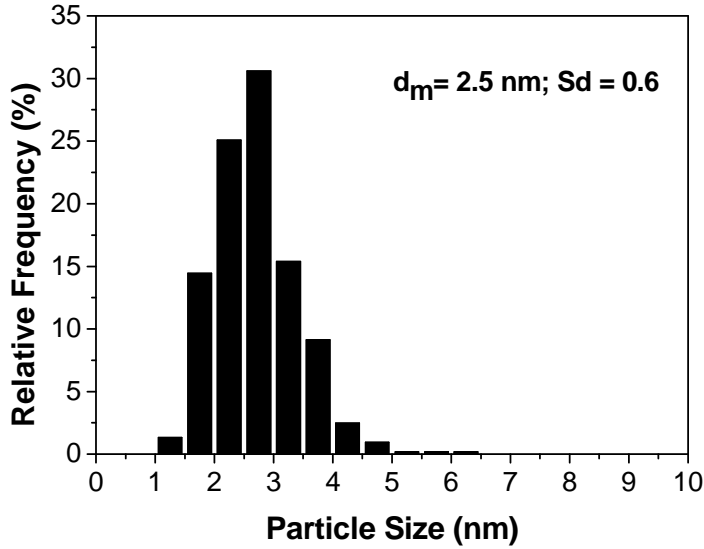
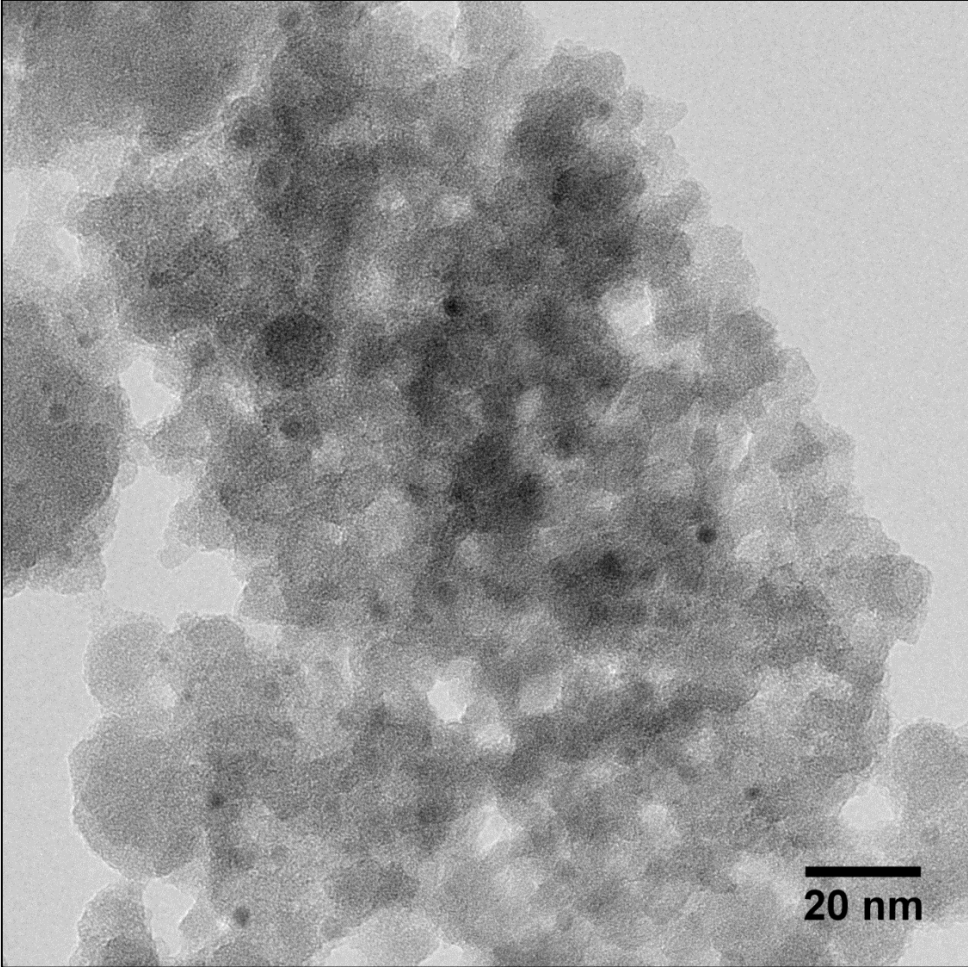


Figure 2. HRTEM micrograph of Cu nanoparticles and inverted FFT pattern taken from A and B squared areas, respectively.

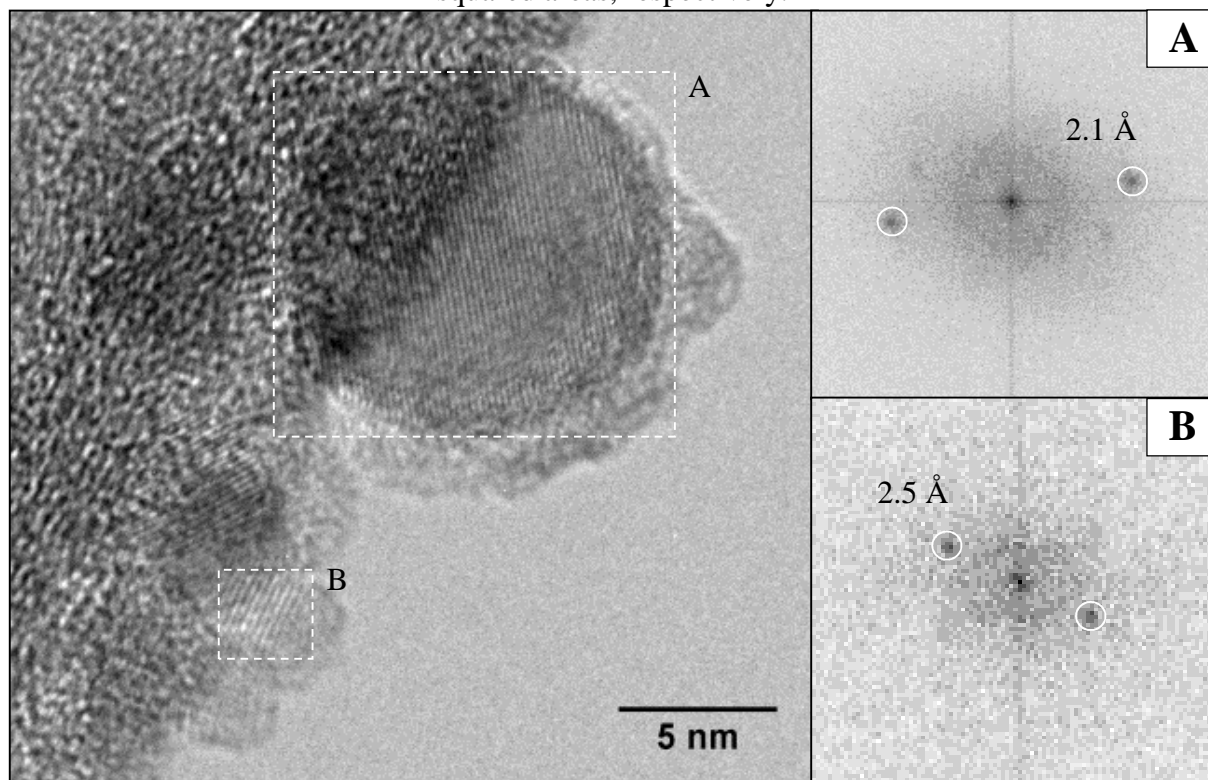


Figure 3. TPR profiles of Cu/AP-SiO₂: freshly prepared (blue line), reduced with phenylhydrazine (red line) and air-exposed after the reduction (green line).

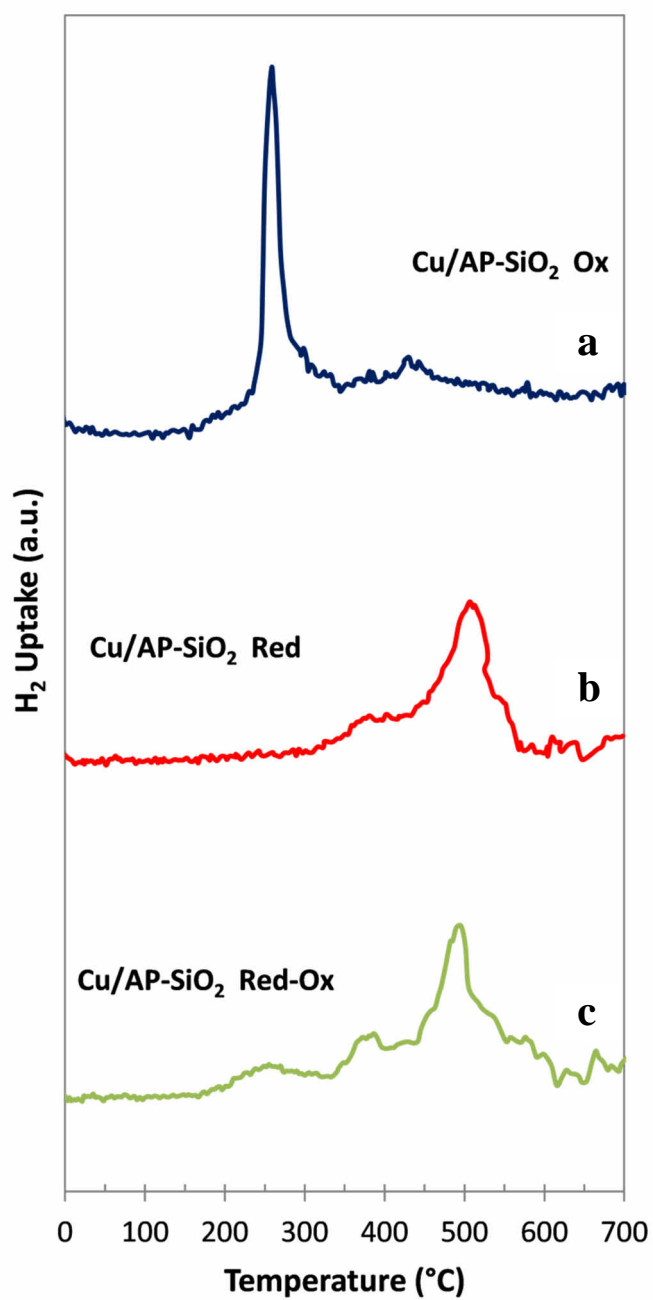
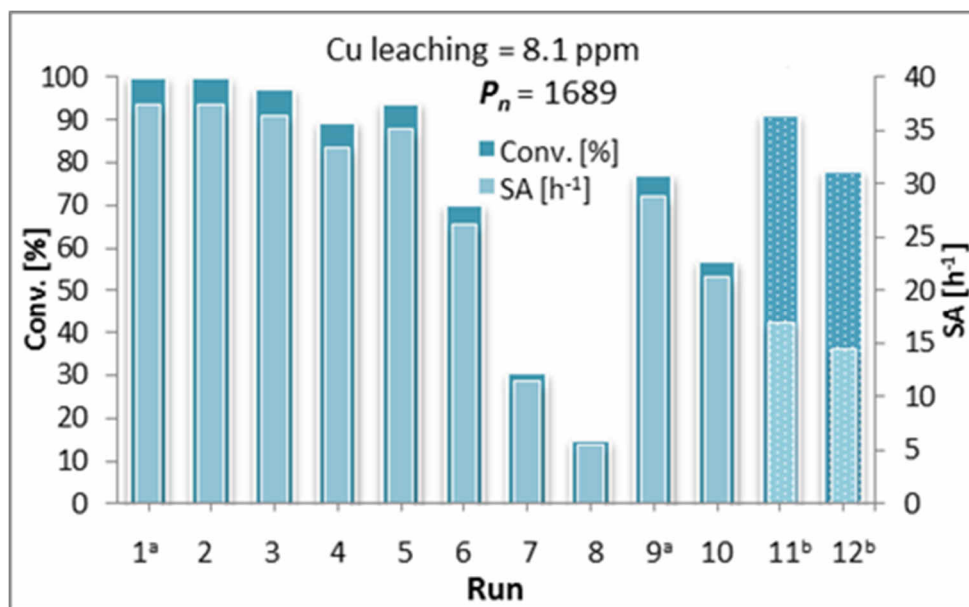


Figure 4. Continuous-flow click reaction between phenyl acetylene and benzyl azide using Cu/APSiO₂ (0.55 wt.%).



Reaction conditions for each run: Cu/APSiO₂ 0.55 wt.% (230 mg, 0.02 mmol of Cu), benzylazide (3.75 mmol), phenylacetylene (4.5 mmol), THF (15 mL), PhNHNH₂ (9.8 μL, 0.1 mmol), flow-rate = 50 μL/min, T = 25°C. a) Pre-activated with PhNHNH₂ (69 μL, 0.7 mmol in 5 mL THF); b) 25 μL/min flow-rate, pre-activated and reaction run in presence of PhNHNH₂ (69 μL, 0.7 mmol) added to the feed.

Table 1. CuAAC reaction in batch reaction conditions using Cu/APSiO₂ catalyst

Table 2. CuAAC reaction in continuous-flow reaction conditions using Cu/APSiO₂ catalyst

Table 3. Substrate scope in continuous-flow CuAAC reaction using Cu/APSiO₂ catalyst

Table 1.

Entry	Catalyst	Time [h]	Conversion [%] ^[a]	Specific Activity (SA) [h ⁻¹] ^[b]	Leaching [%] ^[c]
1	Cu/APSiO ₂ 1.0 wt. %	2	38	9.5	0.005
		6	100		
2	Re-cycled from run 1	2	21	5.25	< limit
		6	100		
3	Re-cycled from run 2	2	9	2.25	0.05
		24	99		
4	Re-cycled from run 3	24	79	1	0.06
5 ^[d]	Cu/APSiO ₂ 1.0 wt. %	2	70	17.5	1.9
		4	100		
6	Re-cycled from run 5	2	50	12.5	1.5
		6	100		
7	Re-cycled from run 6	2	15	3.75	1.3
		4	30		
		12	100		
8	CuI/APSiO ₂ 1.0 wt. %	2	71	17.7	16
		6	93		
9	Re-cycled from run 8	2	22	5.5	14
		6	76		
10 ^[d]	Re-cycled from run 9	2	29	7.3	5
		6	66		

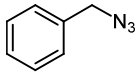
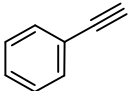
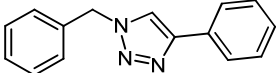
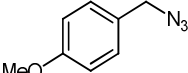
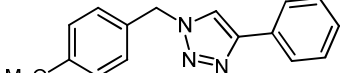
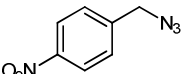
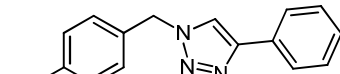
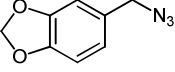
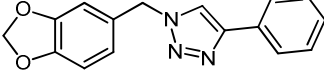
Reaction conditions: Cu/APSiO₂ 1.0 wt. % (65 mg, 0.01 mmol of Cu) benzyl azide (0.5 mmol, 1 equiv.), phenyl acetylene (0.6 mmol, 1.2 equiv.), THF (2 mL), T = 25°C. [a] determined by ¹H NMR; [b] Calculated as moles of benzyl azide converted/moles of Cu per hour (calculated after 2 h); [c] determined by ICP-OES, on the basis of the total available copper; [d] catalyst pre-activated using PhNHNH₂ (34 μL, 0.35 mmol) in THF (5 mL).

Table 2.

Entry	Conversion [%] ^[a]	Specific Activity (SA) [h ⁻¹] ^[b]	Leaching [%] ^[c]
1 ^[d]	99	24.7	< 0.01
2	73	18.3	0.2
3	50	12.5	0.3
4 ^[d]	85	21.2	2.7
5 ^[e]	100	25.0	1.2
6 ^[e]	94	23.5	5.2
7 ^[e]	79	19.7	4.8

Reaction conditions: Cu/APSiO₂ 1.0 wt.% (190 mg, 0.03 mmol of Cu), benzyl azide (3.75 mmol, 1 equiv.), phenyl acetylene (4.5 mmol, 1.2 equiv.), THF (15 mL), flow rate = 50 μ L/min, T = 25°C, t = 5 h. [a] determined by ¹H NMR; [b] Calculated as moles of benzyl azide converted/moles of Cu per hour (calculated after 2 h); [c] determined by ICP-OES, on the basis of the total available copper; [d] catalyst pre-activated using PhNHNH₂ (103 μ L, 1.05 mmol) in THF (5 mL); [e] PhNHNH₂ (30 μ L, 0.30 mmol) was added to the reaction feed.

Table 3.

Substrate 1	Substrate 2	Product	Conversion [%] ^[a]
			99
			99
			99
			99

Reaction conditions: Cu/APSiO₂, 0.55 wt.% (223 mg, 0.019 mmol of Cu), benzyl azide (2.5 mmol, 1 equiv.), phenyl acetylene (3.0 mmol, 1.2 equiv.), THF (10 mL), PhNHNH₂ (9 μL, 0.095 mmol), flow-rate = 50 μL/min, T = 25°C. Before each run the catalyst was activated with PhNHNH₂ (66 μL, 0.67 mmol in 5 mL THF). [a] Calculated by ¹H NMR.

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