Copper(II) SBA-15: A reusable catalyst for azide–alkyne cycloaddition

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Abstract: The azide-alkyne cycloaddition reaction was investigated under catalytic conditions involving a copper (II) loaded silica based mesoporous material. Cu(II) SBA-15 demonstrated a high catalytic effect in 1,4-triazoles synthesis in organic. No additives such as a base or a reductant are required. Quantitative yields were obtained and a mere filtration of the mesoporous material which retains copper (II) allows the recovery of the catalyst. In addition, up to 5 times recycling of the catalyst was achieved without loss of the activity affording 1,4-triazoles in a yield up to 98%.

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Cergy-Pontoise, March 21th 2013

Journal of molecular Catalysis A Editor

Please find enclosed a manuscript entitled "Copper(II) SBA-15: a reusable catalyst for azide-alkyne cycloaddition". This work concerns the use of supported Copper(II) on a mesoporous material, as catalyst in the 1,3 dipolar cycloaddition. We demonstrated the efficiency of the catalyst towards various alkynes and azides and its reusability without loss of reactivity.

We also showed that, from a mechanistic point of view, Copper(II) seems acting as Copper(I), with the formation of a metal-carbon bond as usually described in this reaction and not as Lewis acid. This is sustained by different experiments such as deuteration of the alkyne, oxidative conditions for the reaction and kinetic studies. It is noteworthy that is the first time that this kind of reactivity is proposed for Copper(II).

Moreover, I declare that all authors are aware of the submission and agree to its publication. The submission is original, and is not under consideration for publication elsewhere.

Hoping that this work could be published in J. Mol Cat. A,

Sincerely yours,

Pr Nadège Lubin-Germain

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Copper(II) SBA-15: a reusable catalyst for
azide-alkyne cycloaddition

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Highlights

Copper(II) catalyses the Alkyne-Alkyne cycloaddition reaction

Cu-SBA-15 operates by a Copper(I)-like mechanism leading complete regioselectivity

The catalyst can be reused without loss of yield and regioselectivity

Copper(II) SBA-15: a reusable catalyst for azide-alkyne cycloaddition

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Abstract.

The azide-alkyne cycloaddition reaction was investigated under catalytic conditions involving a copper (II) loaded silica based mesoporous material. Cu(II) SBA-15 demonstrated a high catalytic effect in 1,4-triazoles synthesis in organic. No additives such as a base or a reductant are required. Quantitative yields were obtained and a mere filtration of the mesoporous material which retains copper (II) allows the recovery of the catalyst. In addition, up to 5 times recycling of the catalyst was achieved without loss of the activity affording 1,4-triazoles in a yield up to 98%.

Keywords: Click Chemistry; Mesoporous materials; Cycloaddition, Recycling, Heterogeneous Catalysis, Copper(II).

1. Introduction

The copper-catalyzed azide-alkyne cycloaddition (CuAAC) is the landmark reaction in click chemistry and originates from the pioneering works of Sharpless *et al.*¹ and Meldal *et al.*² Copper (I) catalysis accelerates dramatically the Huisgen 1,3-dipolar reaction and leads to a high regioselectivity in favor of the 1,4-isomer of the triazole product. The copper (I) catalysts generally originate from copper (I) salts in presence of a base and/or a ligand, *in situ* reduction of copper (II) salts usually by ascorbate, and/or a mixture of copper (0) and copper (II) species.³ Heterogeneous copper (I) sources have also been described as they present a great advantage concerning catalyst removal, recovery and recycling. Cu(I) salts have been supported on ionic resins,⁴ various polymeric backbones,⁵ silica,⁶ ionic liquids,⁷ montmorillonite,⁸ zeolites,⁹ or biopolymers.¹⁰ The main drawback is that such heterogeneous catalysts frequently suffer from the thermodynamic instability of Cu(I) which is prone to oxidation or disproportionation. Therefore, Cu(II) has recently been immobilized on alumina,¹¹ silica,¹² anatase,¹³ various polymeric backbones,¹⁴ heteropolyacids,¹⁵ minerals,¹⁶ or biooligomers¹⁷ with or without the presence of a sacrificial reducing agent.

With respect to our work, we have already been concerned with controlling the regioselectivity of the reaction in microreactors such as micelles.¹⁸ Herein we have explored the usefulness of mesoporous material and the potential role of the pores in the catalysis of the process. Indeed copper loaded on silica type materials as MCM-41 and SBA-15 have been shown to be very useful in selective catalytic experiments.¹⁹

2. Experimental Methods

2.1. Characterization of the mesoporous Cu(II) SBA-15

The SBA-15 material was prepared according to a well-established procedure.¹ This mesoporous silica (50 mg) was then suspended for 10 min at room temperature in 20 mL of a $5 \cdot 10^{-2}$ mol/L aqueous solution of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ containing a particular amount of a solution of 28% (w/w) NH_4OH in order to obtain pH 10.5.² The material was then filtered, washed profusely with water to ensure the removal of all free Cu(II) ions and dried in an oven at 60°C for 4 h to give a bluish solid. Control of the time and pH of impregnation is crucial for the copper loading.

The copper uptake was then determined by UV-visible spectroscopy. A sample of Cu(II) SBA-15 (10 mg) is suspended in 5 mL 2% (w/w) aqueous HNO_3 and stirred for 15 minutes at room temperature, vigorously in order to ensure the best homogeneity possible in solution and filtered. UV absorbance of the solution was measured and the copper content was calculated with the standard calibration curve.

Each batch of Cu(II) SBA-15 is further characterized by IR spectroscopy and N_2 -adsorption measurement. The following table gives the detailed values of Pore volume and Pore diameter as well as the BET Surface area for the freshly prepared Cu(II) SBA-15, the Cu(II) SBA-15 after several runs (simply filtered after the last run) and the Cu(II) SBA-15 thoroughly rinsed after the last run.

2.2. General Procedure for Cu(II) SBA-15 Azide- Alkyne Cycloaddition

¹ N. Brodie-Linder, G. Dosseh, C. Alba-Simionesco, F. Audonnet, M. Impérator-Clerc, *Mater. Chem. Phys.* **2008**, 108, 73-81.

² N. Brodie-Linder, R. Besse, F. Audonnet, S. LeCaer, J. Deschamps, M. Impérator-Clerc, C. Alba-Simionesco, *Micropor. Mesopor. Mater.* **2010**, 132, 518-525.

Alkyne (0.5 mmol), azide (0.55 mmol) and Cu(II) SBA-15 (25 mg, 8 mol% Cu) were stirred in dichloromethane (2 mL) overnight. The mixture was filtered and the solid was washed twice with 2 mL of dichloromethane. The filtrate was concentrated by evaporation under vacuum. Excess of azide can be removed after immobilization on a triphenylphosphine resin. In the case of highly polar substrates, the solid was washed twice with 2 mL of acetonitrile.

2.3. General procedure for catalyst recycling

To a screw-capped vial were successively added ethyl propiolate (50 μ L ; 0.49 mmol), benzyl azide (73.2 mg ; 1.15 eq.), dichloromethane (2 mL) and finally the Cu(II)-SBA 15 (25 mg ; 7.5% Cu w/w ; 6 mol%). The reaction was stirred overnight and the catalyst was recovered by filtration over a nylon membrane (0.45 μ m, Millipore®) and washed with dichloromethane (2 $\times$ 2 mL). The combined organic solvent was evaporated under vacuo yielding the desired triazole (97-110 mg ; 87-97 %). After the 5th run we recovered 23.9 mg of the catalyst (over the 25 mg used for the 1st reaction), hence a recovery of 93% over 5 runs (99% average recovery per run).

3. Results and Discussion

3.1. Catalysis

One of us recently reported the conditions for the controlled Cu(II) loading in SBA-15 materials from 6 to 20% Cu (w/w).²⁰ It was shown that the amount of Cu(II) loaded on the SBA-15 surface could be controlled by a reaction in aqueous copper solutions at ambient temperature in 10 minutes. It was also shown that good copper dispersion over the surface was achieved. For the azide-alkyne cycloaddition reaction, we synthesized an SBA-15 material using the identical method given in ref. 20. The copper loaded SBA-15 material was

prepared in an aqueous copper nitrate solution ($5 \cdot 10^{-2}$ M) at pH 10.5. The pH was adjusted by the addition of an aqueous solution of NH_4OH (28% w/w). The SBA-15 copper loaded blue powder (Cu(II) SBA-15) was characterized by N_2 adsorption analysis giving a pore size of 7.0 nm, a surface area of $306 \text{ m}^2 \text{ g}^{-1}$ and a pore volume of $0.483 \text{ cm}^3 \text{ g}^{-1}$. The copper was extracted from the Cu(II) SBA-15 material with a 2% HNO_3 aqueous solution which was analyzed by UV-visible spectroscopy giving a copper content at 10% (w/w).

The cycloaddition between ethyl propiolate and benzyl azide was first investigated using an increasing amount of Cu(II) SBA-15 in dichloromethane. The conversion into the 1,4-disubstituted triazole was determined by ^1H -NMR spectroscopy after 2 hours of reaction (Table 1). We were delighted to discover that a copper (II) catalyst could efficiently catalyze at room temperature such a reaction, without further addition of a reducing agent which would have allowed the existence of Cu(I) species. The reaction is totally regioselective as in the Cu(I) cycloaddition.

Table 1. Catalyst amount optimization

In order to demonstrate the scope of this catalysis, various alkynes and azides were tested using a moderate amount (8 mol%) of the catalyst (Table 2). The reaction proceeded efficiently with ethyl propiolate (entries 1-5), 3,3-diethoxyprop-1-yne (entries 6-9) and 4-bromobut-1-yne (entries 10-14). The isolated yields are particularly high, sometimes quantitative (entries 1, 3, 12), with benzyl azides.

Table 2. Scope and limitations of the catalyzed cycloaddition

When propargylamine was used, the reaction proceeded instantaneously but the triazole was recovered in very poor yield probably due to the amino complexation to copper (entry 20). This CuAAC rate acceleration by amino group complexation has already been

observed.²¹ The same observation could be made concerning alcohol-containing reactants in a less important manner (entries 15-19).

Since no reaction was observed with octyne and 2,3,4,6-tetra-*O*-benzyl- β -D-glucopyranosylacetylene (entries 21 and 22), it is supposed that the catalysis was impeded in these two cases by the size of the molecules (20 Å) compared to that of the pores (70 Å) which contain the copper catalytic species. Such an effect of the importance of the size of the pores was not observed with Cu(I)-zeolites which accept any substrate.^{9b} Our observation opens the way to the possibility of tuning the size of the pores in concordance with the substrates. Concerning octyne, we can also take into account the hydrophilic character of the pores and we can postulate that the octyne preferred to remain outside in the organic phase.

3.2. Recycling of the Cu(II) SBA-15

The reaction was tested on ethyl propiolate with benzylazide and we demonstrated that it proceeded with the same yield for at least five times (Figure 1). After each run, the catalyst can be almost quantitatively recovered by a mere filtration over a 0.45µm nylon membrane.

Figure 1. Cu(II) SBA-15 reusability.

After the last catalytic cycle, a more thorough washing was performed and the material was analyzed in order to control the state of the catalytic surface. The IR spectra found in Figure 2 indicate that no build-up of organic materials on the surface is occurring. This is also corroborated by N₂ volumetric adsorption analysis where only slight changes in the pore structure can be observed (*see Supporting Information*). In addition, the content of copper remained identical indicating that no leaching occurred.

Figure 2. IR spectra of Cu(II) SBA-15 materials before and after several catalytic cycles.

3.3. Mechanistic studies

To our knowledge, the first example of the use of Cu(II) as the reactive catalytic species in the Huisgen reaction was described in aqueous medium.²² Later on, a di-copper (II) substituted silicotungstate was shown to catalyze both the oxidative alkyne-alkyne homocoupling and the Huisgen reaction; the high yield in 1,2,3-triazoles in that reaction was proven to be due to the preformation of a Cu(I) acetylide.^{15a} With Cu(OAc)₂ as catalyst, a fast reaction occurred with organic azides capable of chelation-assisted copper coordination at the alkylated nitrogen position.²³

3.4. Oxidation state of Copper

In these cases, the authors suggest that Cu(II) undergoes reduction to Cu(I) via alcohol (solvent) oxidation and/or alkyne homocoupling; they gave experimental evidence of the formation of a mixed-valency dinuclear copper (I/II) species. They proposed that the copper centers function as a Lewis acid to enhance the electrophilicity of the azido group, whereas the other one is a two-electron reducing agent in oxidative metallacycle formation.²⁴

At this stage of discussion, we must remember that, as early as 2002, Sharpless *et al.* noted that even Cu(0) could be used as a source of the catalytic process, although these reactions took longer to proceed to completion.^{1,25} Recently Cu(0) nanoparticles as nanocatalysts were proved to be particularly active in the process.²⁵ Copper (II) has been reported to be the reactive catalytic species in other cases as well.²⁶

Our copper source was loaded onto a heterogeneous catalyst which hampers direct observation of the oxidation state; therefore indirect measurement might give information about the mechanism. No spectroscopic evidences concerning the formation of the homocoupling 1,3-diyne were found, either by NMR or GC-MS. Thus, reduction to Cu(I) seems unlikely.

In order to probe the oxidation state of the copper ions, we studied the influence of an atmosphere of molecular oxygen. Air oxidation of Cu(I) to Cu(II) is generally fast (thus explaining the instability of Cu(I) ions) and has been proven here when copper(I) iodide was introduced into vials that were successively flushed (for 5 min) and kept (for ½ h) separately under either O₂ or Ar atmosphere. Complexation by addition of NH₄OH solution occurs readily in the case of oxygen producing a blue solution (characteristic for Cu^{II}(NH₃)_n ions). In the case of argon, this blue solution was observed only after few minutes. We have then performed the cycloaddition under O₂ atmosphere and shaded from the light (Figure 3). In that case, if Cu(I) happened to be formed then it would instantly be oxidized to Cu(II) again. This reaction was monitored by GC-MS and the conversion is complete within 24 hours, just as the classical conditions.

Figure 3. Cycloaddition under O₂ atmosphere.

3.5. Kinetic study

Further information about the catalysis can be disclosed by comparison between the rates of cycloaddition between Cu(I) and Cu(II). In order to have similar reaction conditions (especially heterogeneous) the choice of the Cu(I) catalyst turned to be copper(I) iodide. Parallel reactions were carried out in CDCl₃ using Cu(II) SBA-15 (6 mol%) and CuI (0.3 mol%) and monitored by ¹H-NMR at given times (Figure 4). At this loading of catalyst, the rate of the reaction involving Cu(II) SBA-15 is much higher than the one of CuI (around 4 times). So if the copper (I) ions are the only one involved in the catalysis, 20% of the total amount of the Cu(II) bound to the surface of SBA-15 has to be reduced to Cu(I), which is highly unlikely to occur. Therefore, copper (II) is believed to play a crucial role for this reaction.

Figure 4. Kinetic experiment.

3.6. Acetylide copper intermediate

Deuterium exchange experiments can also give us insights into the reaction mechanism. We have first prepared ethyl deuteriopropiolate under basic classical conditions. GC-MS showed deuterium incorporation over 99% (Figure 5). This deuterated alkyne was then submitted to the usual cycloaddition conditions. No deuterium was incorporated into the triazole ring (confirmed either by ^1H -NMR and GC-MS) thus indicating the cleavage of the C–D bond and the formation of a copper-carbon bond can be postulated. Therefore, Lewis acidic mechanism (as exemplified with zeolites^{9c}) can be ruled out.

Figure 5. Deuteration experiment.

3.7. A dinuclear mechanism

Although copper (II) reduction to Cu(I) by a hydrogen-abstraction/proton-delivery/electron-gain mechanism is a remote possibility,²⁶ the previous set of experiments led us to hypothesize the formation of the triazole through the following mechanism involving only Cu(II) species (Figure 6). The complete 1,4-regioselectivity is rationalized through a covalent bond between copper and the alkynes.

Figure 6. Simplified mechanism of the Cu(II) SBA-15 catalyzed Huisgen reaction.

It was observed that dinuclear alkynyl copper complexes exhibit superior reactivity toward organic azides compared to their monomeric counterparts.²⁷ Such complexes were supposed to be involved in the recent description of the copper catalyzed Huisgen reaction,^{16a,23c,26} and were recently unveiled.²⁸ Since the pore surface of the catalyst is covered with copper (II) atoms, approximately 2 Cu(II) atoms per nm², we can presume that the formation of a dinuclear complex is not out of the question. Since we have not detected alkyne oxidative homocoupling products, we can hypothesize that the formation of a Cu(II) acetylide complex

(Figure 6) is a key and rate-determining step.^{16a,26,28} Once the dinuclear alkynyl copper complex is formed, it can undergo a classical evolution *via* a metallacycle.^{16a,23c,26,28} Protodemetallation can subsequently occur through internal proton delivery from the residual silanol groups of the surface.

Two supplementary experiments were performed using Cu(II)-SBA 15 with different porosity or Cu loading (Figure 7).

Figure 7. Loading and sizes of the pores.

These three results revealed the predominant importance of the loading and reinforced the hypothesis of a bimetallic mechanism. In addition, the pore size may have a great effect on the reactivity as the reaction is believed to occur inside the pores (as corroborated by N₂ volumetric adsorption of the catalyst without washing). The influence of these parameters is currently under investigation and will be reported in due time.

4. Conclusion

We have shown herein that our Cu(II) SBA-15 material can be used successfully as a reusable catalyst for an azide-alkyne cycloaddition reaction without degradation. The conversion can be as high as 99 % and a total regioselectivity is obtained. To our knowledge, this is the first time that a copper (II) SBA-15 material has been shown to be active as a reusable catalyst for azide-alkyne cycloaddition reactions.

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Entry	Alkyne 1 : R	Azide 2 : R'	Product 3 :
			Yield*
1	1a : COOEt	2a : PhCH ₂	3aa : 98%
2	1a : COOEt	2b : EtOCOCH ₂	3ab : 76%
3	1a : COOEt	2c : <i>p</i> -F-C ₆ H ₄ CH ₂	3ac : 99%
4	1a : COOEt	2d : 2-oxolan-CH ₂	3ad : 87%
5	1a : COOEt	2e : HOCH ₂ CH ₂	3ae : 64%
6	1b : (EtO) ₂ CH	2a : PhCH ₂	3ba : 83%
7	1b : (EtO) ₂ CH	2b : EtOCOCH ₂	3bb : 66%
8	1b : (EtO) ₂ CH	2d : 2-oxolan-CH ₂	3bd : 56% ^(†)
9	1b : (EtO) ₂ CH	2e : HOCH ₂ CH ₂	3be : 35%
10	1c : BrCH ₂ CH ₂	2a : PhCH ₂	3ca : 67%
11	1c : BrCH ₂ CH ₂	2b : EtOCOCH ₂	3cb : 72%
12	1c : BrCH ₂ CH ₂	2c : <i>p</i> -F-C ₆ H ₄ CH ₂	3cc : 98%
13	1c : BrCH ₂ CH ₂	2d : 2-oxolan-CH ₂	3cd : 57%
14	1c : BrCH ₂ CH ₂	2e : HOCH ₂ CH ₂	3ce : 52%

15	1d: CH ₂ OH	2a: PhCH ₂	3da: 68%
16	1d: CH ₂ OH	2b: EtOCOCH ₂	3db: 65%
17	1d: CH ₂ OH	2c: <i>p</i> -F-C ₆ H ₄ CH ₂	3dc: 72%
18	1d: CH ₂ OH	2d: 2-oxolan-CH ₂	3dd: 46%
19	1d: CH ₂ OH	2e: HOCH ₂ CH ₂	3de: 26%
20	1e: CH ₂ NH ₂	2a: PhCH ₂	3ea: 17%
21	1f: <i>n</i> -C ₆ H ₁₃	2b: EtOCOCH ₂	3fb: –
22	1g: 2,3,4,6-tetra- <i>O</i> -benzyl-β-D- <i>glucopyranosyl</i>	2b: EtOCOCH ₂	3gb: –

* Isolated Yield. ^(†) Isolated as the aldehyde.

Table

Entry	Cu(II) SBA-15	Conversion [*]
1	–	Traces
2	4 mol%	34%
3	8 mol%	75%
4	16 mol%	100%

^{*} evaluated by ¹H-NMR

Figure

Figure

Figure

Figure

Figure

Figure

Copper(II) SBA-15: a reusable catalyst for azide-alkyne cycloaddition

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General Informations

^1H and ^{13}C NMR spectra were recorded in a suitable deuterated solvent on a Bruker DPX-250 (250 MHz for ^1H & 42.5 MHz for ^{13}C) or on a Jeol 400-ECX (400 MHz for ^1H & 100 MHz for ^{13}C). High resolution mass spectra were obtained with an MS Jeol 700 spectrometer or a LTQ orbitrap spectrometer. Optical rotations were determined at 25 °C in CHCl_3 , 589 nm, on a JASPO DIP 370 instrument and IR spectra were recorded on a Bruker Tensor 27 spectrophotometer. Melting points (uncorrected) were determined on a Buchi B-545. Elemental analyses were done at the Central Service of Analysis (CNRS, Vernaison). Thin layer chromatography was carried out on silica gel plates (Macherey-Nagel), spots were detected with UV light and revealed with H_2SO_4 solution. Flash chromatography was performed with silica gel 60, 40-63 μm .

Copper content was determined on a JASCO UV Spectrometer.

Nitrogen adsorption of the prepared SBA-15 materials was measured with a BELJAPAN volumetric adsorption analyser model BELSORP-MINI II (BelJapan, Inc., Japan). Before measurements, the SBA-15 Cu materials were pre-treated under vacuum at 383 K for 24 h. BET (Brunauer–Emmett–Teller) surface area was calculated from the N_2 adsorption data in a relative pressure range from 0.05 to 0.2. We checked that the regression coefficient was greater than 0.999. The cross sectional area of the nitrogen molecule was assumed to be 16.2 Å². The pore volume was estimated from the amount of nitrogen adsorbed at a relative pressure corresponding at the end of the capillary condensation (typically 0.80). The mesoporous size distribution was determined from the adsorption branch of the isotherms using the BJH method.¹

Characterization of the mesoporous Cu(II) SBA-15

The SBA-15 material was prepared according to a well-established procedure.² This mesoporous silica (50 mg) was then suspended for 10 min at room temperature in 20 mL of a $5 \cdot 10^{-2}$ mol/L aqueous solution of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ containing a particular amount of a solution of 28% (w/w) NH_4OH in order to obtain pH 10.5.³ The material was then filtered, washed profusely with water to ensure the removal of all free Cu(II) ions and dried in an oven at 60°C for 4 h to give a bluish solid. Control of the time and pH of impregnation is crucial for the copper loading.

The copper uptake was then determined by UV-visible spectroscopy. A sample of Cu(II) SBA-15 (10 mg) is suspended in 5 mL 2% (w/w) aqueous HNO_3 and stirred for 15 minutes at room temperature, vigorously in order to ensure the best homogeneity possible in

¹ E.P.Barrett, L.G.Joyner, P.P. Halenda, *J. Am. Chem. Soc.* **1951**, 73, 373-380

² N. Brodie-Linder, G. Dosseh, C. Alba-Simionesco, F. Audonnet, M. Impérator-Clerc, *Mater. Chem. Phys.* **2008**, 108, 73-81.

³ N. Brodie-Linder, R. Besse, F. Audonnet, S. LeCaer, J. Deschamps, M. Impérator-Clerc, C. Alba-Simionesco, *Micropor. Mesopor. Mater.* **2010**, 132, 518-525.

solution and filtered. UV absorbance of the solution was measured and the copper content was calculated with the standard calibration curve.

Each batch of Cu(II) SBA-15 is further characterized by IR spectroscopy and N₂-adsorption measurement. The following table gives the detailed values of Pore volume and Pore diameter as well as the BET Surface area for the freshly prepared Cu(II) SBA-15, the Cu(II) SBA-15 after several runs (simply filtered after the last run) and the Cu(II) SBA-15 thoroughly rinsed after the last run.

	V _p , Pore volume (cm ³ g ⁻¹)	A _{BET} , Surface area (m ² g ⁻¹)	d _p , Pore diameter (nm)
Native Cu(II) SBA-15	0.483	306	7.0
Cu(II) SBA-15 after runs	0.281	191	5.5
Cu(II) SBA-15 after rinsing with acetonitrile	0.408	261	6.2

We can clearly see a decrease in pore volume and diameter and surface area in the material after several runs of reaction and without rinsing. The deformation of the hysteresis loop indicates a variation in pore size or some pore blocking. This can be attributed to the organic materials remaining from the reaction. After intensive rinsing, the different values increase and approach those of the original material before the catalytic runs. The slight differences can be explained by complexation of CH₃CN to the copper thus reducing the different parameters.

Figure 1: N₂-adsorption of Cu(II) SBA-15

Figure 2: IR analysis of Cu(II) SBA-15

General Procedure for Cu(II) SBA-15 Azide- Alkyne Cycloaddition

Alkyne (0.5 mmol), azide (0.55 mmol) and Cu(II) SBA-15 (25 mg, 8 mol% Cu) were stirred in dichloromethane (2 mL) overnight. The mixture was filtered and the solid was washed twice with 2 mL of dichloromethane. The filtrate was concentrated by evaporation under vacuum. Excess of azide can be removed after immobilization on a triphenylphosphine resin. In the case of highly polar substrates, the solid was washed twice with 2 mL of acetonitrile.

Ethyl 1-benzyl-1,2,3-triazole-4-carboxylate (3aa)⁴: Prepared from 49 mg (0.50 mmol) of propiolic acid ethyl ester and 73 mg (0.55 mmol) of benzyl azide. The product was obtained as an off-white solid (113 mg, 98 %). mp: 93-94 °C. FTIR: ν 3112, 3066, 3038, 2849, 1725, 1538, 1239 and 1048 cm^{-1} . ^1H NMR (250 MHz, CDCl_3): δ 1.21 (t, $J = 7.2$ Hz, 3H), 4.21-4.16 (m, 2H), 5.14 (s, 2H), 7.31-7.28 (m, 1H),

⁴ S. Chassaing, M. Kumarraja, A. Sani Souna Sido, P. Pale, J. Sommer, *Org. Lett.* **2007**, 9, 883-886

7.37-7.34 (m, 2H), 7.82-7.79 (m, 2H) and 7.95 (s, 1H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 13.7, 50.5, 62.0, 121.1, 125.4, 127.9, 128.5, 130.1, 147.6, 166.1 ppm. LC-MS: ELSD pur. 98 %, UV pur. 100 %; R_t = 4.75 min; m/z : 232 ($[\text{M}+\text{H}]^+$).

Ethyl 1-(ethoxycarbonylmethyl)-1,2,3-triazole-4-carboxylate (3ab):⁵ Prepared from 50 μL (0.50 mmol) of propiolic acid methyl ester and 71 mg (0.55 mmol) of ethyl azidoacetate. The product was

obtained as a beige solid (86 mg, 76 %). mp: 100-102°C. FTIR: ν 3111, 2986, 1757, 1718, 1534, 1463, 1375, 1253 and 1022 cm^{-1} . ^1H NMR (250 MHz, CDCl_3): δ 1.26 (t, J = 7.5 Hz, 3H), 1.36 (t, J = 7.5 Hz, 3H), 4.22 (q, J = 7.5 Hz, 2H), 4.40 (q, J = 7.5 Hz, 2H), 5.22 (s, 2H), 8.26 (s, 1H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 14.0, 14.3, 51.0, 61.4, 62.7, 160.5, 165.7 ppm. LC-MS: ELSD pur. 91 %, UV pur. 100 %; R_t = 5.37 min; m/z : 228 ($[\text{M}+\text{H}]^+$).

Ethyl 1-(4-fluorobenzyl)-1,2,3-triazole-4-carboxylate (3ac):

Prepared from 50 μL (0.50 mmol) of propiolic acid methyl ester and 83 mg (0.55 mmol) of 4-fluorobenzylazide. The product was obtained as a beige solid (123 mg, 99%). mp: 102-104°C. FTIR: ν 3134, 2981, 1715, 1538, 1220, 1045 cm^{-1} . ^1H NMR (250 MHz, CDCl_3): δ 1.30 (t, J = 7.5 Hz, 3H), 4.32 (q, J = 7.5 Hz, 2H), 5.49 (s, 2H), 7.22-6.82 (m, 4H), 7.96 (s, 1H) ppm. ^{13}C NMR (62.5 MHz, CDCl_3): δ 14.3, 53.7, 61.3, 116.3 (d, $J_{\text{C-F}}$ = 21.8 Hz), 129.7 (d, $J_{\text{C-F}}$ = 3.5 Hz), 130.2 (d, $J_{\text{C-F}}$ = 8.5 Hz), 130.4, 160.8 (d, $J_{\text{C-F}}$ = 25.9 Hz), 165.0 ppm. HRMS: Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_3\text{O}_2\text{F}$: 249.0914. Found: 249.0913.

Ethyl 1-((tetrahydrofuran-2-yl)-1,2,3-methyl)triazole-4-carboxylate (3ad): Prepared from 50 μL (0.50 mmol) of propiolic acid methyl ester and 69 mg (0.55 mmol) of 2-(azidomethyl)-tetrahydrofurane. The

product was obtained as a yellow oil (97 mg, 87%). FTIR: ν 3134, 2978, 1718, 1540, 1463, 1225, 1039. ^1H NMR (250 MHz, CD_3CN): δ 1.1 (m, 1H), 1.6 (m, 1H), 1.8 (m, 1H), 2.05 (m, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 4.2 (m, 1H), 4.33 (m, 3H), 4.5 (m, 1H). ^{13}C NMR (62.5 MHz, CD_3CN): δ 14.5, 26.2, 29.2, 54.7, 62.7, 68.9, 77.7, 129.9, 142.0, 161.7. HRMS: Calcd for $\text{C}_{10}\text{H}_{16}\text{N}_3\text{O}_3$: 226.1192. Found: 226.1188.

Ethyl 1-(2-hydroxyethyl)-1,2,3-triazole-4-carboxylate (3ae):⁶ Prepared from 50 μL (0.50 mmol) of propiolic acid methyl ester and

⁵ Palacios, F.; Ochoa de Retana, A. M.; Pagalday, J.; Sanchez, J. M. *Org. Prep. Proced. Int.* **1995**, 27, 603–612

⁶ A. Megia-Fernandez, M. Ortega-Muñoz, J. Lopez-Jaramillo, F. Hernandez-Mateo, F. Santoyo-Gonzalez, *Adv. Synth. Catal.* **2010**, 352, 3306-3320

47 mg (0.55 mmol) of 2-azidoethanol. The product was obtained as a yellow oil (60 mg, 64%). FTIR: ν 3365, 3138, 2938, 1718, 1542, 1203, 1040. ^1H NMR (250 MHz, CD_3CN): δ 1.2 (t, $J = 7.5$, 3H), 3.1 (t, OH), 3.9 (m, 2H), 4.35 (q, $J = 7.5$, 2H), 4.45 (m, 2H), 8.3 (s, 1H). ^{13}C NMR (69.9 MHz, CD_3CN): δ 14.5, 53.7, 61.1, 61.7, 129.8 ppm. HRMS: Calcd for $\text{C}_7\text{H}_{12}\text{N}_3\text{O}_3$: 186.0879. Found: 186.0874.

1-Benzyl-4-diethoxymethyl-1,2,3-triazole (3ba)⁷: Prepared from 72 μL (0.50 mmol) of propionaldehyde diethyl acetal and 73 mg (0.55 mmol) of benzyl azide. The product was obtained as a yellow solid (108 mg, 83%).

mp = 60°C. FTIR: ν 3120, 3073, 2983, 2929, 2891, 1455, 1267, 1094, 1052. ^1H NMR (300 MHz, CDCl_3): δ 1.21 (t, $J = 7.0$ Hz, 6H), 3.62 (2q, $J = 7.1$ Hz, 4H), 5.50 (s, 2H), 5.68 (s, 1H), 7.25-7.35 (m, 5H), 7.49 (s, 1H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 15.1, 54.2, 61.6, 96.8, 121.8, 128.1, 128.7, 129.1, 134.5, 147.5. LC-MS: ELSD pur. 100%, UV pur. 100%; $R_t = 8.35$ min; m/z : 234 ($[\text{M}+\text{H}-(\text{CH}_2\text{CH}_2)]^+$, 90%), 284 ($[\text{M}+\text{Na}]^+$, 10%).

1-Ethoxycarbonylmethyl-4-diethoxymethyl-1,2,3-triazole (3bb)⁷:

Prepared from 72 μL (0.50 mmol) of propionaldehyde diethyl acetal and 71 mg (0.55 mmol) of ethyl azidoacetate. The product was obtained as a yellow oil (85 mg, 66%). FTIR: ν 3136, 2987, 2883, 1750, 1218,

1064, 1048, 1023. ^1H NMR (300 MHz, CDCl_3): δ 1.12-1.22 (m, 9H), 3.57 (2q, $J = 6.9$ Hz, 4H), 4.51 (q, $J = 7.2$ Hz, 2H), 5.15 (s, 2H), 5.75 (s, 1H), 7.73 (s, 1H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 14.4, 15.5, 51.2, 61.8, 62.7, 97.0, 124.0, 148.1, 166.2. LC-MS : ELSD pur. 100%, UV pur. 100%; $R_t = 5.33$ min; m/z : 230 ($[\text{M}+\text{H}-(\text{CH}_2\text{CH}_2)]^+$, 80%), 280 ($[\text{M}+\text{Na}]^+$, 20%).

1-((tetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazole-4-carbaldehyde (3bd):

Prepared from 72 μL (0.50 mmol) of propionaldehyde diethyl acetal and 69 mg (0.55 mmol) of 2-(azidomethyl)-tetrahydrofurane. The product

was obtained as a yellow oil (71mg, 56%). FTIR: ν 3130, 2952, 2864, 1529, 1248, 1040. ^1H NMR (250 MHz, CD_3CN): δ 1.6 (m, 1H), 1.7 (m, 1H), 1.8 (m, 1H), 2.1 (m, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 4.2 (m, 1H), 4.4 (m, 1H), 4.5 (m, 1H), 8.4 (s, 1H), 10 (s, 1H). ^{13}C NMR (62.5 MHz, CD_3CN): δ 26.2, 29.2, 54.8, 68.9, 77.7, 128.7, 148.0, 185.7. HRMS: Calcd for $\text{C}_8\text{H}_{12}\text{N}_3\text{O}_2$: 182.0930. Found: 182.0930.

2-(4-(Diethoxymethyl)-1,2,3-triazol-1-yl)ethanol (3be)⁸: Prepared from 72 μL (0.50 mmol) of propionaldehyde diethyl acetal and 47 mg (0.55 mmol) of 2-azidoethanol. The product was obtained as a yellow

⁷ C. Girard, E. Önen, M. Aufort, S. Beauvière, E. Samson, and J. Herscovici *Org. Lett.*, **2006**, 8, 1689–1692

⁸ I. Lee, Y. S. Choe, J. Y. Choi, K.-H. Lee, B.-T. Kim, *J. Med. Chem.* **2012**, 55, 883-892

oil (37 mg, 35%). FTIR: ν 3365, 3133, 2877, 1691, 1531, 1040. ^1H NMR (250 MHz, CDCl_3): δ 1.20 (t, $J = 7.5$, 6H), 2.24 (bs, 1H), 3.75 (q, $J = 7.5$, 4H), 4.11-4.08 (m, 2H), 4.60-4.57 (m, 2H), 5.70 (s, 1H), 7.75 (s, 1H).

1-Benzyl-4-(2-bromoethyl)-1,2,3-triazole (3ca)⁹: Prepared from 47 μL (0.50 mmol) of 4-bromo-1-butyne and 73 mg (0.55 mmol) of benzyl azide. The product was obtained as a white solid (88 mg, 67%). mp = 79°C. FTIR: ν 3130, 3067, 3032, 2952, 2921, 1455, 1449, 1438, 1262, 1215, 1205, 1127, 1051, 815, 723, 696. ^1H NMR (300 MHz, CDCl_3): δ 3.24 (t, $J = 6.8$ Hz, 2H), 3.61 (t, $J = 6.8$ Hz, 2H), 5-49 (s, 2H), 7.26-7.21 (m, 2H) and 7.38-7.31 (m, 4H). ^{13}C NMR (75.5 MHz, CDCl_3): 29.4, 31.4, 54.0, 145.2, 121.6, 127.9, 128.6, 129.0, 134.6. LC-MS: ELSD pur. 100%, UV pur. 100%; $R_t = 6.39$ min; m/z : 266 ($[\text{M}+\text{H}]^+$, 90%),

Ethyl 2-(4-(2-bromoethyl)-1,2,3-triazol-1-yl)acetate (3cb): Prepared from 47 μL (0.50 mmol) of 4-bromobut-1-yne and 71 mg (0.55 mmol) of ethyl azidoacetate. The product was obtained as a white solid (93 mg, 72%). mp = 64°C. FTIR: ν 3130, 2984, 1737, 1550, 1204. ^1H NMR (400 MHz, CDCl_3): δ 1.24 (t, $J = 7.5$ Hz, 3H), 3.33 (t, $J = 6.9$ Hz, 2H), 3.6 (t, $J = 6.9$ Hz, 2H), 4.2 (q, $J = 7.5$ Hz, 2H), 5.1 (s, 2H), 7.5 (s, 1H) ppm. ^{13}C NMR (400 MHz, CDCl_3): 14.0, 29.3, 31.4, 50.8, 62.4, 123.2, 145.2, 166.3. LC-MS : ELSD pur. 100%, UV pur. 100%; $R_t = 5.56$ min; m/z : 262 ($[\text{M}+\text{H}]^+$, 90%). HRMS: Calcd for $\text{C}_8\text{H}_{13}\text{BrN}_3\text{O}_2$: 262.0191. Found: 262.0200.

1-(4-Fluorobenzyl)-4-(2-bromoethyl)-1,2,3-triazole (3cc): Prepared from 72 μL (0.50 mmol) of 4-bromobut-1-yne and 83 mg (0.55 mmol) of 4-fluorobenzylazide. The product was obtained as a beige solid (117 mg, 82%). mp: 80-82°C. FTIR: ν 3132, 2950, 1553, 1217, 1052. ^1H NMR (400 MHz, CDCl_3): δ 3.22 (m, 2H), 3.58 (m, 2H), 5.43 (s, 2H), 7.20-6.98 (m, 4H), 7.54 (s, 1H). ^{13}C NMR (400 MHz, CDCl_3): δ 29.4, 31.4, 53.3, 116.0, 121.5, 129.8, 130.5, 145.3, 161.5, 164.0 ppm.

4-(2-bromoethyl)-1-((tetrahydrofuran-2-yl)methyl)-1,2,3-triazole (3cd): Prepared from 72 μL (0.50 mmol) of 4-bromobut-1-yne and 69 mg (0.55 mmol) of 2-(azidomethyl)tetrahydrofuran. The product was obtained as a yellow oil (73 mg, 57%). FTIR: ν 3409, 2942, 2807, 1551, 1380, 1219, 1056. ^1H -NMR (250 MHz, CDCl_3): δ 2.04-1.63 (m, 4H), 3.30-3.19 (m, 2H), 3.61-3.19 (m, 2H),

⁹ V. Fiandanese, F. Iannone, G. Marchese, A. Punzi *Tetrahedron* **2011**, 67, 5254–5260

3.40-3.89 (m, 4H), 4.64-4.30 (m, 3H), 5.52-4.29 (m, 3H) and 8.19 (s, 1H) ppm. HRMS (ESI): Calcd for $C_9H_{15}BrN_3O$ ($M+H$): 260.0398. Found: 260.0407.

2-(4-(2-bromoethyl)-1,2,3-triazol-1-yl)ethanol (3ce): Prepared from 72 μ L (0.50 mmol) of 4-bromobut-1-yne and 47 mg (0.55 mmol) of 2-azidoethanol. The product was obtained as a yellow oil (40 mg, 52%).

FTIR: ν 3308, 2930, 1424, 1262, 1055. 1H -NMR (250 MHz, CD_3CN): δ 3.12 (t, $J = 7.1$ Hz, 2H), 3.20 (Br s, OH), 3.57 (t, $J = 7.1$ Hz, 2H), 3.75 (t, $J = 7.1$ Hz, 2H), 4.28 (t, $J = 7.1$ Hz, 2H) and 7.59 (s, 1H). ^{13}C -NMR (62.5 MHz, CD_3CN): δ 30.1, 32.9, 53.4, 61.3, 124.1, 143.0 ppm. HRMS: Calcd for $C_7H_{11}BrN_3O$: 220.0085. Found: 220.0085.

1-(Benzyltriazol-4-yl)methanol (3da)⁷: Prepared from 28 mg (0.50 mmol) of propargyl alcohol and 73 mg (0.55 mmol) of benzylazide. The product was obtained as a white solid (64 mg, 68 %). mp : 76-78°C.

FTIR: ν 3257, 3144, 3091, 2953, 2920, 1451, 1048. 1H -NMR (300 MHz, $CDCl_3$): δ 4.11 (s, 1H), 4.78 (s, 2H), 5.49 (s, 2H), 7.30 (m, 5 H), 7.50 (s, 1H). ^{13}C -NMR (75.5 MHz, $CDCl_3$): δ 54.1, 56.0, 122.0, 128.1, 128.7, 129.1, 134.5, 148.0. LC-MS : ELSD pur. 97%, UV pur. 100%; $R_t = 3.41$ min; m/z : 190 ($[M+H]^+$).

Ethyl 2-[4-(hydroxymethyl)triazol-1-yl]acetate (3db)⁷: Prepared from 28 mg (0.50 mmol) of propargyl alcohol and 71 mg (0.55 mmol) of ethyl azidoacetate. The product was obtained as a pale yellow oily solid (60 mg, 65 %).

FTIR: ν 3110, 3076, 3038, 2849, 1708, 1210, 1023. 1H -NMR (300 MHz, $CDCl_3$): δ 1.26 (t, $J = 7.2$ Hz, 3H), 4.21 (q, $J = 7.2$ Hz, 2H), 4.72 (s, 2H), 5.12 (s, 2H), 7.67 (s, 1H). ^{13}C -NMR (75.5 MHz, $CDCl_3$): δ 14.0, 50.8, 56.1, 62.4, 123.8, 148.3, 166.5. LC-MS: ELSD pur. 99 %, UV pur. 100%; $R_t = 3.02$ min; m/z : 186 ($[M+H]^+$), 208 ($[M+Na]^+$).

(1-(4-Fluorobenzyl)-1,2,3-triazol-4-yl)methanol (3dc)¹⁰: Prepared from 28 mg (0.50 mmol) of propargyl alcohol and 83 mg (0.55 mmol) of 4-fluorobenzylazide. The product was obtained as a yellow oil (74 mg, 72%).

1H -NMR (250 MHz, $CDCl_3$): δ 2.72 (m, 2H), 5.06 (bs, 1H), 5.47 (s, 2H), 7.23-7.02 (m, 4H), 7.54 (s, 1H).

(1-((Tetrahydrofuran-2-yl)methyl)-1,2,3-triazol-4-yl)methanol (3dd): Prepared from 28 mg (0.50 mmol) of propargyl alcohol and 69 mg (0.55 mmol) of 2-azidoethanol. The product was obtained as a white solid (64 mg, 68 %).

¹⁰ B. R. Buckley, S. E. Dann, H. Heaney, E. C. Stubbs *Eur. J. Org. Chem.* **2011**, 4, 770–776

mmol) of 2-(azidomethyl)tetrahydrofuran. The product was obtained as a yellow oil (42 mg, 46%). FTIR: ν 3357, 2923, 2871, 1559, 1224, 1049. $^1\text{H-NMR}$ (250 MHz, CDCl_3): δ 2.04-1.63 (m, 4H), 3.33 (bs, 1H), 3.82-3.73 (m, 2H), 4.60-4.26 (m, 3H), 5.52-4.29 (m, 2H), 8.53 (s, 1H) ppm. HRMS (ESI): Calcd. for $\text{C}_8\text{H}_{14}\text{N}_3\text{O}_2$ (M+H): 184.1086. Found: 184.1092.

2-(4-(Hydroxymethyl)-1,2,3-triazol-1-yl)ethanol (3de)¹¹: Prepared from 28 mg (0.50 mmol) of propargyl alcohol and 47 mg (0.55 mmol) of 2-azidoethanol. The product was obtained as a yellow oil (19 mg, 26%). FTIR: ν 3276, 2876, 1558, 1430, 1358, 1232, 11136, 1045, 1007. $^1\text{H-NMR}$ (250 MHz, CDCl_3): δ 1.89 (bs, 1H), 3.80 (bs, 1H), 4.08 (t, $J = 7.5$, 2H), 4.49 (t, $J = 7.5$, 2H), 4.78 (s, 2H), 7.66 (s, 1H).

(1-Benzyl-1,2,3-triazol-4-yl)methanamine (3ea)¹²: Prepared from 23 mg (0.50 mmol) of propargylamine and 73 mg (0.55 mmol) of benzylazide. The product was obtained as a white solid (16 mg, 17 %). $^1\text{H-NMR}$ (250 MHz, CDCl_3): δ 2.18 (bs, 2H), 4.29 (s, 2H), 5.49 (s, 2H), 7.30 (m, 5 H), 7.88 (s, 1H).

General procedure for catalyst recycling

To a screw-capped vial were successively added ethyl propiolate (50 μL ; 0.49 mmol), benzyl azide (73.2 mg ; 1.15 eq.), dichloromethane (2 mL) and finally the Cu(II)-SBA 15 (25 mg ; 7.5% Cu w/w ; 6 mol%). The reaction was stirred overnight and the catalyst was recovered by filtration over a nylon membrane (0.45 μm , Millipore®) and washed with dichloromethane (2×2 mL). The combined organic solvent was evaporated under vacuo yielding the desired triazole (97-110 mg ; 87-97 %). After the 5th run we recovered 23.9 mg of the catalyst (over the 25 mg used for the 1st reaction), hence a recovery of 93% over 5 runs (99% average recovery per run).

¹¹ Y.-L. Zhao, W. R. Dichtel, A. Trabolsi, S. Saha, I. Aprahamian, J. Fraser Stoddart, *J. Am. Chem. Soc.* **2008**, *130*, 11294-11296

¹² H.A. Orgueira, D. Fokas, Y. Isome, P. C.-M. Chan and C. M. Baldino *Tetrahedron Lett.* **2005**, *46*, 2911-2914