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Sol–gel entrapped Cu in a silica matrix: An efficient heterogeneous nanocatalyst for Huisgen and Ullmann intramolecular coupling reactions

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ABSTRACT

A recyclable catalytic system has been developed that comprises an inorganic polymer matrix consisting of non-functionalized silica, which encapsulates copper by direct interaction with the matrix. Cu is fixed to a silica support of nanometric dimensions by physical entrapment within a silica sol–gel matrix. Samples with different Cu loadings were studied in order to maximize and optimize the amount of entrapped Cu within the silica matrix. This entrapment limits the diffusion of the metal to the solution, thus ensuring negligible contamination of the product by the metal while simultaneously providing a stabilizing environment. This robust and versatile heterogeneous catalyst was evaluated in Huisgen and Ullmann intramolecular coupling reactions.

1. Introduction

Metal-catalyzed reactions occupy a prominent place among the synthetic methods of Organic Chemistry. These transformations allow efficient access to wide range of complex structures using mild and environmentally friendly experimental conditions. Much of the progress made in this area has followed the development of the homogeneous or heterogeneous catalysts that are available today. Both catalytic systems have characteristic advantages and disadvantages. In homogeneous catalysis, the catalyst is soluble in the reaction medium and this usually results in a more efficient catalytic process and a high selectivity. However, this approach does suffer from the problems of separation of the catalyst from the reaction mixture and recycling. As a result, heterogeneous catalysis is preferred for industrial-scale processes [1], mainly due to the ability to recover and reuse the catalyst and the avoidance of contamination of the final products by toxic transition metals used as catalysts in many fundamental reactions (e.g., coupling reactions, oxidations and hydrogenations). However, the application of this approach in areas such as pharmaceutical and agrochemical industries remains limited due to the difficulties in meeting the strict controls established by the regulatory agencies in relation to the amounts of metals in medicines and pesticides (generally low ppb range) [2]. In addition to the aspects described above, there are other factors such as intrinsic reactivity and instability of the catalytic species that impose particular experimental conditions (e.g., Cu^+), thus limiting the extensive application of these systems.

One of the most successful strategies in this area involves the heterogenization of the catalytic species by immobilization into organic [3–6] (e.g., polystyrene or dendrimers) or inorganic [7,8] (e.g., silica, zeolites or Al_2O_3) polymeric materials. In particular, catalysis with metal-doped silicates is an emerging technology that is of increasing interest for the scientific community [9–11]. The structural features of silica make it an excellent support for catalytic applications, particularly when compared to conventional supports (e.g., organic-based polymers). Although they have been extensively employed, organic matrices have intrinsic limitations as catalyst supports. For example, their functionality can be highly dependent on the solvent (swelling) and this can seriously affect reaction rates. Moreover, these supports can only host a relatively low catalyst loading and the weak ligation of metallic species could allow some leaching of the catalytic species, particularly

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when highly coordinating solvents and elevated temperatures are employed. Silica supports work under a wide range of experimental conditions – in both organic and aqueous solvent systems – and they are easy to handle, do not suffer from static issues and are readily amenable to automation. In addition, silica is mechanically stable, works in any format, is easily scaled and requires little washing because it does not swell in any solvent. The entrapment of catalytic species within sol–gel silica matrixes not only permits facile recycling of the catalyst, but also provides a stabilizing environment that increases the catalytic activity. At the same time, this entrapment protects the catalyst from redox changes and incompatible chemicals, thus allowing multistep one-pot reactions to be carried out with entrapped catalysts in the presence of entrapped catalyst poisons [12,13]. Some recent examples with $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ have highlighted the potential of this field [14,15].

The abundance and increasing applications of copper-catalyzed reactions demand novel active and recyclable immobilized copper(I) catalysts. Two good examples of reactions in which copper(I) plays a central role are the well-established Huisgen Copper Alkyne-Azide Cycloaddition (CuAAC) [16–21] and the Ullmann reaction [22]. A current trend in these transformations is the heterogenization of the catalyst [23–34]. While current methodologies represent major progress in this field, challenges associated with the synthesis, reactivity and leaching profiles of these catalytic systems remain partially unsolved. In particular, the long and tedious synthetic procedures generally employed for the heterogenization of copper preclude the widespread use of these conventional heterogeneous catalytic systems. However, interesting approaches have been performed in the preparation of new nanostructured copper-based systems [35–42]. Despite the extraordinary simplicity offered by the sol–gel method for the effective trapping of metallic species in silica [43], only three studies concerning the synthesis and study of SiO_2–Cu materials have been reported [44–46]. While these references provided a proof of concept, several facets of these catalytic materials remain unexplored. In particular, the optimization of the synthesis (copper loading levels), the exhaustive study of the leaching of the metal from the polymeric matrix and the extension of this approach to other transformations must be addressed. In the context of a programme aimed at the development of novel polymer-supported catalytic systems [47–50], we report here the synthesis, characterization and study of the catalytic activity of a novel catalytic system consisting of copper species entrapped within the inner pores of a non-functionalized silica matrix. The presence of copper in the silica matrix leads to a catalyst with high microporosity [43,51]. Additionally, the inorganic matrix provides chemical, thermal and mechanical stability, which gives rise to a highly robust encapsulated nanocatalyst that displays the benefits of both homogeneous and heterogeneous catalysts. Furthermore, the material exhibits excellent catalytic activity and selectivity in different reactions and solvents, produces negligible leaching of the catalytic species to the reaction media and can be easily recovered and recycled. For these reasons, this catalyst exemplifies the concept of semi-heterogeneous catalyst [52].

2. Experimental

2.1. General remarks

Commercially available reagents and starting materials were purchased and used from containers without further purification. Tetraethyl orthosilicate (TEOS, 99.0%) was purchased from Fluka. Absolute ethanol (reagent grade) and ammonia (25.0% NH_4OH solution in water) were purchased from Merck. Water was purified in a Milli-Q filtration unit from Millipore Co. and had a resistivity of 18.2 MΩ cm. Organic extracts were dried with anhydrous Na_2SO_4. Solvents were dried and purified by standard methods. All reactions were monitored by TLC with 2.5 mm Merck silica gel GF 254 strips and the purified compounds showed a single spot. Detection of compounds were performed by UV light and/or iodine vapour. The synthesis, isolation and purification of CuAAC compounds were accomplished using the equipment for parallel synthesis. A PLS (6 × 4) Organic Synthesizer was used for the synthesis of compounds. Ullmann reactions were performed in an Anton Paar Microwave (Monowave 300) synthesizer. Isolation of precipitated/triturated products was performed in a 12-channel vacuum manifold from Aldrich. Chromatographic purification was carried out by preparative TLC. The synthesized compounds were characterized by spectroscopic and analytical data. The NMR spectra were recorded on Bruker AM300 MHz (^1H) and 75 MHz (^{13}C) and XM500 spectrometers. Chemical shifts are given as δ values against tetramethylsilane as internal standard and J values are given in Hz. Proton and carbon nuclear magnetic resonance spectra (^1H, ^{13}C NMR) were recorded in $CDCl_3$. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. EPR experiments were performed on a Bruker EMX spectrometer. Mass spectra were obtained on a Varian MAT-711 instrument. High-resolution mass spectra (HR-MS) were obtained on an Autospec Micromass spectrometer. Inductively coupled plasma mass spectroscopic (ICP-MS) analysis of compounds **3a**, **3b** and **8d** was performed on a Varian 820-MS spectrometer (after microwave-assisted digestion of the samples). The morphology of the SiO_2–Cu catalyst was observed by Scanning Electron Microscopy (SEM, JEOL 6400) and by Transmission Electron Microscopy (TEM, JEOL JEM-1011). The surface of the SEM sample was coated with gold (∼200 Å thickness) prior to imaging in order to minimize charging. Energy Dispersive Spectrometry (EDS) elemental analysis of the catalyst was carried out on an Oxford INCA instrument attached to a scanning electron microscope in the scanning range 0–10 keV.

2.2. Synthesis of SiO_2–Cu catalyst

The SiO_2–Cu catalyst described here was obtained in a one-pot procedure using a modified sol–gel process by the addition of copper iodide during a hydrolysis/condensation reaction of a non-functionalized tetra-silicon alkylalkoxide. This procedure led to metal immobilization within the silica matrix, with the metal physically entrapped as the polymeric system grew. The catalyst was prepared by a modified Stöber method [53] as follows: a mixture of NH_4OH (7.47 mL), H_2O (1.59 mL) and absolute ethanol (87.11 mL) was stirred at room temperature in a 500 mL conical flask. TEOS (3.83 mL) was added dropwise to the above solution. 5 min after the addition of TEOS the mixture turned white and the required amount of CuI was slowly added to the solution. SiO_2–Cu catalysts with different Cu contents were prepared in order to optimize the loading of Cu in the silica matrix. Different amounts (0.02, 0.05, 0.10, 0.20, 0.30, 0.40, 0.50, and 0.80 g) of CuI were added to the hydrolysis/condensation reaction of the SiO_2. The mixture was stirred for 12 h at room temperature and was then centrifuged at 3000 rpm for 15 min and washed by repeated redispersion three times in pure ethanol and three times in deionized water. The precipitate was dried at 45 °C overnight. The final sample was a fine blue powder. Bare SiO_2 particles were synthesized by the same procedure as used for SiO_2–Cu but without the addition of CuI. The catalyst was subjected to a final treatment. The catalyst (1 g, blue powder) was suspended in a solution of sodium ascorbate (40 mL, 0.5 M) in water and stirred for 24 h. The colour of the catalyst changed from light blue to green and finally evolved into a greyish colour (see Fig. 4). The material was filtered off, washed with Milli-Q water and diethyl ether, dried in an oven and stored under vacuum prior to use in the reactions. All compounds were characterized by ^1H

NMR and ^{13}C NMR spectroscopy and by HRMS. The spectroscopic data are provided in the supporting information.

2.3. General procedure for the CuAAC reaction employing SiO_2–Cu in DMF or t-*BuOH/H_2O, using organic azides and alkynes (Method A)*

To an equimolar mixture (1 mmol) of acetylenic derivative and the corresponding organic azide in dimethylformamide (5 mL) [or a mixture of *t*-BuOH/H_2O (3:1)] was added diethylisopropylamine (3 mmol) and SiO_2–Cu (32 mg, 0.05 mmol Cu). The reaction mixture was stirred at room temperature for 3–5 h and filtered. The filtrate was evaporated to dryness and the corresponding 1,4-substituted 1,2,3-triazole was purified by chromatographic methods.

2.4. General procedure for CuAAC (3 component version) reaction employing SiO_2–Cu in t-*BuOH/H_2O (Method B)*

SiO_2–Cu (32 mg, 0.05 mmol Cu) was added to an equimolar mixture (1 mmol) of the acetylene derivative and the corresponding alkyl halide, sodium azide and diethylisopropylamine (3 mmol) in a 3:1 mixture of *t*-BuOH/H_2O (6 mL). The reaction mixture was stirred at room temperature for 3–6 h. The catalytic system was removed by filtration and the product was extracted with diethyl ether and dried under reduced pressure. The solution was filtered and the filtrate was evaporated to dryness. The corresponding 1,4-substituted 1,2,3-triazole product was then purified.

*2.5. General procedure for the synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones*

A 5 mL process vial was charged with 2-bromophenol (**5a**) (0.6 mmol), 2-chloroamide **6a** (0.5 mmol), SiO_2–Cu (33 mg, 10 mol% Cu), Cs_2CO_3 (1.0 mmol) and DMF (5 mL). The vessel was sealed under N_2 and exposed to microwave heating for 60–90 min at 100 °C. The reaction tube was cooled to room temperature and ethyl acetate (20 mL) was added. The resulting suspension was filtered. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (Hex/EtOAc = 4:1–2:1, v/v) to give the desired product **8a**. The identity and purity of the products was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis and by HRMS.

2.6. Hot filtration test for CuAAC

In two Kimble vials, twin CuAAC experiments (A and B) using benzyl azide (1 mmol) and phenylacetylene (1 mmol) in DMF (5 mL) were performed in the presence of the SiO_2–Cu catalyst (32 mg, 0.05 mmol Cu). Once the transformations had reached 50% completion (TLC control: AcOEt/Hexane 1:3), the catalyst was removed from one of the reactions (experiment A) by hot filtration of the solids through a preheated syringe and the solids were then washed with hot solvent (5 mL). The clear solution containing the filtrate and the washings was allowed to react further in the absence of solids in another Kimble vial. Both reactions (experiments A and B) were stirred for 8 h and the same work up described above was applied to the other reaction containing SiO_2–Cu catalyst (experiment B). The filtrates were evaporated to dryness and the corresponding 1,4-substituted 1,2,3-triazole then purified. The yields of the Huisgen products **3a** in the two reactions – with and without solid catalyst – were compared (experiment A = 52% yield; experiment B = 90% yield).

2.7. Hot filtration test for Ullmann intramolecular coupling reaction

Twin experiments (A and B) with 5-fluoro-bromophenol (**5b**) (0.6 mmol), 2-chloro-*N*-(4-ethoxyphenyl) acetamide (**6b**) (0.5 mmol), potassium carbonate (1 mmol) and the SiO_2–Cu (33 mg, 10 mol% Cu) catalyst in DMF (5 mL) were carried out for 20 min at 100 °C under MW heating. After this time, both transformations had reached approximately 50% conversion (TLC control: AcOEt/Hexane, 1:2). In one of the experiments (A), the solids (SiO_2–Cu catalyst and potassium carbonate) were removed by hot filtration using a preheated hot syringe and the filtrate was transferred to another Kimble vial and 1 mmol of potassium carbonate was added. Heating was continued in both reactions for 1 hour and the reactions were assessed by TLC (AcOEt/Hexane, 1:2). Reaction A gave only the intermediate compound **7d** (70% yield, and only traces of compound **8d)**. Experiment B (containing SiO_2–Cu catalyst) gave **8d** in 83% yield.

An inductively coupled plasma-mass spectrometry (ICP-MS) study of the obtained filtrates showed that the copper loss from the catalyst was negligible. ICP-MS analysis for filtrates of compound **3a**: 0.2003 ± 0.0231 ppb. **3b**: 0.1009 ± 0.0200 ppb. **8d**: 0.1007 ± 0.01110 ppb.

3. Results and discussion

3.1. Design, synthesis and characterization of the SiO_2–Cu catalyst

We initially focussed on the synthesis of the catalytic system by entrapment of copper species within the silica matrix through the sol–gel method. Physical entrapment, in addition to providing a stabilizing environment for copper species, is expected to limit the diffusion of such species to the solution, thus avoiding contamination of products with traces of metal. With the aim of developing catalysts that would be applicable to a wide range of synthetic transformations, different copper sources (e.g., CuCl, CuI, $CuNO_2$ or $CuSO_4$) were initially evaluated by considering parameters such as catalytic performance, oxidation state, solubility and price. Two sources (CuI and $CuSO_4$) were selected for preliminary exploration by a slight modification of Stöber's method [53]. It was gratifying to find that, irrespective of the copper source, the modified sol–gel procedure (see experimental part) afforded the targeted catalytic systems as pale blue particles. The process is straightforward, experimentally simple, and delivered nanoparticles with yields greater than 80%. Modification of the reaction conditions allowed modulation of both the concentration of copper species (0.45–12.83%) and the dimensions (90–150 nm) of the particles. It should be highlighted that the catalytic system described here did not contain functionalized spacers, since the copper species are attached to the solid support by physical entrapment between the polymer chains, which are synthesized during the hydrolytic polymerization that produces the material. As the evaluated copper sources (CuI and $CuSO_4$) provided particles with similar physical appearance and copper loading, we subsequently focussed on the study of catalytic systems obtained with CuI.

The morphologies of bare SiO_2 and the resulting SiO_2–Cu catalyst were analyzed by SEM and TEM. The micrographs of bare SiO_2 and the SiO_2–Cu catalyst are displayed in Fig. 1a–d. Bare SiO_2 particles (Fig. 1a) are monodisperse non-aggregated spheres with a mean diameter of 250 nm, whereas the SiO_2–Cu catalyst (Fig. 1b–d) shows how the addition of CuI to the hydrolysis/condensation reaction of SiO_2 changed the morphology and size of the SiO_2 particles. These images reveal that the SiO_2–Cu is composed of a dense agglomerate of polydisperse nanoparticles with an average

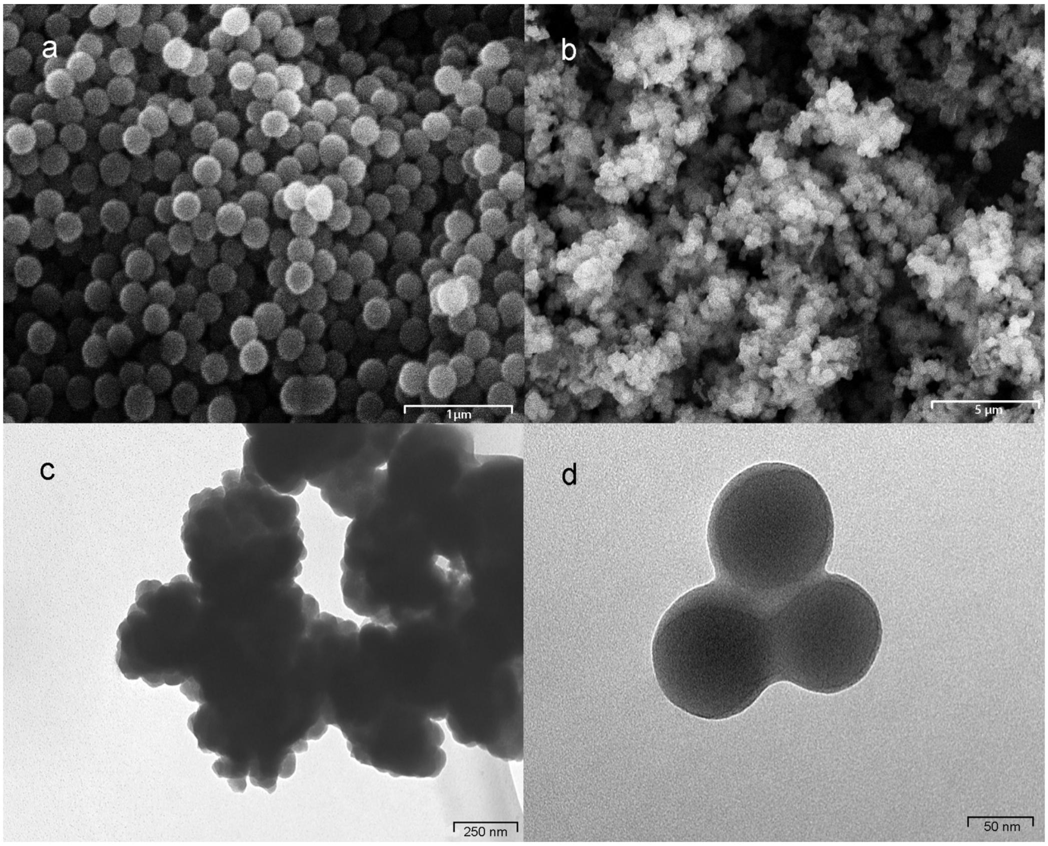


Fig. 1. SEM micrographs of (a) bare SiO_2, (b) SiO_2–Cu catalyst (9.4 wt.% Cu) and TEM micrographs (c, d) of SiO_2–Cu catalyst (9.4 wt.% Cu).

diameter of less than 100 nm. Details of the coalesced particles are shown in Fig. 1c and d.

As previously documented, the presence of the Cu species during the gelation process favours microporosity, thus increasing the specific area of the silica matrix [43,51]. As can be seen in the images, large pores are observed between the masses. These macropores also facilitate the diffusion of the reactants through the catalyst. The EDS results (Fig. 2) unequivocally confirm the encapsulation of the Cu within the hybrid catalyst and elements other than Cu, Si and O were not detected in the samples. The porous nature of the polymeric structure provides a large surface area on which the metal compounds can be trapped, thereby increasing the distribution of the catalyst within the nanoparticle matrix and enhancing the catalytic performance of the system. Additionally, such porosity facilitates the movement of reactants through the polymeric matrix to the immobilized catalyst and also the return of the product(s) to the solution once the reaction has taken place.

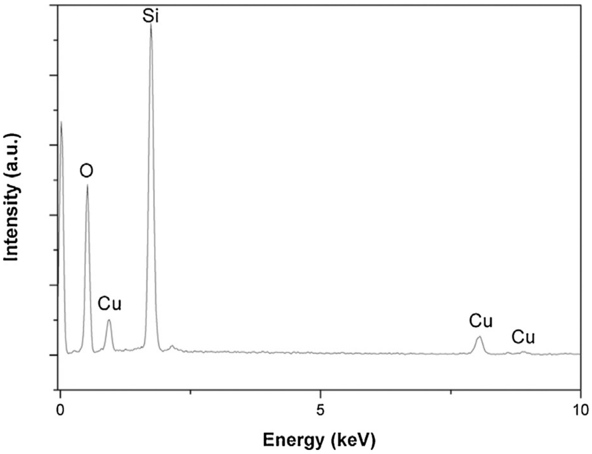


Fig. 2. EDS spectrum of the SiO_2–Cu catalyst (9.4 wt.% Cu).

In order to determine the efficiency of the copper entrapment during the synthesis of the catalysts, a preliminary study was carried out with variable quantities of CuI (0.02, 0.05, 0.10, 0.20, 0.30, 0.40, 0.50 and 0.80 g). In all syntheses the other reactants and solvent quantities were kept constant. The quantitative determination of the fraction of entrapped Cu in the inorganic matrix was measured by ICP. In agreement with previous EDS determinations (Fig. 2), the ICP studies confirmed the presence of Cu in the catalysts. Quantitative analysis confirmed that catalytic systems were obtained with variable loadings (0.05–9.4 wt.%) of the encapsulated metal. The results were compared graphically with the theoretical weight fraction assuming that 100% of the added Cu was entrapped (Fig. 3). It can be seen from Fig. 3 that for levels of less than 9.4 wt.% of entrapped Cu, the weight fraction of entrapped Cu is practically identical to the calculated value. This indicates that all of the CuI added was trapped in these cases. Above 9.4 wt.% of entrapped Cu, the fraction between free Cu and trapped Cu increases to the same extent as the increase in the added CuI. Therefore, the optimal amount of added CuI for the synthesis conditions described was 0.4 g, which corresponds to 9.4 wt.% of entrapped Cu.

The catalytic systems obtained in this work had a characteristic pale blue colour regardless of the copper source employed in the synthesis, and this physical appearance suggests the prominence of Cu(II) species. Samples of both materials were analyzed by EPR. These studies unequivocally confirmed the presence of cupric species within these materials, thus indicating that CuI is oxidized during the sol–gel procedure. The pale blue appearance of the catalyst and the characteristic intense EPR signal for paramagnetic

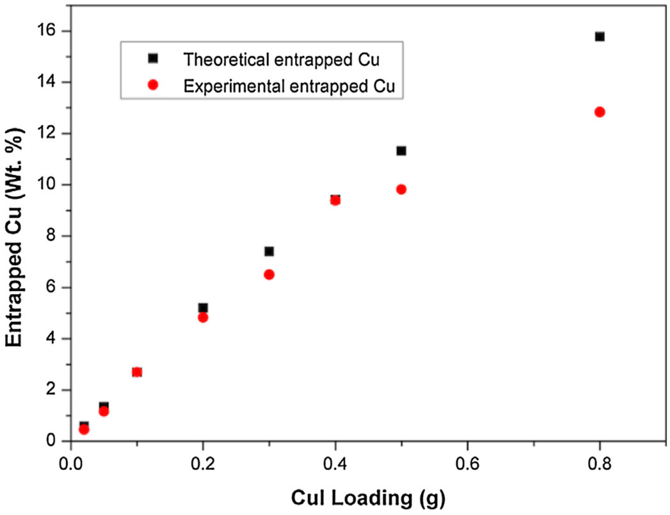


Fig. 3. Entrapped Cu in the SiO_2–Cu catalyst as a function of CuI loading.

Cu(II) at a field/[G] value of about 3.250 [Cu(I) is EPR-inactive] are shown in Fig. 4. The majority of copper-catalyzed transformations employ Cu(I) species and, inspired by Sharpless's CuAAC procedures [20], it was envisaged that treatment of this catalytic system with a mild reducing agent would enable the reduction of the Cu(II) to Cu(I) species. It was gratifying to verify that when the catalyst was stirred with an aqueous solution of sodium ascorbate (0.5 M, room temperature for 24 h) complete modification of its physical appearance and EPR profile were observed. It can be seen in Fig. 4b that, after ascorbate treatment, the pale blue colour had changed to grey. Similarly, EPR experiments unequivocally demonstrated that complete reduction of Cu(II) species occurred in both catalytic systems irrespective of the copper source (CuI or $CuSO_4$). The superimposed EPR spectra obtained for a representative catalyst of the initial (blue powder) and final (grey powder) samples are shown in Fig. 4c. These results suggest the presence of free copper(I) species within the material.

3.2. *Study of the catalytic activity*

Once the synthesis of the SiO_2–Cu catalyst had been optimized and it had been confirmed that copper was entrapped within the matrix of the catalyst, the catalytic performance was evaluated in two model copper-catalyzed reactions (CuAAC and Ullman reactions). On the basis of the optimum copper entrapment results (Fig. 3), it was decided to employ the catalyst that had a final copper content of 9.4 wt.%.

3.3. *Huisgen 1,3-dipolar cycloaddition (CuAAC)*

The effectiveness of the SiO_2–Cu nanocatalyst in CuAAC was initially evaluated in two solvents (DMF and *t*-BuOH/H_2O) with two organic azides (**1a**–**b**) and terminal acetylenes (**2a**–**b**), with DIPEA employed as a base (Table 1). In these studies equimolar amounts of the reactants were treated with SiO_2–Cu with different copper loadings. The reaction mixtures were subjected to orbital stirring at 40 °C for the required time (3–5 h) and the effect of the solvent on the outcome of the reaction was investigated. The use of other bases, such as TEA or potassium carbonate, did not improve the yields. We were pleased to observe that simple mixing of commercially available organic azides (**1a**–**b**) and acetylenes (**2a**–**b**) with SiO_2–Cu (Table 1) led to smooth cycloaddition to afford the desired 1,2,3-triazoles regardless of the modified parameters. The reported yields are the mean of at least two experiments in which freshly prepared catalysts were used.

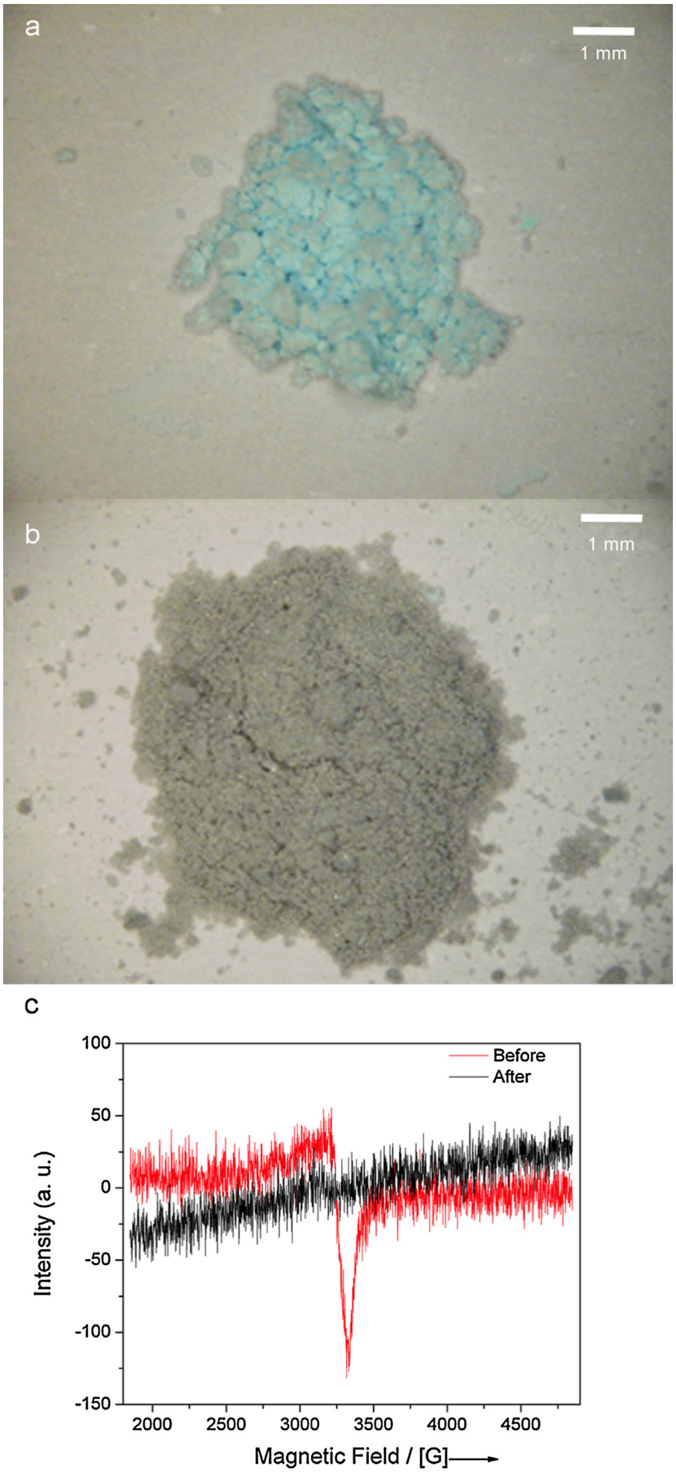
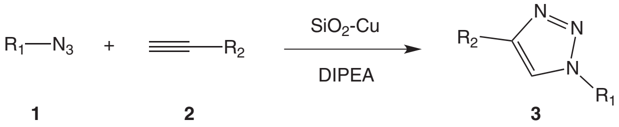
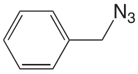
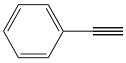
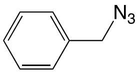
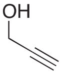
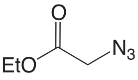
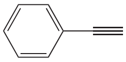
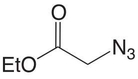
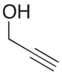


Fig. 4. (a) SiO_2–Cu before treatment with sodium ascorbate. (b) SiO_2–Cu after treatment with sodium ascorbate. (c) EPR experiment showing the characteristic signal of the paramagnetic Cu(II) state (top, corresponding to the sample before treatment) and the Cu(I) showing the absence of a signal (bottom).

A serious limitation for the widespread application of the copper-mediated Huisgen cycloaddition in drug discovery programmes arises from the relatively low abundance of structurally diverse collections of commercially available organic azides. In addition, purification of the product is difficult when the reaction

Table 1
Representative 1,2,3-triazoles **3** obtained on employing the initial conditions.



Entry	Compound	Substrate (**1a–b**)	Alkyne (**2a–b**)	Time (h)[a,b]	Yield (%)[a,b]
1	**3a**	 **1a**	 **2a**	4[a], 3[b]	90[a], 91[b]
2	**3b**	 **1a**	 **2b**	4[a], 3[b]	89[a], 90[b]
3	**3c**	 **1b**	 **2a**	5[a], 4[b]	83[a], 98[b]
4	**3d**	 **1b**	 **2b**	5[a], 4[b]	87[a], 92[b]

Conditions: acetylene derivative (1 mmol), organic azide (1 mmol), DIPEA (3 mmol), SiO_2–Cu (0.05 mmol Cu), rt.

[a] DMF as solvent.

[b] *t*-BuOH/H_2O (3:1) as solvent.

is incomplete and some alkyl azides decompose rapidly with the risk of explosion upon distillation. Furthermore, alkyl azides generally have boiling points similar to those of the corresponding alkyl bromides. Thus, we decided to initiate a systematic study of the versatility of the nucleophilic substitution of the halide using NaN_3 [52–61] in *t*-BuOH/H_2O at room temperature (Table 2). The initial exploration was aimed at the direct synthesis of 1,2,3-triazoles **3** and the reaction of benzyl bromide, sodium azide and phenylacetylene in the presence of TEA was chosen as a model transformation. The procedure involved mixing equimolar quantities of these reagents and the sol–gel material [SiO_2–Cu (5 mol% Cu)] in *t*-BuOH/H_2O with vigorous stirring at room temperature to give the corresponding 1,2,3-triazoles in good yields. Once the reaction had finished, the catalytic system was removed by filtration and the product was extracted with diethyl ether and dried under reduced pressure. These reaction conditions provided excellent yields of triazoles **3** (Table 2) irrespective of the nature of the alkyne and the alkyl bromide. A common feature of these experiments was the absence of homocoupling byproducts (Table 2).

3.4. Intramolecular Ullmann coupling reactions

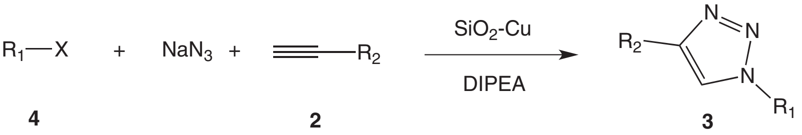
Recent advances in copper-catalyzed reactions have stimulated a plethora of novel improvements in Ullmann's reaction [62–66], especially for copper-catalyzed Ullmann *N*-arylations [67–69,22,70]. In this context, one-pot Ullmann-based strategies are particularly attractive as they enable the rapid and efficient assembly of diverse heterocyclic compounds [71–76]. With the aim of making a preliminary assessment of the usefulness of the novel catalytic systems in a representative one-pot Ullmann reaction, the reaction between 2-bromophenol (**5a**) and 2-chloro-*N*-(4-methylphenyl)acetamide (**6a**) was studied. These model substrates were submitted to classical Ullmann coupling conditions with dioxane or DMF as the solvent and conventional heating in a sealed tube (range of temperatures from 90 to 120 °C). Variable equivalents of Cs_2CO_3 were also used. In most cases the reaction was successful (60–75% yield), but the long reaction times (24–48 h) and the presence of the intermediate in the reaction mixtures led us to evaluate the use of microwave heating. Finally, the best conditions identified were as follows: 2-bromophenol (0.6 mmol), 2-chloro-*N*-(4-methylphenyl)acetamide (0.5 mmol), SiO_2–Cu (100 mg, 14 mol% Cu) and Cs_2CO_3 (1.0 mmol) in DMF (5.0 mL) under N_2 at 100 °C under MW irradiation. The starting materials were consumed completely and the expected product **8a** was obtained in 90% yield after 1 h (Table 3, entry 1). A set of *o*-bromophenols and 2-chloro-*N*-(aryl)acetamides were then selected for the synthesis of other 2*H*-1,4-benzoxazin-3-(4*H*)-ones (Table 3). A plausible pathway for the formation of 2*H*-1,4-benzoxazin-3-(4*H*)-ones is proposed in Table 3. The target compounds are formed in two steps. Firstly, in the presence of Cs_2CO_3, an intermolecular nucleophilic substitution between *o*-bromophenol and the 2-chloroacetamide affords the key ether intermediate **7** (Table 3). Indeed, the ether intermediate **7d** was isolated during the reaction of **5b** with **6b** under conventional heating (see supporting information). The efficiency of the two-step transformation, which does not require any additional ligand, demonstrates the catalytic performance and versatility of the catalytic system reported here and highlights the favourable environment provided by the polymeric matrix for the stabilization of Cu(I) species.

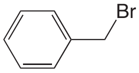
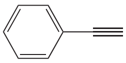
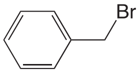
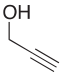
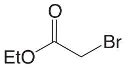
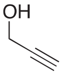
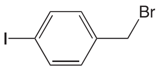
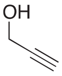
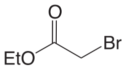
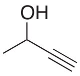
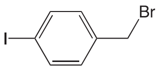
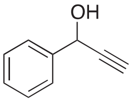
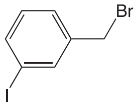
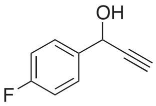
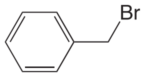
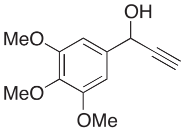
3.5. Recyclability

The recyclability of the supported catalyst was examined in two representative transformations of each reaction studied (i.e., the Huisgen 1,3-dipolar cycloaddition and Ullmann intramolecular coupling reaction). Firstly, it was verified that, after washing (with water and diethyl ether) and drying under vacuum, the heterogeneous catalytic system recovered from the reaction could be reused at least ten times in new reactions without a significant drop in product yield (the average yields for the target structures are shown in Table 4) and generate products with purities similar to those obtained in the first run.

In addition to its catalytic efficacy and recyclability, the leaching of metal to the reaction media is a key issue to be considered during the development of heterogeneous catalytic systems. We have taken into consideration the fact that the two

Table 2
Representative 1,2,3-triazoles obtained on employing the optimized conditions.



Entry	Compound	Alkylating agent (**4a–d**)	Alkyne (**2a–f**)	Time (h)	Yield (%)
1	**3a**	 **4a**	 **2a**	4	98
2	**3b**	 **4a**	 **2b**	4	89
3	**3d**	 **4b**	 **2b**	6	83
4	**3e**	 **4c**	 **2b**	3	87
5	**3f**	 **4b**	 **2c**	6	85
6	**3g**	 **4c**	 **2d**	3	88
7	**3h**	 **4d**	 **2e**	3	92
8	**3i**	 **4a**	 **2f**	3	80

Reaction conditions: acetylenic derivative (1 mmol), alkyl halide (1 mmol) and sodium azide (1 mmol), DIPEA (3 mmol), SiO_2–Cu (0.05 mmol Cu) in 6 mL of *t*-BuOH/H_2O (3:1), rt. 3–6 h.

transformations evaluated in this study have quite different reaction conditions (mechanism, temperature range and solvent). This is particularly the case for oxidative addition, which occurs in the Ullmann reaction and is a key factor in the leaching phenomenon. In an effort to obtain evidence to support true heterogeneous catalysis or to ascertain whether migration from the polymeric matrix produces active homogeneous copper species, two additional experiments (hot filtration tests for the Huisgen CuAAC and Ullmann reactions and a three-phase test) [77–81] were designed (Scheme 1).

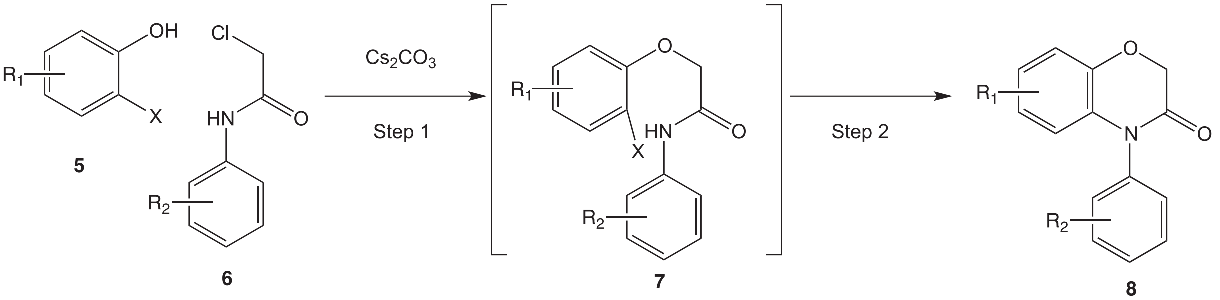
3.6. Hot filtration test

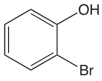
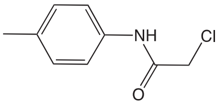
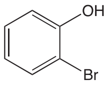
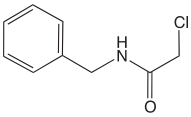
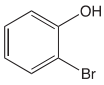
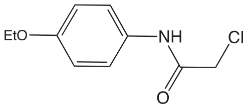
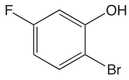
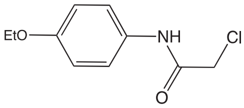
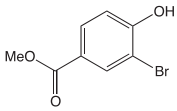
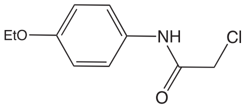
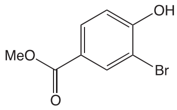
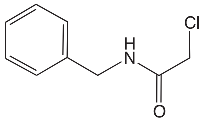
One issue that must be addressed when using heterogeneous catalysts is metal leaching from the solid to the solution. With the aim of obtaining information on this matter a hot filtration test was performed for both reactions:

(a) CuAAC: Twin CuAAC experiments using benzyl azide and phenylacetylene in DMF were performed in the presence of the SiO_2–Cu catalyst. Once the transformations had reached 50% completion, the catalyst was removed from one of the reactions by hot filtration of the solids through a preheated syringe and the solids were then washed with hot solvent. After the solids had been filtered off, the clear solution containing the filtrate and the washings was allowed to react further in the absence of solids. Comparison of the yields of the Huisgen products in the reactions – both with and without solid catalyst – established that filtration of the solids stopped the reaction. This suggests that leaching of copper did not occur during the reaction. In contrast, the reaction carried out without filtration proceeded further to give **3a** with a final conversion of 90%.

(b) Ullmann intramolecular coupling reaction: Twin experiments with 5-fluoro-bromophenol (**5b**), 2-chloro-*N*-(4-ethoxyphenyl) acetamide (**6b**), potassium carbonate and the SiO_2–Cu catalyst in DMF were carried out for 20 min at 100 °C under MW heating. After this time, both transformations had reached approximately 50% conversion. The SiO_2–Cu catalyst was removed by filtration in one of the experiments. Filtration was performed using a preheated hot syringe and the

Table 3
Proposed reaction pathway and structure of 2*H*-1,4-benzoxazin-3-(4*H*)-ones **8a–f**.[a]



Entry	Compound	*o*-Halophenol (**5a–c**)	Alkylating agent (**6a–c**)	Time (h)[b]	Yield (%)[b]
1	**8a**	 5a	 6a	1	90
2	**8b**	 5a	 6c	1	87
3	**8c**	 5a	 6b	1.5	80
4	**8d**	 5b	 6b	1	83
5	**8e**	 5c	 6b	1.5	89
6	**8f**	 5c	 6c	1.5	88

[a] *Reagents and conditions*: 2-bromophenol **5a–c** (0.6 mmol), 2-chloroamide **6a–c** (0.5 mmol), SiO_2–Cu (0.1 mmol Cu) and Cs_2CO_3 (1.0 mmol) in DMF (5.0 mL), 100 °C, MW heating, 1–1.5 h, under N_2.
[b] Isolated yield.

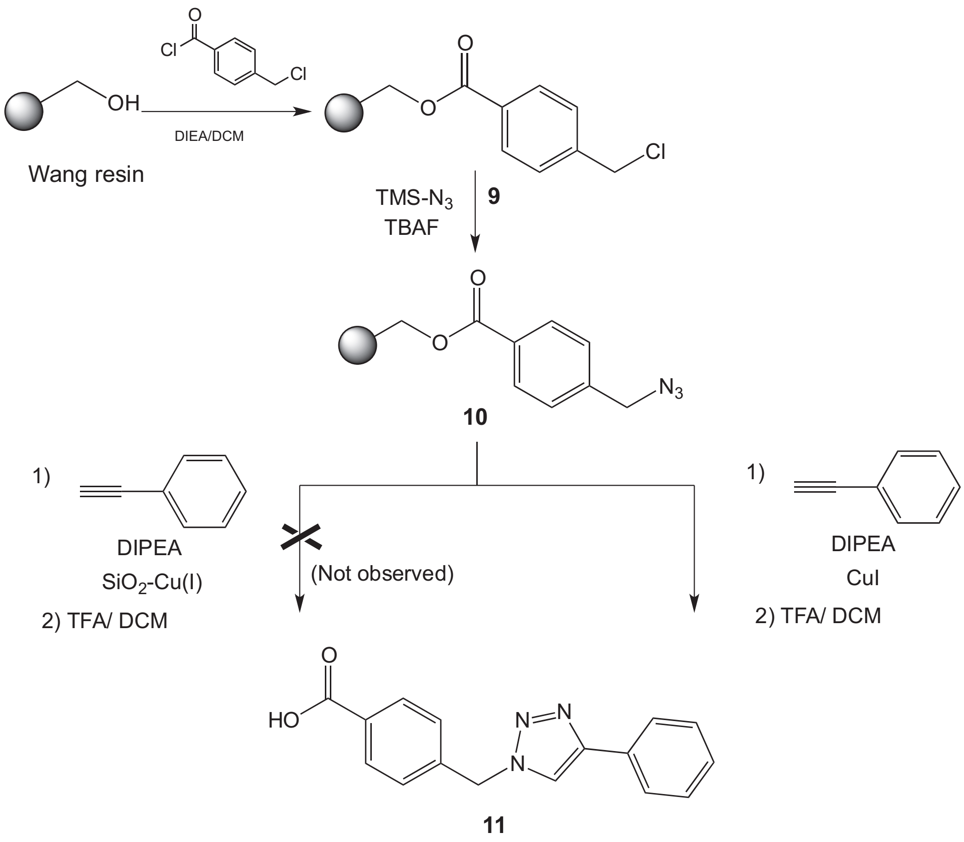
contents were transferred to another Kimble vial and 2 equiv. of potassium carbonate were added. Heating was continued in both reactions for 1 hour and the reactions were assessed by TLC. It was found that the reaction without catalyst had not progressed further to the final product **8d**. Furthermore, a greater amount of intermediate **7d** (formed by intermolecular nucleophilic substitution) was isolated in this reaction. By contrast, in the other experiment (containing SiO_2–Cu the catalyst) compound **8d** was isolated in 83% yield.

3.7. Three-phase test

The immobilized catalyst was exposed to soluble reactants and reagents bound to a solid support. If an active catalyst leaches from the immobilized media it will result in conversion of the resin-bound reagent. With this aim in mind, the supported benzyl azide **10** was prepared (Scheme 1). Polystyrene-bound 4-benzyloxybenzyl alcohol (1.25 mmol/g, Wang resin) was chosen as the alternative support due to its rapid and efficient cleavage

Table 4
Number of cycles and average yields for representative reactions using SiO_2–Cu.

Cycles/compound	1	2	3	4	5	6	7	8	9	10	Av. yield (%)
3a	93	93	91	91	91	90	89	88	87	87	90
3b	89	89	89	89	89	88	88	88	88	87	88
8a	90	90	90	89	89	88	87	86	85	85	87
8b	87	87	87	87	86	86	86	85	85	85	86



Scheme 1. . Three-phase test performed for SiO_2–Cu.

protocol. Firstly, 4-(chloromethyl)benzoyl chloride was tethered to Wang resin under basic conditions and the resulting material was subsequently incubated with trimethylsilyl azide and TBAF (Scheme 1) to generate the polymer-bound reactive 1,3-dipolar compound **10**. The immobilized azide **10** was then subjected to 1,3-dipolar cycloaddition (Scheme 1) using phenylacetylene (**2a**) as the dipolarophile along with one of the catalysts described here [SiO_2–Cu(I), copper loading: 9.4%]. In a parallel experiment, the supported azide **10** and **2a** were reacted in the presence of DIPEA and copper(I) iodide (Scheme 1). After 24 h at room temperature, complete conversion of **2a** was observed with only the latter experiment affording (after appropriate work-up and cleavage) 4-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]benzoic acid (**11**). These findings are consistent with the results obtained during the determination of copper in two representative 1,2,3-triazoles in the series (compounds **3a** and **3b**). Inductively coupled plasma mass spectroscopy (ICP-MS) analysis did not show the presence of copper traces in the 1,2,3-triazoles **3a** and **3b** (see experimental part). These findings unequivocally confirm that soluble copper species are not involved in the catalytic cycle of the Huisgen 1,3-dipolar cycloaddition on employing SiO_2–Cu(I) and that the catalysis is only promoted heterogeneously by the solid catalyst.

4. Conclusions

In summary, SiO_2–Cu has been shown to be a highly active, robust and versatile catalyst for the Huisgen 1,3-dipolar cycloaddition and intramolecular Ullmann coupling reactions. The experiments reported here demonstrate that SiO_2–Cu constitutes a novel recyclable heterogeneous catalyst that exhibits negligible leaching of metal to the reaction media. The results of loading studies show that the optimal amount of copper entrapped in the silica matrix is 9.4 wt.%. Given the current interest in reusable copper nanoparticles and the scarcity of reusable and versatile solid catalysts for a range of reactions, the copper-supported catalyst presented here constitutes a step forward in the development of highly active, heterogeneous and reusable catalysts.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.apcata.2015.05.025

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