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Highlights

Copper nanoparticles supported on silica coated maghemite as versatile, magnetically recoverable and reusable catalyst for alkyne coupling and cycloaddition reactions.

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- Copper nanoparticles on nanosized magnetic support as catalyst for alkyne synthetic transformations
- Commercially available silica coated maghemite (MagSilica) is used as magnetic support
- The nanocatalyst is easily recovered and reused by means of an external magnet
- High versatility of the catalyst for high atom economy alkyne coupling and cycloaddition reactions

Copper nanoparticles supported on silica coated maghemite as versatile, magnetically recoverable and reusable catalyst for alkyne coupling and cycloaddition reactions.

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Dedicated to Prof. Miguel Yus on occasion of his 65th birthday

Abstract

A versatile and magnetically recoverable catalyst consisting of copper nanoparticles on silica coated maghemite nanoparticles (MagSilica®) is presented. The catalyst has been prepared under mild conditions by fast reduction of anhydrous CuCl₂ with lithium sand and a catalytic amount of DTBB (4,4'-di-*tert*-butylbiphenyl) as electron carrier, in the presence of the magnetic support. The catalyst has been fully characterized and its performance in different coupling and cycloaddition reactions of terminal alkynes has been studied. This new copper-based catalyst has shown to be very efficient and easily reusable in the Glaser alkyne dimerization reaction in THF, the multicomponent Huisgen 1,3-dipolar cycloaddition reaction in water and the three-component synthesis of propargylamines under solvent free conditions.

Keywords: Copper nanoparticles; Magnetic support; Alkyne; Coupling; Cycloaddition

1. Introduction

Alkynes are core building blocks for the construction of highly functionalized organic substructures, which are essential in the synthesis of many industrial products, molecular materials and bioactive compounds. In particular, metal-catalyzed coupling and cycloaddition reactions of terminal alkynes provide a key tool for accessing to complex organic structures from simple and readily available starting materials [1]. Prominent examples in this regard are the coupling of terminal alkynes for the synthesis of 1,3-diynes (Glaser

dimerization) [2], multicomponent reactions (MCR) involving aldehydes, amines and terminal alkynes [3] for the synthesis of propargylamines, and the 1,3-dipolar cycloaddition of azides and terminal alkynes to yield 1,2,3-triazoles (Huisgen reaction) [4] which is the paradigm of a click reaction. In all the above mentioned transformations, copper catalysts have been by far the most studied ones, however, most of the catalytic systems are homogeneous, hampering the recovery and recycling of the catalyst. Regardless of the chemical transformation considered, it is broadly accepted that homogeneous catalysts are intrinsically more active and selective than heterogeneous ones, while these latter allow an easier and more economical separation and reuse of the catalyst. In any case, the use of highly efficient, economic and recoverable catalysts, with low or null toxicity is essential from the green chemistry perspective. In this context, the synthesis of transition metal nanoparticles and their application in catalysis have received considerable attention in recent years [5]. Due to their high surface area, these nanosized metal particles often show a remarkable catalytic performance, and are considered to be on the frontier between the homogeneous and heterogeneous catalysis, preserving the main advantages of both methodologies. However, in practice, the separation and recovery of these nanocatalysts from the reaction medium by using standard techniques (filtration, centrifugation) is not always easy due to the nanometric size of the particles. To overcome this drawback, metal nanoparticles are supported over a variety of organic and inorganic supports. Among them, magnetic nanomaterials have emerged lately as a very attractive alternative since their high surface area allows higher catalyst loading than many conventional supports, and their magnetic properties enables the simple and efficient recovery of the catalyst by means of an external magnet [6]. The magnetic nanoparticles utilized as supports usually consist of core-shell structures, being iron oxides (Fe_xO_y) the most commonly used ones. The coating of these magnetic nanomaterials prevents aggregation/oxidation and serves as platform for the catalyst. For this purpose, silica has been widely used because of its stability under different reaction conditions and due to the fact that it can be easily functionalized for diverse applications [7].

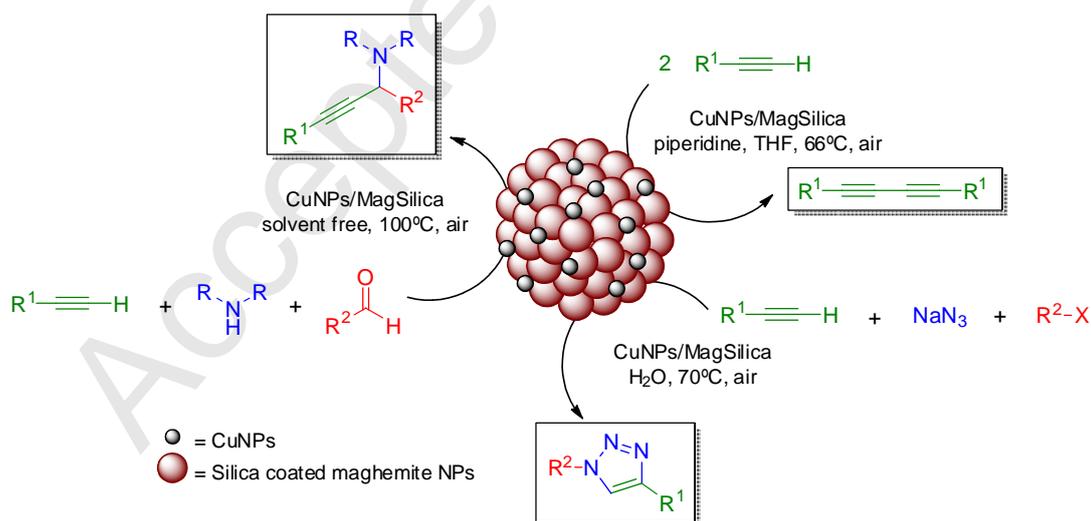
On the other hand, besides recovery and reuse, the simplicity in catalyst preparation is a very important issue from the practical and utility point of view. Examples of heterogeneous copper-catalysts that are easy to prepare, versatile and reusable in the three above mentioned alkyne transformations, are scant. The heterogeneous copper-catalyzed homocoupling of terminal alkynes has been a subject of recent interest but have rarely been studied. For instance, a CuAl hydrotalcite exhibited excellent recyclability at room

temperature in acetonitrile, although stoichiometric amounts of *N,N,N,N*-tetramethylethylenediamine (TMEDA) and catalyst (110 mol%) were required [8]. Copper(I) zeolites were tested for the title reaction in *N,N*-dimethylformamide (DMF) at 110 °C and 30 mol% copper loading, with no apparent possibility of catalyst recycling [9]. Mizuno and co-workers reported a catalyst consisting of $\text{Cu}(\text{OH})_x/\text{TiO}_2$ (5 mol% Cu) that did not require the presence of a base and showed high catalytic activity in toluene at 100 °C under 1 atm O_2 [10]. Only one recycling experiment was described in this article, which showed a slight decrease in yield (from 90 to 82%). A very similar scenario can be found in the literature with regard to the A^3 coupling reaction for the synthesis of propargylamines. The catalytic activation of the C–H bond of terminal alkynes has been achieved with complexes or salts of the late transition metals (e.g., Ir, Zn, Fe, Co, Ni, Ag, Au, Ir, Ru, but also In), but copper has been by far the most studied metal [11]. However, most of the catalytic systems reported are homogeneous in nature, making the recovery and recycling of the catalyst troublesome. Impregnated copper on magnetite has been reported to be a heterogeneous and reusable copper-based catalyst for the A^3 coupling [12], but some copper and iron leaching has been observed, and the preparation of the catalyst requires 24 hours of stirring and several days of drying before its use. With regard to the three-component 1,3-dipolar cycloaddition reaction, examples about the use of heterogeneous catalysts that can be recovery and reuse for this important transformation are also scarce. In this sense, some reports on the copper-catalyzed multi-component synthesis of triazoles in water, using heterogeneous catalysts, have appeared in the literature [13]. For example, copper nanoparticles on alumina catalyzed the multicomponent synthesis of 1,2,3-triazoles, in modest to good yields, however, only activated organic halides were reported and the preparation of the catalyst seems rather tedious, through an aerogel method under supercritical conditions [13a]. Porphyrinatocopper nanoparticles onto activated multi-walled carbon nanotubes has been also used as heterogeneous catalyst in the three-component 1,3-dipolar cycloaddition reaction with epoxides (not with the more abundant organic halides) [13b]. Reactions proceed at room temperature although the catalyst preparation is rather laborious and time consuming (synthesis of carbon nanotubes followed by oxidation, UV and microwave radiation, and anchoring of the complex through ultrasonic, microwave, and dichloromethane treatment).

In the last years, some of us have been actively working on new methodologies for the preparation of transition metal nanoparticles (NPs) and their application in important organic transformations, mainly in

reduction and coupling reactions. The methodologies that we developed are simple and economic ones, and consist in the fast reduction of transition metal chlorides with lithium sand and a catalytic amount of an arene as electron carrier, in tetrahydrofuran as solvent and at room temperature. We have found that by using this methodology, CuCl_2 or $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ are suitable precursors for the synthesis of very reactive CuNPs, with a size distribution in the range of 3.0 ± 1.5 nm [14]. These naked CuNPs, generated in situ, efficiently promoted the Glaser dimerization of terminal alkynes [15] and the Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes [16]. More recently, the same methodology was applied for the synthesis of CuNPs supported on activated carbon and titania. The CuNPs/C catalyst showed a remarkable versatility in the multicomponent Huisgen cycloaddition in water [17], while the CuNPs/titania efficiently catalyzed the homocoupling of terminal alkynes [18] and the solvent-free three-component coupling of aldehydes, amines and alkynes [19].

Driven by our continuing interest in this family of CuNPs-based catalysts and with the aim to expand and improve their catalytic applications, we want to present herein a new magnetically recoverable catalyst consisting in the synthesis of CuNPs (3.0 ± 0.8 nm) over commercially available silica coated maghemite nanoparticles (MagSilica®, 5-30 nm), and the study of its catalytic performance in three important synthetic transformations involving terminal alkynes (Scheme 1).



Scheme 1

2. Experimental

2.1. Materials

All moisture sensitive reactions were carried out under a nitrogen atmosphere. Anhydrous tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl. Other solvents were treated prior to use by standard methods [20]. All starting materials were of the best available grade (Aldrich, Fluka, Merck) and were used without further purification. Commercially available copper(II) chloride dihydrate was dehydrated upon heating in oven (150 °C, 45 min) prior to use for the preparation of CuNPs. MagSilica® was provided by Evonik Industries AG (Essen, Germany). Column chromatography was performed with Merck silica gel 60 (0.040–0.063 μm , 240–400 mesh). Thin layer chromatography (TLC) was performed on precoated silica gel plates (Merck 60, F254, 0.25 mm).

2.2. Instrumentation and analysis

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 spectrophotometer using CDCl_3 as the solvent and tetramethylsilane (TMS) as internal reference. Mass spectra (EI) were obtained at 70 eV on a Hewlett Packard HP-5890 GC/MS instrument equipped with a HP-5972 selective mass detector. Infrared (FT-IR) spectra were obtained on a Nicolet-Nexus spectrophotometer. The purity of volatile compounds and the chromatographic analyses (GC) were determined with a Shimadzu GC-14B instrument equipped with a flame-ionisation detector and a 30 m column (HP-5MS, 0.25mm, 0.25 μm), using nitrogen as carrier gas.

2.3. CuNPs/MagSilica catalyst preparation.

A mixture of lithium sand (21 mg, 3.0 mmol) and 4,4'-di-*tert*-butylbiphenyl (DTBB, 26 mg, 0.1 mmol) in THF (3 mL), was stirred at room temperature under nitrogen atmosphere. When the reaction mixture turned dark green (15-30 min), indicating the formation of the corresponding lithium arenide, anhydrous CuCl_2 was added (134 mg, 1.0 mmol). The resulting suspension was stirred until it turned black (15-30 min), indicating the formation of copper(0) nanoparticles. Then, it was diluted with THF (10 mL) and MagSilica (500 mg) was added. The resulting suspension was stirred for 1 h, and then bidistilled water (2 mL) was added for eliminating the excess of lithium. The resulting solid was filtered under vacuum in a Buchner funnel and washed successively with water (10 mL) and acetone (10 mL). Finally, the solid was dried under vacuum (5 Torr) for 2 hours.

2.4. CuNPs/MagSilica catalyst characterization.

The freshly prepared catalyst was characterized by Transmission Electron Microscopy (TEM) in a JEOL JEM-2100F-UHR instrument, operated at an acceleration voltage of 200 kV. Approximately one hundred metal particles were measured to perform the particle size distribution.

Copper content in the supported catalyst was determined by Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES), in a Spectro Arcos instrument.

The catalyst specific surface area was measured by BET method, from a N₂ isotherm at 77K in NOVA 1200e apparatus.

The reducibility of the supported catalysts was analyzed by Temperature Programmed Reduction (TPR) in a home-made equipment. Before reduction, the samples were treated with flowing Ar at 300 °C. Then, a flowing mixture (20 mL/min) of 10 % H₂/Ar was introduced, raising the temperature at 8 °C/min from room temperature up to 550 °C. The TPR profile was obtained following the H₂ consumption with a TCD detector.

X-ray diffraction (XRD) analysis were performed using a Bruker AXS D8 Advance diffractometer, equipped with a Cu-Kα_{1,2} radiation source.

Atomic absorption spectroscopy was carried out in a Perkin Elmer AA700 spectrometer.

2.5. CuNPs/MagSilica catalyzed homocoupling of terminal alkynes. General procedure.

To a vigorously stirred suspension of the CuNPs/MagSilica catalyst (70 mg) in THF (4 mL) the corresponding alkyne (1.0 mmol) was added, followed by the dropwise addition of piperidine (85 mg, 99 μL, 1.0 mmol). The reaction flask was introduced in a preheated silicon oil bath at a temperature high enough to ensure the reflux of the solvent (66 °C), and stirred at this temperature until total conversion of the starting alkyne (TLC, GC). The above described procedure was followed for the catalyst recovery and reaction products isolation.

2.6. CuNPs/MagSilica catalyzed multicomponent Huisgen 1,3-dipolar cycloaddition reaction. General procedure.

To a vigorously stirred suspension of the CuNPs/MagSilica catalyst (40 mg) and NaN₃ (72 mg, 1.1 mmol) in water (2 mL), the corresponding alkyl halide (1.0 mmol) was added dropwise, followed by the addition of the terminal alkyne (1.0 mmol). The reaction mixture was stirred at 70 °C until total conversion of the starting alkyne (TLC, GC). The triazole product formation can be easily visualized as a solid floating on the water

surface. Then, the catalyst was immobilized by means of a permanent magnet placed on the outer wall of the reaction flask, and was successively washed with water (2 mL) and CH_2Cl_2 (10 mL). Finally, the catalyst was dried under vacuum (5 Torr) for its recovery and reuse.

The possibility of catalyst leaching in the reaction media was evaluated by measuring the copper concentration in the reaction mixture, by means of atomic absorption spectroscopy.

2.7. CuNPs/MagSilica catalyzed three-component coupling of aldehyde, amine and terminal alkyne. General procedure.

The corresponding aldehyde (1.0 mmol), amine (1.1 mmol) and terminal alkyne (1.0 mmol) were successively added to the CuNPs/MagSilica catalyst (10 mg), and then stirred at 100 °C until total conversion of the starting alkyne (TLC, GC). The catalyst was immobilized by means of a permanent magnet placed on the outer wall of the reaction flask, and washed twice with Et_2O (10 mL each). Finally, the catalyst was dried under vacuum (5 Torr) for its recovery and reuse.

3. Results and discussion

3.1. Preparation and characterization of the catalyst.

As described in the Experimental section, the catalyst was prepared by addition of MagSilica to a suspension of CuNPs readily generated from anhydrous copper(II) chloride, lithium sand, and a catalytic amount of DTBB (10 mol%) in THF at room temperature. The CuNPs/MagSilica catalyst was characterized by means of transmission electron microscopy (TEM), energy dispersive X-ray (EDX), powder X-ray diffraction (XRD), temperature programmed reduction (TPR), and inductively coupled plasma atomic emission spectroscopy (ICP-AES).

The copper loading fixed to MagSilica was 6.8wt% as determined by ICP-AES. The TPR profile of the catalyst is shown in Figure 1. The consumption peak is assigned to copper oxidized species. The amount of hydrogen consumed corresponds to the reduction of the whole CuO present in the catalyst, which is being reduced to Cu(0). Since the samples were not previously calcined, the presence of these species indicates that CuNPs are being oxidized during handling of the catalyst under air. Besides, no peaks attributable to the support reduction were detected. Since maghemite reduction occurs in the temperature range of the TPR

experiments [21], the lack of iron species available for reduction strongly suggests that the magnetic core is fully coated by the SiO₂ shell.

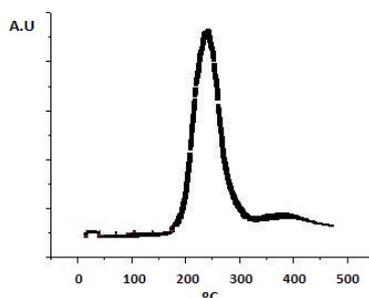


Figure 1. TPR profile for CuNPs/MagSilica catalyst.

Analysis by TEM showed the presence of well dispersed spherical nanoparticles on the magnetic support, with a narrow size distribution and an average particle size of 3.0 ± 0.8 nm (Figure 2), thus demonstrating that the nanometric dimension of the CuNPs is not lost upon supporting on the silica coated maghemite nanoparticles. This is a remarkable result since previous attempts by some of us for supporting CuNPs on SiO₂, using this same methodology, led to the formation of CuNPs with an average size of around 20 nm.

The average particle size of copper in CuNPs/MagSilica was recalculated to metal dispersion (D), following the relationship from Scholten et al. [22]: $D = 10^{21} \times 6 \times M \times \rho_{\text{site}} / (d \times \rho_{\text{metal}} \times N)$, where D is the copper dispersion ($\text{Cu}_{\text{sup}}/\text{Cu}_{\text{total}}$) M, the atomic weight (63.5g/mol), ρ_{site} the copper surface density (13.5 Cu atoms/nm²) [23], d is the particle size (in nm), ρ_{metal} , the metal density (8.96 g/cm³) and N the Avogadro number. Thus a copper dispersion of 32% was obtained for the catalysts.

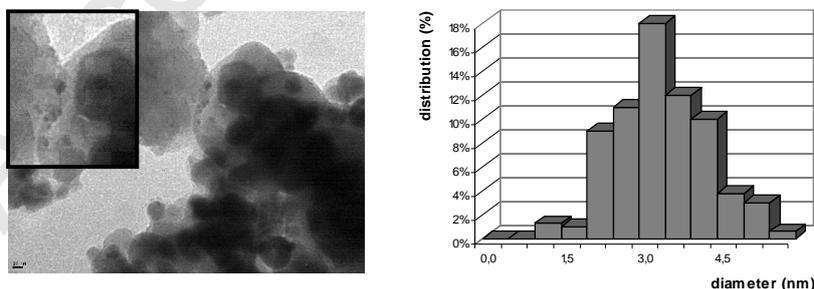


Figure 2. TEM micrograph and size distribution graphic of CuNPs/MagSilica catalyst.

Energy dispersive X-ray analysis on various regions confirmed the presence of copper, with energy bands of 8.04, 8.90 (K lines) and 0.92 keV (L line). The XRD diffractogram showed the support diffraction pattern,

but no diffraction peaks owing to copper species were detected, this could be attributed to the amorphous character of the oxidized CuNPs deposited on the support and/or to the existence of crystal domains below 10 nm in size.

The BET surface area of CuNPs/MagSilica was 27 m²/g, which is the same as the corresponding to the bare support. It is important to note that the dispersion of copper attained in the CuNPs/MagSilica catalyst is relatively high (32%), considering that the surface area of the support is rather low.

3.2. Evaluation of the catalyst performance in alkyne coupling and cycloaddition reactions.

The CuNPs/MagSilica catalyst was tested in three different terminal-alkyne transformations: the homocoupling of terminal alkynes (Glaser dimerization), the multicomponent 1,3-dipolar cycloaddition of terminal alkynes, sodium azide and alkyl halides, and the three-component synthesis of propargylamines from aldehydes, amines and terminal alkynes (A³ coupling). The catalyst was used as prepared, without any pre-treatment. The amount of CuNPs/MagSilica catalyst needed and the optimal reaction conditions were determined independently for each of the three reactions studied.

3.2.1. Direct homocoupling of terminal alkynes catalyzed by CuNPs/MagSilica.

As shown in Table 1, the reaction conditions were optimized using phenylacetylene as model compound. The addition of piperidine as base (1 equiv. referred to the starting alkyne), in order to promote a base-assisted deprotonation of the starting alkyne, and heating at 66 °C (reflux temperature of THF) was essential to obtain the maximum yield of the desired 1,3-diyne product in minimum reaction time. Other bases tested, such as triethylamine, pyridine, sodium carbonate and cesium carbonate, under the same reaction conditions gave poorer results in terms of conversion to the alkyne dimerization product. These reaction conditions were applied at different catalyst loading, and it was found that 70 mg of CuNPs/MagSilica (7.5 mol% Cu) was the optimum amount of catalyst for this reaction.

For the optimized conditions the specific rate, expressed as moles of alkyne converted per g copper was 1.7 x 10⁻⁵ while the TOF number was 3.5 x 10⁻³ s⁻¹.

Under the optimized conditions phenylacetylene gave the homocoupled diyne product in only 2 hours of reaction time and in high yield (Table 2, entry 1). A similar reactivity was observed for 4-methylphenylacetylene (Table 2, entry 2). In contrast, 4-*N,N*-dimethylaminophenylacetylene showed to be less reactive under the same reaction conditions (Table 2, entry 3), probably due to the presence of a strong

electron releasing group at the 4-position of the phenyl group, which could be hampering the formation of the corresponding copper acetylide.

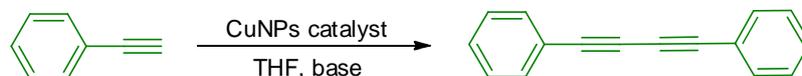


Table 1. Optimization of reaction conditions for alkyne homocoupling reaction.^a

Entry	Amount of catalyst (mg)	Copper content (mol%) ^b	Base	T (° C)	t (h)	Yield (%) ^c
1	100	10.7	piperidine	66	2	94
2	70	7.5	piperidine	66	2	95
3	40	4.3	piperidine	66	10	10
4	20	2.2	piperidine	66	20	traces
5	70	7.5	other ^d	66	8	traces
6	70	7.5	piperidine	25	8	5

^a Alkyne (1 mmol), base (1 mmol), in THF as solvent and under air.

^b Referred to the starting alkyne.

^c GC yield based on the starting alkyne.

^d Other bases tested: sodium carbonate, triethylamine, pyridine, cesium carbonate.

Aliphatic alkynes such as 1-octyne, 1-dodecyne, 1-ethynylcyclohex-1-ene and 4-phenyl-1-butyne, gave the corresponding 1,3-diyne products in good to excellent yields but in higher reaction times (Table 2, entries 4-7). These results are in agreement with the fact that aliphatic terminal alkynes are sluggish in undergoing Glaser dimerization, probably due to the weaker acidity of the acetylenic proton [24].

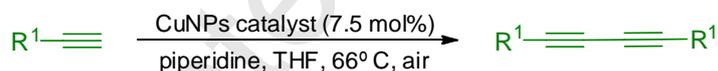


Table 2. CuNPs/MagSilica catalyzed homocoupling of terminal alkynes.

Entry	R ¹	t (h)	Yield (%) ^b
1	Ph	2	95
2	4-CH ₃ C ₆ H ₄	2	83
3	4-(CH ₃) ₂ NC ₆ H ₄	14	58
4	<i>n</i> -C ₆ H ₁₃	15	90
5	<i>n</i> -C ₁₀ H ₂₁	18	88
6	<i>c</i> -C ₆ H ₉	24	72
7	Ph(CH ₂) ₂	24	75

^a Reaction conditions: alkyne (1 mmol), piperidine (1 mmol), CuNPs/MagSilica (70 mg), 66° C, in THF as solvent and under air.

^b Isolated yield after column chromatography (hexane-EtOAc), based on the starting alkyne.

3.2.2. Multicomponent synthesis of 1,2,3-triazoles in water catalyzed by CuNPs/MagSilica.

The CuNPs/MagSilica catalyst demonstrated to be very efficient in the multicomponent 1,3-dipolar cycloaddition of terminal alkynes and organic azides generated *in situ* from sodium azide and different organic halides. As shown in Table 3, phenylacetylene and benzyl bromide were selected as model starting compounds for the optimization of the reaction conditions. Interestingly, from the different solvents and solvent/co-solvent mixtures tested, water was found to be the most effective for this reaction (Table 3, compare entries 1, 4, 5 and 6). Thus, using 40 mg of CuNPs/MagSilica catalyst (4.3 mol% Cu) and heating at 70 °C in water, the reaction of phenylacetylene with benzyl bromide and sodium azide, gave 1-benzyl-4-phenyl-1*H*-1,2,3-triazole almost quantitatively in only 1 hour of reaction time (Table 3, entry 1).

The specific rate for this reaction at the above described conditions is 6×10^{-5} moles converted per gram of copper and per second, while the TOF number is 0.012 s^{-1} . When THF is employed as the solvent, the TOF number is notably lower ($1 \times 10^{-4} \text{ s}^{-1}$) than that of the reaction performed in water. The depletion in the rate would be related to the fact that the *in situ* generation of the organic azide is hampered in the organic solvent, due to the low solubility of the starting sodium azide in the reaction medium.

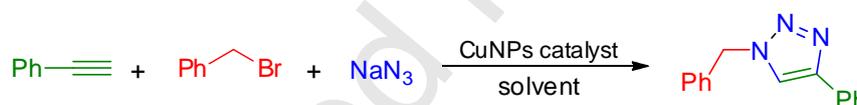


Table 3. Optimization of reaction conditions for the multicomponent synthesis of 1,2,3-triazoles.^a

Entry	Amount of catalyst (mg)	Copper content (mol%) ^b	Solvent	T (°C)	t (h)	Yield (%) ^c
1	40	4.3	H₂O	70	1	98
2	20	2.2	H ₂ O	70	12	10
3	40	4.3	H ₂ O	25	10	25
4	40	4.3	DMF/H ₂ O (9:1)	70	12	15
5	40	4.3	MeOH/H ₂ O (9:1)	70	12	85
6	40	4.3	THF	70	10	8

^a Phenylacetylene (1 mmol), benzyl bromide (1 mmol), sodium azide (1.1 mmol), under air.

^b Referred to the starting alkyne

^c GC yield based on the starting alkyne.

The same methodology was successfully applied to other aryl acetylenes bearing both electron-withdrawing or electron-releasing groups attached to the aromatic ring (Table 4, entries 2 and 3). Aliphatic alkynes, such as 1-hexyne and cyclohexylacetylene also gave the corresponding triazole products in good yield, although in longer reaction times compared with their aryl counterparts (Table 4, entries 4 and 5). The propargyl ether

tetrahydro-2-(prop-2-ynoxy)-2H-pyran, gave a doubly heterocyclic triazole product in good yield (Table 4, entry 6). Then, the catalyst was tested for the reaction of phenylacetylene and alkyl halides other than benzyl bromide. Benzyl chloride, 4-methylbenzyl bromide, 2-nitrobenzyl bromide and 4-vinylbenzyl chloride gave the corresponding triazole products in good yield (Table 4, entries 7-10), whereas the strongly deactivated 4-methoxybenzyl chloride, as expected, gave poorer results (Table 4, entry 11). Finally, *n*-nonyl iodide reacted sluggishly and heating to 100 °C was necessary to enhance the yield and minimize the reaction time (Table 4, entry 12).

It is worthy of note that the degree of copper leaching during these experiments was below the atomic absorption spectrometry sensitivity threshold, since no presence of copper was detected in the aqueous phase of three different samples.

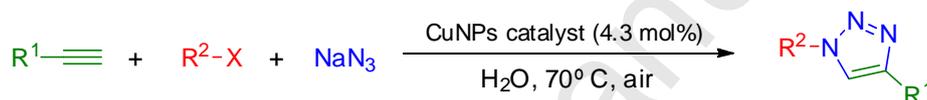


Table 4. CuNPs/MagSilica catalyzed multicomponent synthesis of 1,2,3-triazoles.^a

Entry	R ¹	R ² -X	t (h)	Yield (%) ^b
1	Ph	PhCH ₂ Br	1	98
2	4-BrC ₆ H ₄	PhCH ₂ Br	3	95
3	4-(CH ₃) ₂ NC ₆ H ₄	PhCH ₂ Br	2	98
4	<i>n</i> -C ₄ H ₉	PhCH ₂ Br	8	93
5	<i>c</i> -C ₆ H ₁₁	PhCH ₂ Br	6	95
6	(2-tetrahydropyranyloxy)methyl	PhCH ₂ Br	5	85
7	Ph	PhCH ₂ Cl	2	83
8	Ph	4-CH ₃ C ₆ H ₄ CH ₂ Br	4	75
9	Ph	2-NO ₂ C ₆ H ₄ CH ₂ Br	2	77
10	Ph	4-CH ₂ =CHC ₆ H ₄ Cl	8	70
11	Ph	4-CH ₃ OC ₆ H ₄ CH ₂ Cl	8	50
12	Ph	<i>n</i> -C ₉ H ₁₉ I	9	74 ^c

^a Reaction conditions: alkyl halide (1 mmol), alkyne (1 mmol), sodium azide (1.1 mmol), CuNPs/MagSilica (40 mg), 70° C, in water as solvent and under air, unless otherwise stated.

^b Isolated yield after column chromatography (hexane-EtOAc), based on the starting alkyne.

^c Reaction performed at 100° C.

3.2.3. Three-component synthesis of propargyl amines from aldehydes, alkynes and amines (A³ coupling) catalyzed by CuNPs/MagSilica.

The reaction conditions were optimized using benzaldehyde, phenylacetylene and morpholine (1:1:1.1) in the absence of solvent (Table 5). The reaction temperature was varied from 50 to 100 °C, and the amount of

catalyst from 40 to 2.5 mg. As shown in Table 5, the best conditions, in order to obtain the A³ coupling product while minimizing the dimerization of the starting alkyne, were found to be the use of 10 mg of CuNPs/MagSilica (1.1 mol% Cu) at 100 °C; under these conditions the reaction proceeded to the formation of the corresponding propargylamine in only 1 h of reaction time and in 84% yield (Table 5, entry 5).

Under the optimized reaction conditions, other alkynes such as 4-methylphenylacetylene, 1-ethynylcyclohexene and 1-dodecyne were reacted with benzaldehyde and morpholine which also gave the A³ coupling product in good yield and in short reaction times (Table 6, entries 2, 3 and 4, respectively).

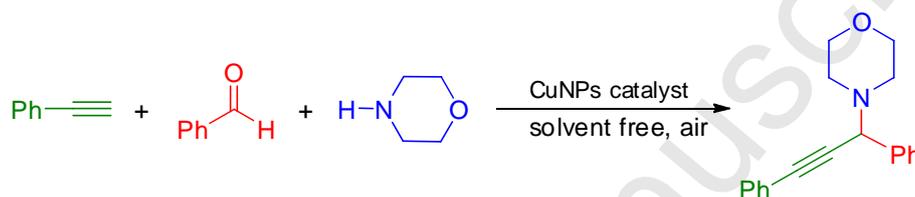


Table 5. Optimization of reaction conditions for the three-component synthesis of propargylamines.^a

Entry	Amount of catalyst (mg)	Copper content (mol%) ^b	T (° C)	t (h)	Yield (%) ^c
1	40	4.3	50	10	20
2	40	4.3	76	8	48
3	20	2.2	76	8	53
4	20	2.2	100	14	68
5	10	1.1	100	1	84
6	5	0.6	100	5	60

^a Phenylacetylene (1 mmol), benzaldehyde (1 mmol), morpholine (1.1 mmol), under air.

^b Referred to the starting alkyne.

^c GC yield based on the starting alkyne.

Then, different aldehydes were reacted with phenylacetylene and morpholine under the same conditions, thus 4-methoxybenzaldehyde and the aliphatic aldehyde (*S*)-(-)-citronellal gave the corresponding propargylamine products in good yield (Table 6, entry 5 and 6). In the case of citronellal, the diastereoselectivity of the coupling reaction was practically negligible.

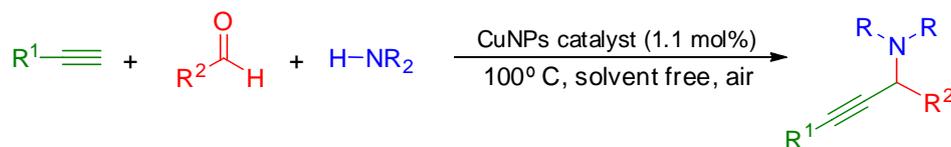


Table 6. CuNPs/MagSilica catalyzed three-component synthesis of propargylamines.^a

Entry	R ¹	R ²	Amine	t (h)	Yield (%) ^b
1	Ph	Ph	Morpholine	1	84
2	4-CH ₃ C ₆ H ₄	Ph	Morpholine	1	83
3	<i>c</i> -C ₆ H ₉	Ph	Morpholine	1	95
4	<i>n</i> -C ₁₀ H ₂₁	Ph	Morpholine	3	89
5	Ph	4-CH ₃ OC ₆ H ₄	Morpholine	3	76
6	Ph	(CH ₃) ₂ C=CH(CH ₂) ₂ CH(CH ₃)CH ₂	Morpholine	2	82
7	Ph	Ph	Pyrrolidine	3	77
8	Ph	Ph	Diethylamine	15	40
9	Ph	Ph	Diisopropylamine	20	20

^a Reaction conditions: alkyne (1 mmol), aldehyde (1 mmol), amine (1.1 mmol), CuNPs/MagSilica (10 mg), 100° C, under air, unless otherwise stated.

^b Isolated yield after column chromatography (hexane-EtOAc), based on the starting alkyne.

Finally, we examined the reaction with amines other than morpholine. As shown in Table 6 (entries 7-9) pyrrolidine, a cyclic secondary amine, gave similar results to those obtained with morpholine when reacted with benzaldehyde and phenylacetylene, whereas acyclic amines such as diethylamine and diisopropylamine rendered the corresponding A³ coupling products after longer reaction time and in modest yield.

3.3. Recovery and reuse of the catalyst.

We selected the three-component synthesis of propargylamines as model reaction for the study of the catalyst performance after various cycles of recovery and reuse. It is worthy of note that, even though the small amount of catalyst utilized (10 mg), it could be separated from the reaction medium, washed and reused very easily, simply with the aid of a permanent magnet placed on the outer wall of the reaction flask, thus minimizing the loss of catalyst which usually occurs in filtration processes. Figure 3 shows the catalyst performance for the A³ coupling of benzaldehyde, 4-methylphenylacetylene and morpholine, after three consecutive cycles without significant loss of catalytic activity. The low diminution in the activity from the first to the third cycle would be related with small losses of catalyst mass during washing procedure. It is important to note that the total mass of catalyst employed is very low (10 mg), thus the loss of only 1 mg of catalyst when handling the sample, means loss of 10% of the total mass of catalyst.

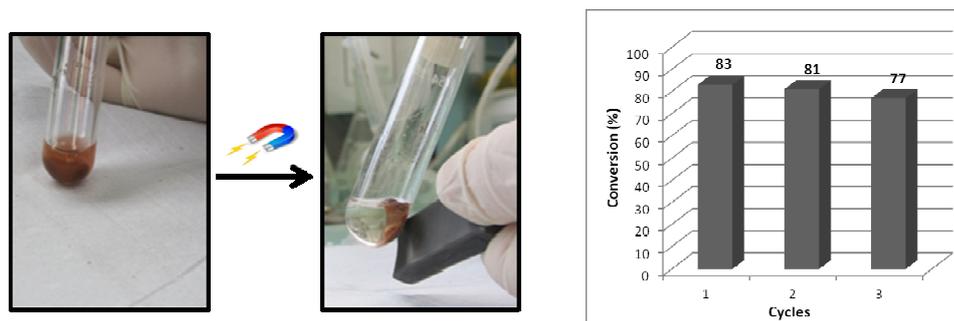


Figure 3. Recovery and recycling of the catalyst in the synthesis of propargylamines.

4. Conclusions

A new copper-based catalyst composed of copper nanoparticles (ca. 3.0 nm) on silica coated maghemite nanoparticles (5-30 nm), was readily prepared under mild conditions and completely characterized. It proved to be an efficient heterogeneous catalyst in three important alkyne transformations of wide synthetic utility. The catalyst could be easily recycled by means of an external magnet and reused without significant loss of catalytic activity. The easy recovery of the catalyst, together with the negligible leaching of metal species (no detected by AAS) and the high atom economy involved in the transformations studied, make this methodology to fulfill the requirements of green catalysis. Although the experimental observations point to a heterogeneous catalytic process, it should not be discarded that the copper supported nanocatalyst could be acting as a reservoir for metal species that leach into solution and re-adsorb [25].

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