

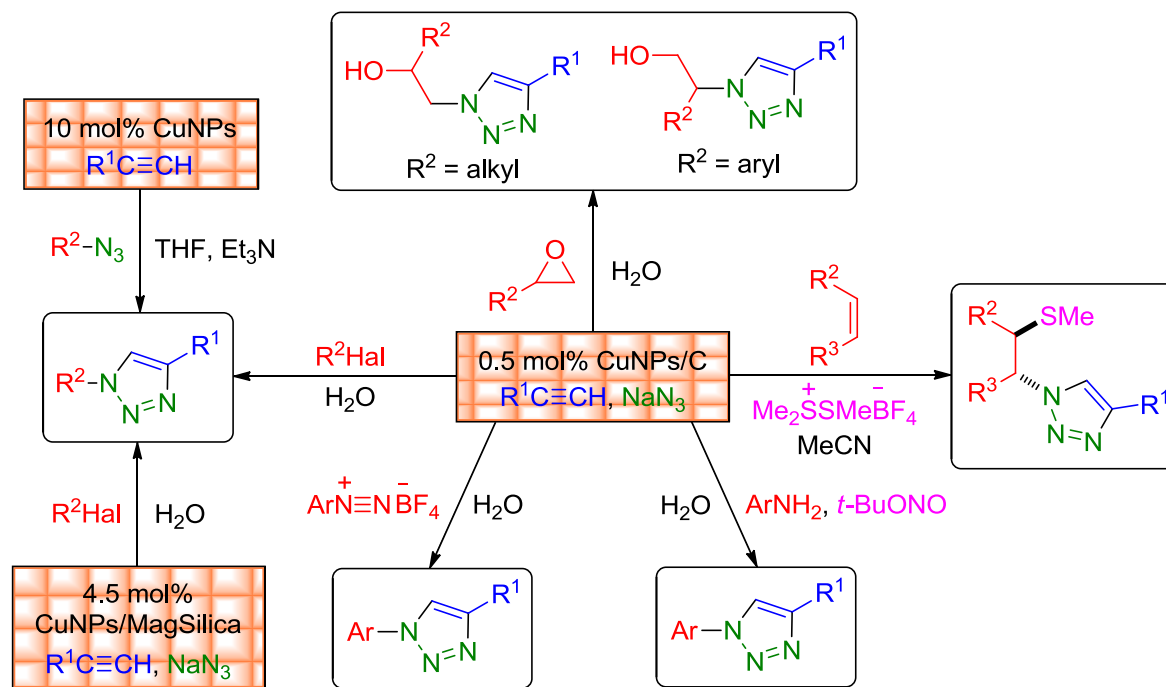
Copper Nanoparticles in Click Chemistry

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CONSPECTUS 1



The challenges of the 21st century demand scientific and technological achievements which must be developed under sustainable and environmentally benign practices. In this vein, Click Chemistry and Green Chemistry walk hand in hand on a pathway of rigorous principles which help to safeguard the health of our planet against negligent and uncontrolled production. The copper-catalyzed azide-alkyne cycloaddition (CuAAC), the paradigm of a click reaction, is one of the most reliable and widespread synthetic transformations in organic chemistry, with multidisciplinary applications. Nanocatalysis is a Green Chemistry tool which can increase the inherent effectiveness of the CuAAC because of the enhanced catalytic activity of nanostructured metals and their plausible reutilization capability as heterogeneous catalysts.

In this account, our contribution to Click Chemistry is described using unsupported and supported copper nanoparticles (CuNPs) as catalysts prepared by chemical reduction. Cu(0)NPs (3.0 ± 1.5 nm) in tetrahydrofuran were found to catalyze the reaction of terminal alkynes and organic azides, in the presence of triethylamine, at rates comparable to those achieved under microwave heating (10–30 min in most cases). Unfortunately, the CuNPs underwent dissolution under the reaction conditions and, consequently, could not be recovered. Compelling experimental evidence on the *in-situ* generation of highly reactive copper(I) chloride and the participation of copper(I) acetylides was provided.

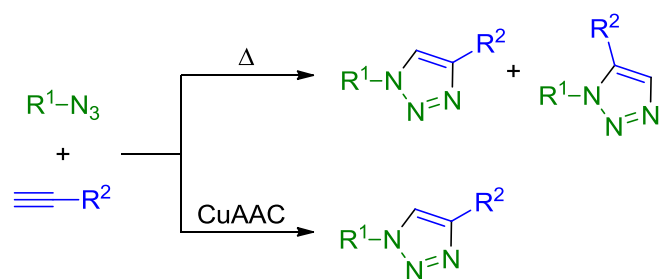
The supported CuNPs were found to be more robust and efficient catalyst than the unsupported counterpart in the following terms: (a) the multicomponent variant of the CuAAC could be applied, (b) with substantial decrease in the metal loading, (c) reactions could be conducted in neat water, and (d) with easy recovery and reutilization of the catalyst. In particular, the catalyst composed of oxidized CuNPs/C ($\text{Cu}_2\text{O}/\text{CuO}$, 6.0 ± 2.0 nm) was shown to be highly versatile and

very effective in the multicomponent and regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles in water from organic halides as azido precursors; magnetically recoverable CuNPs (3.0 ± 0.8 nm)/MagSilica could be alternatively used for the same purpose under similar conditions. Incorporation of an aromatic substituent at the position 1 of the triazole could be accomplished using the same CuNPs/C catalytic system, but starting from aryl diazonium salts or anilines as azido precursors. CuNPs/C in water also catalyzed the regioselective double-click synthesis of β -hydroxy-1,2,3-triazoles from epoxides. Furthermore, alkenes could be also used as azido precursors through a one-pot CuNPs/C-catalyzed azidosulfenylation-CuAAC sequential protocol, providing β -methylsulfanyl-1,2,3-triazoles in a stereo- and regioselective manner. In all the types of reaction studied, CuNPs/C exhibited better behavior than some commercial copper catalysts as regards the metal loading, reaction time, yield and recyclability. Therefore, the results of this study also highlight the utility of nanosized copper in Click Chemistry when compared with bulk copper sources.

1. Introduction

Click Chemistry is a conception of organic synthesis of paramount importance in modern chemistry.¹ Paraphrasing Sharpless *et al.*, Click Chemistry “represents certain highly efficient and reliable reactions which are modular, wide in scope, high yielding, stereospecific, proceed under simple and benign conditions and involve straightforward procedures for product isolation”. The copper-catalyzed azide-alkyne cycloaddition (CuAAC) stands out among this group of select reactions since the capital discovery by the teams of Meldal² and Sharpless³ in the dawn of the 21st century, namely: dramatic acceleration of the Huisgen⁴ 1,3-dipolar cycloaddition reaction of organic azides and alkynes was observed under copper(I) catalysis and mild conditions, together with a high regioselectivity towards the 1,4-regioisomer of the triazole (Scheme 1).⁵ The first decade of Click Chemistry has been recently commemorated;⁶ throughout this time, an increasing number of disciplines⁷ have taken advantage of the unique benefits hold out by the CuAAC, the click reaction *par antonomasia*.

SCHEME 1. The Huisgen and the CuAAC Syntheses of 1,2,3-Triazoles.



Green Chemistry⁸ shares with Click Chemistry some of the aforementioned stringent criteria, by the means of which more efficient and environmentally benign processes can be delineated and implemented. In this context, nanocatalysis has arisen as a competitive and sustainable option to

traditional catalysis because of the high surface-to-volume ratio of the nanoparticles, which heighten their activity and selectivity, preserving the inherent characteristics of a heterogeneous catalyst.⁹ Particularly, inorganic supports of high surface-area can be used to immobilize metal nanoparticles and obtain specially active and recyclable catalysts due to the higher stability and dispersion of the particles.¹⁰ Furthermore, the combined use of water as a solvent with metal nanoparticles is a fast-growing area in response to the general upsurge of interest in minimizing the environmental impact of chemistry.¹¹ With these principles in mind, new possibilities have arisen for the paradigmatic click reaction.

The CuAAC is typically accomplished using copper(I) sources, including: (a) copper(I) salts, (b) *in-situ* reduction of copper(II) salts and (c) comproportionation of copper(0) and copper(II). In 2005, stoichiometric copper metal, in the form of turnings or powder, was found to be a source of the catalytic species implicated in the click reaction.¹² Thereafter, the use of copper nanoparticles (CuNPs) has been increasingly explored as an alternative to bulk copper.¹³

Owing to our interest in metal colloids¹⁴ and initial studies on active copper [produced by reduction of copper(II) chloride dehydrate with lithium metal and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB) in tetrahydrofuran (THF)],¹⁵ the formation of CuNPs from either $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ or anhydrous CuCl_2 was discovered under the above-mentioned conditions. We wish to present herein our contribution to the field of Click Chemistry by means of catalysts which imply both unsupported and supported CuNPs. Pre-formed organic azides and terminal alkynes are used as starting materials in the first case; in the second case, a multicomponent approach is tackled from different azido precursors, sodium azide and terminal alkynes. It must be pointed out that, though this account is focused on heterogeneous catalysis, the fundamental contribution of homogeneous catalysis to the advance of Click Chemistry must not be

disregarded; to speed up the CuAAC at room temperature and decrease the amounts of copper up to a few ppm levels are some praiseworthy achievements of the homogeneous CuAAC.¹⁶

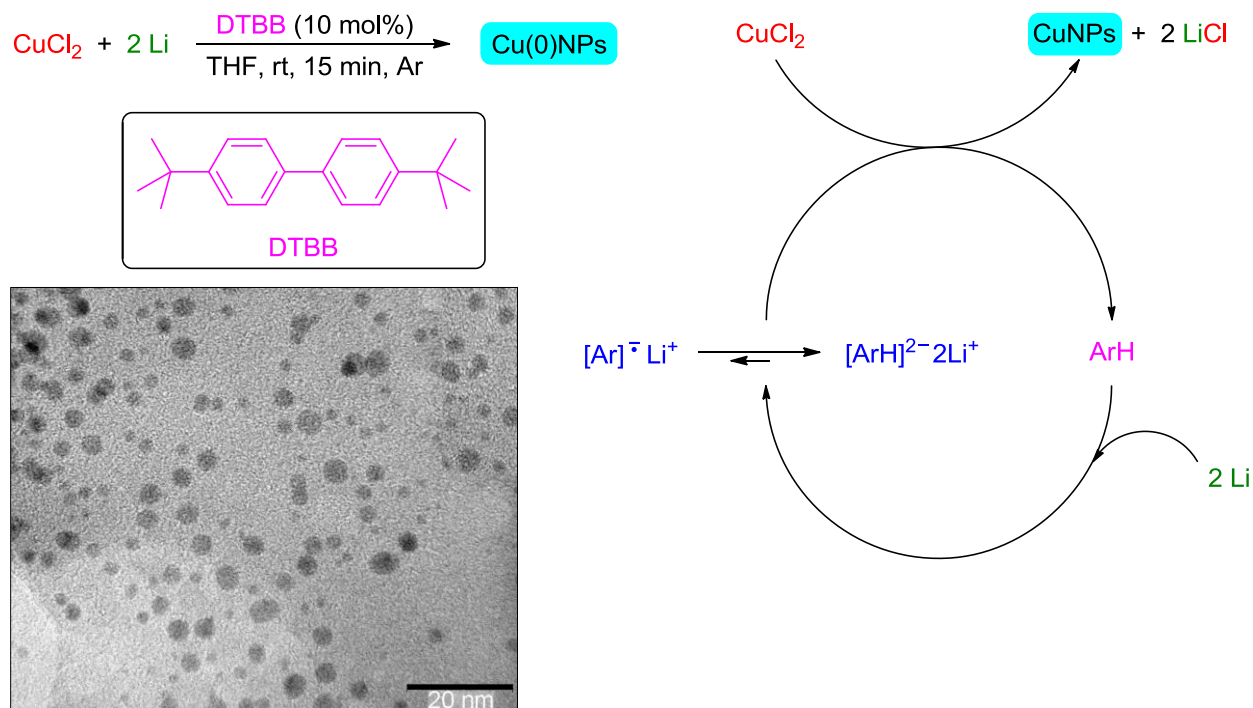
2. Discussion

2.1. Unsupported CuNPs in Click Chemistry

Unsupported CuNPs have been scarcely studied in the CuAAC when compared with the supported counterparts; the inherent tendency to particle agglomeration makes the presence of stabilizing agents or solid supports mandatory in most cases. Pioneering work by the groups of Rothenberg^{17a} and Orgueira^{17b} with Cu(0) nanoclusters was followed by the use of mixed Cu/Cu-oxide nanoparticles^{17c} and PVP-stabilized CuNPs,^{17d} all of which catalyzed the reaction of pre-formed azides and terminal alkynes.

Our group prepared Cu(0)NPs by the fast chemical reduction of anhydrous copper(II) chloride with lithium metal and a catalytic amount of DTBB as electron carrier, in THF at room temperature under argon, in the absence of any added nucleation or anti-agglomeration agent (Figure 1); the chloride anion (accompanied by its Li counteranion, derived from the reductant)^{18a} and, to a lesser extent, the solvent (tetrahydrofuran)^{18b} stabilized the nanoparticles by electrostatic forces. Characterization by transmission electron microscopy (TEM), X-ray photoelectron spectroscopy (XPS), powder X-ray diffraction (XRD), energy-dispersive X-ray (EDX) analysis and selected area electron-diffraction (SAED) pattern, brought into view spherical face-centered-cubic copper(0) nanoparticles with a particle size distribution of *ca.* 3.0 ± 1.5 nm.¹⁹

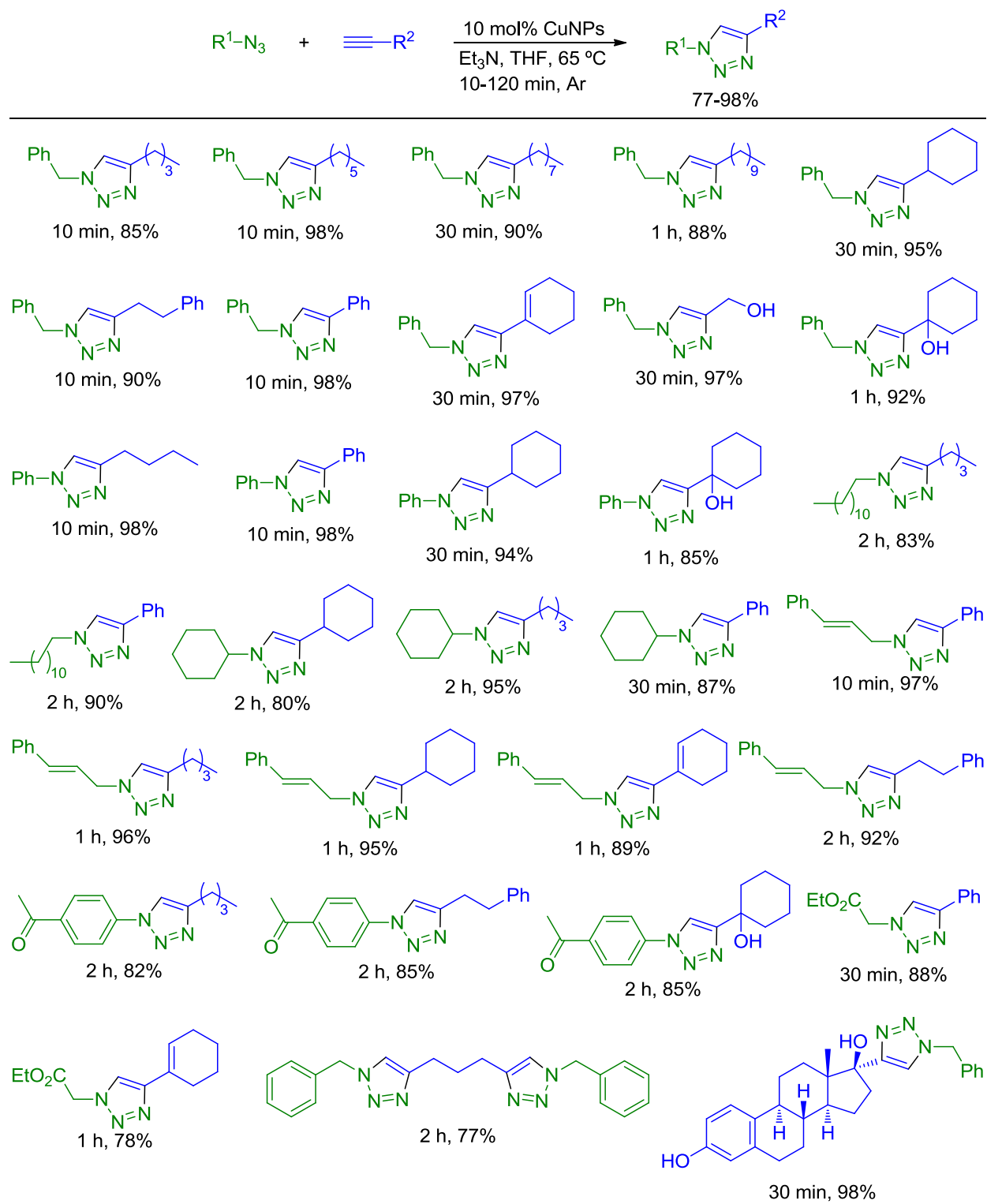
FIGURE 1. Synthesis and TEM Micrograph of the CuNPs (TEM Micrograph Adapted from Ref. 19a with Permission from Elsevier).



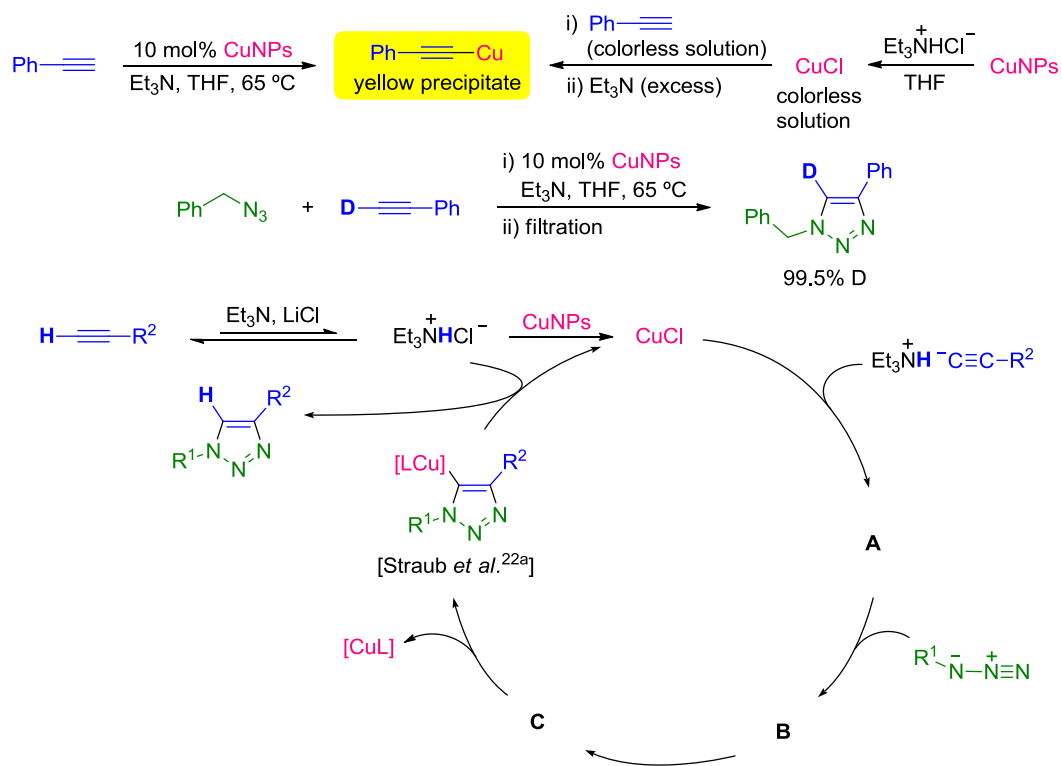
The as-prepared nanoparticles were found to catalyze (10 mol%) the reaction of azides and terminal alkynes using triethylamine as the base in THF at 65 °C under argon. Notably, all reactions were run for 10–120 min in the absence of any stabilizing additive or ligand, with these times being equivalent to those formerly reported under microwave heating.²⁰ The corresponding 1,2,3-triazoles were obtained in excellent isolated yields after simple work-up manipulation such as filtration and crystallization or solvent evaporation (Table 1). The CuNPs in THF exhibited superior catalytic activity in comparison with some commercial copper catalysts but, unfortunately, their dissolution under the reaction conditions precluded their reuse.

Much debate has arisen around the mechanism of the CuAAC.²¹ Based on different experiments,^{19b} a reaction mechanism was proposed whereby copper(I) acetylides appeared as

TABLE 1. AAC Catalyzed by unsupported CuNPs.



SCHEME 2. Selected Experiments for the AAC Catalyzed by CuNPs and Catalytic Cycle with the Intermediates Proposed by Others.



A	B	C	Reference
$[\text{LCu}] \text{---} \text{C}\equiv\text{C-R}^2$	$[\text{LCu}] \text{---} \text{C}\equiv\text{C-R}^2$ $\text{R}^1\text{-N}^-\text{N}^+\text{=N}$	$[\text{LCu}] \text{=C=C-R}^2$ $\text{R}^1\text{-N=N=N}$	Sharpless <i>et al.</i> (2005) ^{12a}
$\left([\text{Cu} \text{---} \text{C}\equiv\text{C-R}^2]_2 \right)_n$ Straub (2007) ^{22b}	$\text{R}^2\text{---C}\equiv\text{Cu-Cu---C}\equiv\text{C-R}^2$ $\text{R}^1\text{-N}^-\text{N}^+\text{=N}$	$\text{R}^2\text{---C}\equiv\text{Cu-Cu=C-R}^2$ $\text{R}^1\text{-N=N=N}$	Heaney <i>et al.</i> (2010) ^{22d}
$[\text{CuL}] \text{---} \text{C}\equiv\text{C-R}^2$	$[\text{CuL}] \text{---} \text{C}\equiv\text{C-R}^2$ $\text{R}^1\text{-N}^-\text{N}^+\text{=N}$	$[\text{CuL}] \text{=C=C-R}^2$ $\text{R}^1\text{-N=N=N}$	Fokin <i>et al.</i> (2007) ^{22c}
$[\text{CuL}] \text{---} \text{C}\equiv\text{C-R}^2$	$[\text{CuL}] \text{---} \text{C}\equiv\text{C-R}^2$ $\text{R}^1\text{-N}^-\text{N}^+\text{=N}$	$[\text{CuL}] \text{=C=C-R}^2$ $\text{R}^1\text{-N=N=N}$	Fokin <i>et al.</i> (2013) ^{22e}

the true intermediate species (Scheme 2). In this mechanism, the *in-situ* generation of CuCl was postulated, after acetylene deprotonation, with the concomitant formation of triethylammonium

chloride (in the presence of LiCl from the preparation of the CuNPs), and the action of the latter on the CuNPs. The reaction of the nascent copper(I) chloride with the acetylide species would furnish the corresponding copper(I) acetylide. From this stage, the catalytic cycle would be akin to that published by others,^{12a,22} with special mention to the recent one disclosed by Fokin *et al.* involving a dinuclear copper intermediate.^{22e} The eventual protonolysis of the resulting copper(I) triazolide complex^{22a} by triethylammonium chloride would lead to the triazole product and CuCl regeneration.

2.2. Supported CuNPs in Click Chemistry

2.2.1. Introduction

Many procedures have been put into practice in order to expand the possibilities of application the CuAAC and increase its efficiency. Among them, those involving three key features in modern synthetic organic chemistry are considered of special interest, namely: (a) multicomponent reactions, which make unnecessary to isolate and manipulate the organic azides since they are produced *in-situ*; consequently, risks are diminished, times are shortened and waste mass is reduced; (b) heterogeneous catalysis, above all nanocatalysis, which is favorable with respect to the homogeneous analogue as the catalyst is more stable and can be often recovered and reused; and (c) aqueous media, the use of which has a beneficial effect in the economy and safety of production, as well as in the environment.

In this sense, various articles on the heterogeneous CuAAC appeared in the literature.²³ Catalysts based on copper(I) immobilized on different supports, such as charcoal,^{23a} zeolites,^{23b} ionic polymer,^{23c} aluminium oxyhydroxide fiber^{23d} or Amberlyst A-21,^{23e} are advantageous because of

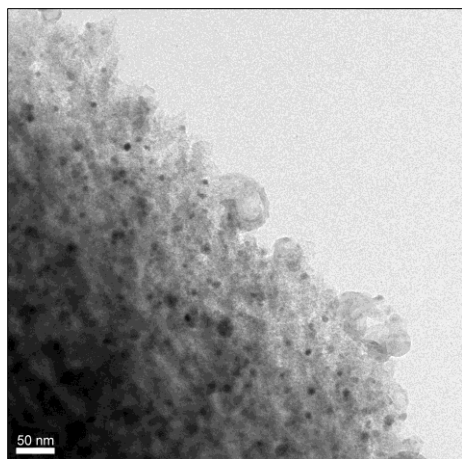
their easy recovery and reutilization potential. All these examples, however, involved pre-formed organic azides.

The one-pot synthesis of 1,4-disubstituted-1,2,3-triazoles from *in-situ* generated azides was originally developed by Fokin *et al.*²⁴ Later on, silica^{25a} and zeolites^{25b} were used as supports for the copper-catalyzed heterogeneous version of the one-pot synthesis. As regards the latter heterogeneous-multicomponent approach but using nanocatalysis, CuNPs/Al₂O₃ catalyzed the synthesis of 1,2,3-triazoles from activated organic halides at room temperature in water;^{26a} the catalyst was reused over three cycles. A highly reusable catalyst consisting of CuI/Cu NPs (80–300 nm) on pre-treated activated carbon was successfully applied to the three-component reaction of activated organic halides in water at 100 °C.^{26b}

2.2.2. Multicomponent synthesis of 1,2,3-triazoles from organic halides as azido precursors catalyzed by CuNPs/C

In order to upgrade the previous unsupported catalytic system and overcome the non-recyclability shortcoming, a variety of supported copper catalysts was obtained by addition of an inorganic support to a suspension of the freshly prepared CuNPs, followed by filtration and drying. The catalysts were not submitted to any thermal or activation treatment but were used in the three-component CuAAC as prepared, with CuNPs/C being the most efficient.²⁷ Analysis by TEM, EDX, XPS and SAED unveiled the presence of spherical Cu₂O/CuO NPs dispersed on the active carbon support with an average size of *ca.* 6.0 ± 2.0 nm (Figure 2).

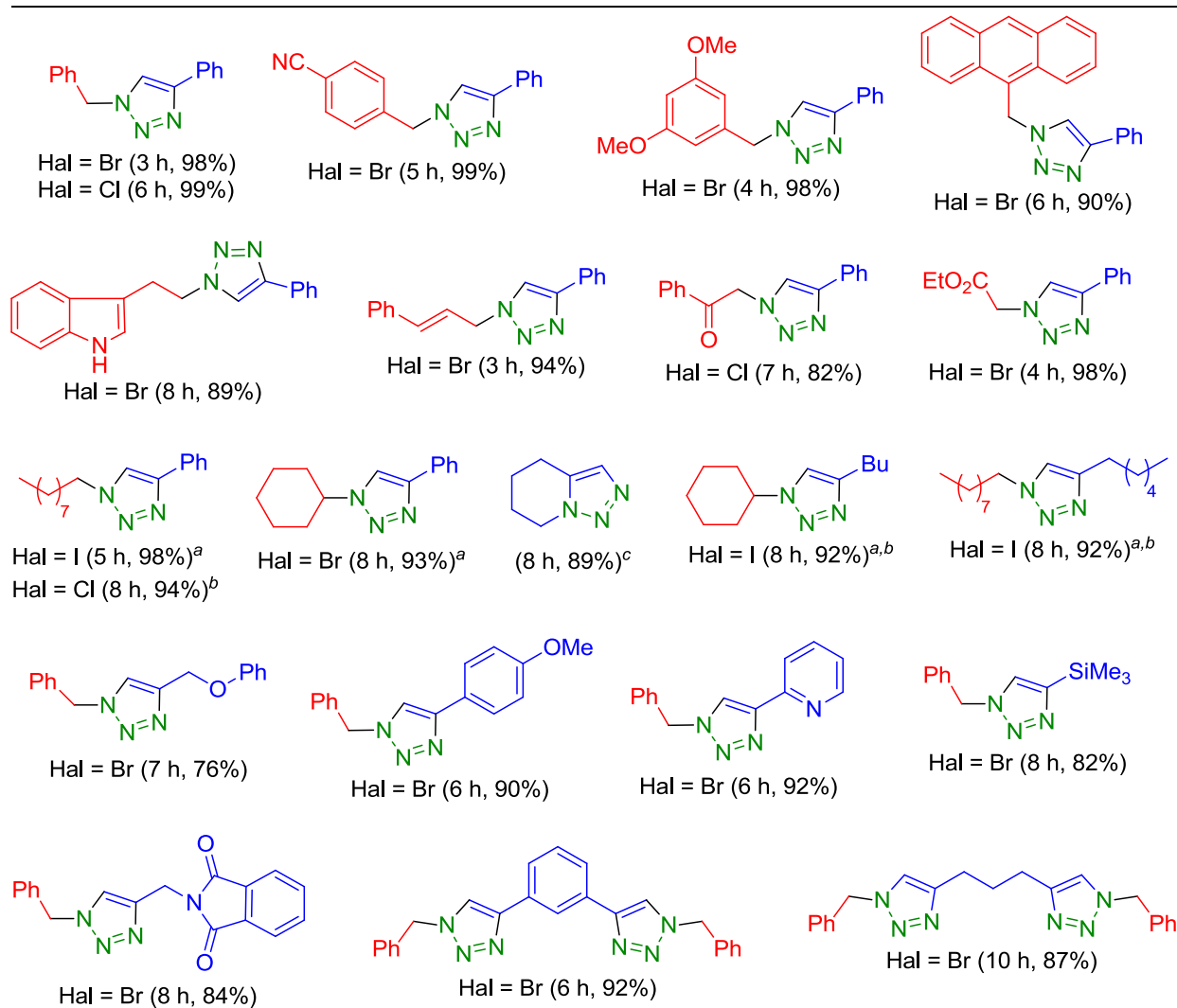
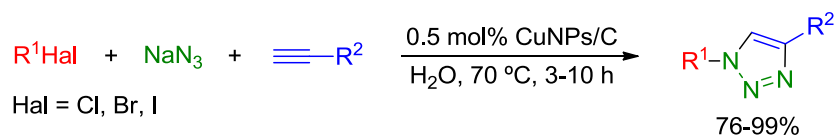
FIGURE 2. TEM Micrograph of CuNPs/C (Reproduced from Ref. 27a with Permission from John Wiley & Sons).



The catalyst, at low loading (0.5 mol%) and in the absence of triethylamine, was applied to the synthesis of 1,4-disubstituted-1,2,3-triazoles through a multicomponent CuAAC in water at 70 °C (Table 2). A wide range of triazoles, including one bicyclic triazole and bistrizoles, were synthesized from activated or non-activated organic halides (chlorides, bromides and iodides) and different terminal alkynes. Deactivated alkyl halides worked better in a H₂O-EtOH 1:1 solvent system, whereas the combination of deactivated alkyl halides with aliphatic alkynes was found to be more reluctant to react. To the best of our knowledge, this was the first report describing the employment of oxidized CuNPs in the multicomponent variant of the click reaction.

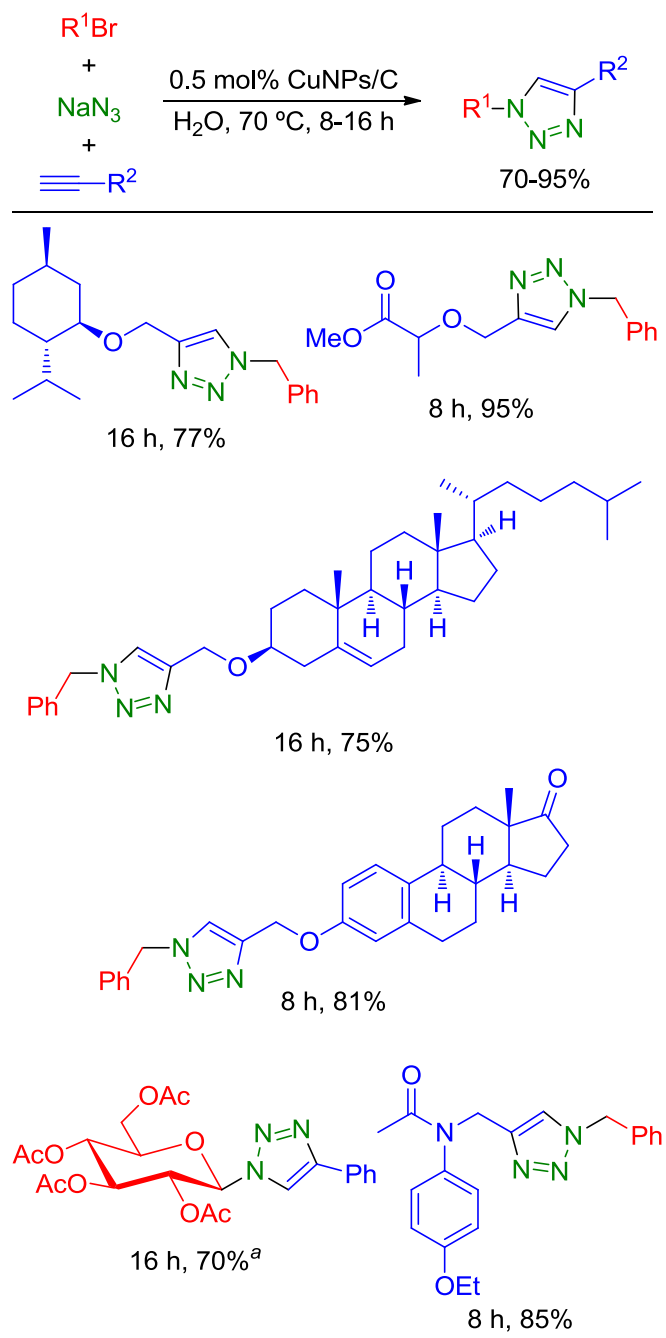
Furthermore, this method was found to be equally effectual and straightforward to prepare some potentially biologically active compounds.²⁸ A series of new triazoles, derived from the natural products (–)-menthol, lactic acid, D-glucose, estrone, and cholesterol, and from the synthetic compound phenacetin, were obtained in good-to-excellent isolated yields (Table 3).

TABLE 2. Three-Component CuAAC from Organic Halides as Azido Precursors.



^a Reaction in H₂O-EtOH 1:1. ^b Reaction at 100 °C. ^c From 6-chlorohex-1-yne.

TABLE 3. Synthesis of Potentially Biologically Active Triazoles.



^a Reaction at 100 °C.

2.2.3. Nature of the CuNPs/C catalyst^{27b}

It is worthwhile mentioning that the progress of the reactions catalyzed by CuNPs/C in water could be followed visually: at the end of the reaction, one solid aggregate comprised of a triazole nucleus and a catalyst cover could be observed at the top of a colorless and transparent solution. The black pieces (white inside) looked almost spherical or with a contour which reminded that of a virus or a naval mine (Figure 3). These shapes can be ascribed to the intermolecular forces acting between two hydrophobic solids in an aqueous liquid.

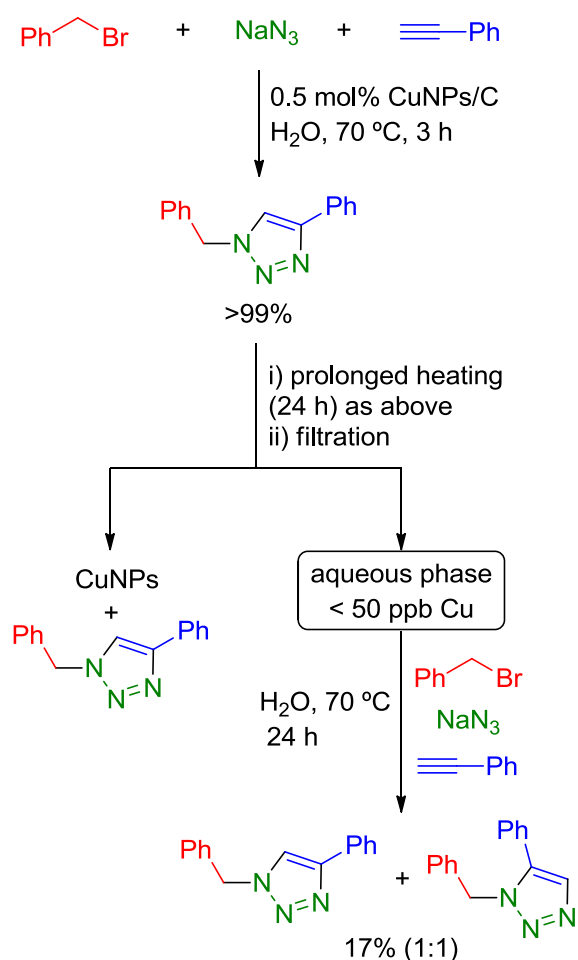
FIGURE 3. Triazole Products Covered with CuNPs/C [*ca.* 8 mm (left) and 10 mm (right)] (Reproduced from Ref. 27b with Permission from The Royal Society of Chemistry).



Despite the amount of catalyst deployed in these reactions was small, it could be retrieved by simple filtration and reutilized, leading to outstanding yields (98–90%) of the triazole product in five consecutive runs, with undetectable copper leaching. In order to unveil the nature of the catalysis, the following protocol was carried out: the resulting mixture of a standard reaction, which contained the 1,2,3-triazole, was further warmed for 24 h with the aim to leach some metal into the solution (Scheme 3). After removal of the catalyst and the product by filtration, the water filtrate was subjected to extraction with ethyl acetate and new starting materials were added to the obtained aqueous phase. When the resulting biphasic liquid was enabled to react by heating at 70 °C for 24 h, two 1,2,3-triazoles were furnished in 17% conversion as a *ca.* 1:1 ratio

of the 1,4- and 1,5-disubstituted regioisomers. This result proved that the reaction took place under thermal conditions in a non-catalyzed mode, what could be asserted by determining the copper content of the resulting aqueous phase (<50 ppb Cu). Although all these experiments denote a process of heterogeneous nature, it cannot be ruled out the likelihood of the catalyst operating as a reservoir for metal species that leach into solution and readsorb.^{18a} Nevertheless, recently, Scaiano et al. combined single-molecule spectroscopy with standard bench scale techniques to examine the CuNP-catalyzed AAC and prove that catalysis occurs at the surface of the CuNPs.²⁹

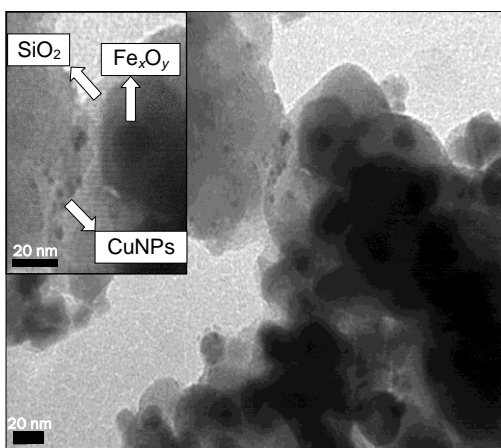
SCHEME 3. Experiments on the Nature of the Catalysis.



2.2.4. Multicomponent synthesis of 1,2,3-triazoles from organic halides as azido precursors catalyzed by CuNPs/MagSilica

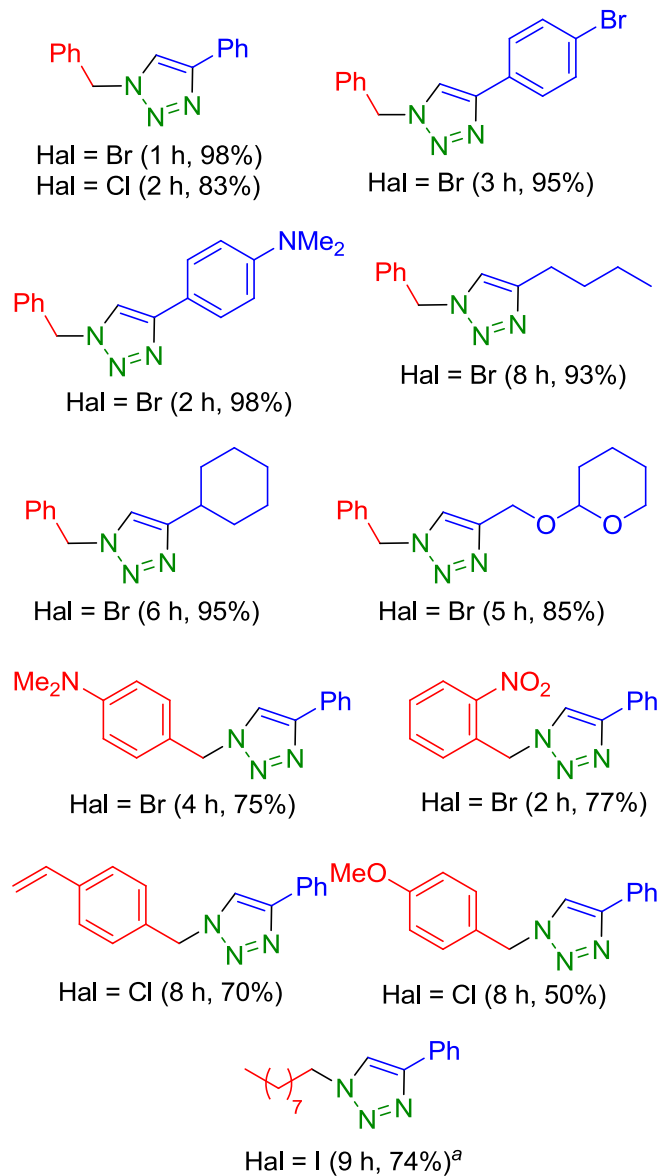
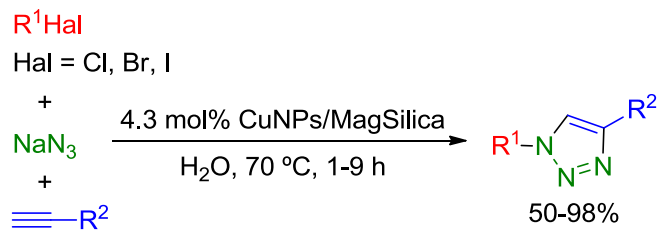
Commercially available silica-coated maghemite nanoparticles (MagSilica®, 5–30 nm) were also deployed as support for CuNPs, the suspension of which was readily generated from anhydrous copper(II) chloride, lithium sand, and a catalytic amount of DTBB (10 mol%) in THF at room temperature.³⁰ TEM revealed the presence of spherical nanoparticles, with an average particle size of 3.0 ± 0.8 nm, well dispersed on the magnetic support (Figure 4).

FIGURE 4. TEM Micrograph of CuNPs/MagSilica (Reproduced from Ref. 30 with Permission from Elsevier).



The CuNPs/MagSilica catalyst manifested a good performance in the three-component CuAAC from organic halides, using 4.3 mol% Cu in water at 70 °C. This procedure was successfully applied to electronically different aryl acetylenes as well as to aliphatic alkynes, though the later required longer reaction times. Heating at 100 °C was essential for the less reactive *n*-nonyl iodide, by which the yield could be increased and the reaction time reduced (Table 4). Notably, the mass of leached copper in these experiments was under the detection level of atomic absorption spectroscopy.

TABLE 4. Three-Component CuAAC from Organic Halides as Azido Precursors.



^a Reaction at 100 °C.

2.2.5. Multicomponent synthesis of 1,2,3-triazoles from aryldiazonium salts and anilines as azido precursors

The synthesis of 1,2,3-triazoles through Click Chemistry generally involves pre-formed azides or the more appropriate *in-situ* generated azides from organic halides. In some cases, however, this synthesis is hampered by the substrate availability and functionality, and a functional group transformation preceding the click reaction is imperative. In this regard, the versatility of the CuNPs/C catalyst was broadened by investigating some alternative azido precursors to the organic halides, which might be suitable for reacting under the conventional reaction conditions. Diazonium salts were discovered to be alternative substrates to the relatively inert aryl halides and were employed in the three-component synthesis of 1,2,3-triazoles, under the same green conditions as those practiced for organic halides (0.5 mol% CuNPs/C, water, 70 °C). In this way, incorporation of an aromatic substituent at position 1 of the triazole was feasible, bearing electronically different groups, in good yields and relatively short reaction times (Table 5).^{27b}

The direct use of anilines as azido precursors was first described by Moses *et al.* in 2007. The reaction of anilines with *t*-BuONO and trimethylsilylazide in CH₃CN led to aryl azides, which were additionally submitted to the click reaction in one pot.^{31a} The rate of formation of the triazoles was substantially enhanced by microwave radiation.^{31b} However, due to the fact that the entire process was sequential, monitoring of the azide formation before the cycloaddition step was indispensable. It was found out that anilines could be directly converted into 1,2,3-triazoles with *t*-BuONO and NaN₃ under the catalysis of CuNPs/C in aqueous medium (Table 6).^{27b} This multicomponent reaction was more convenient since NaN₃ is cheaper than trimethylsilylazide, it is performed in water and monitoring of intermediates was avoided. The methodology was applicable to electronically different anilines and arylacetylenes, as well as to aliphatic alkynes.

TABLE 5. Three-Component Synthesis of 1,2,3-Triazoles from Aryldiazonium Salts as Azido Precursors.

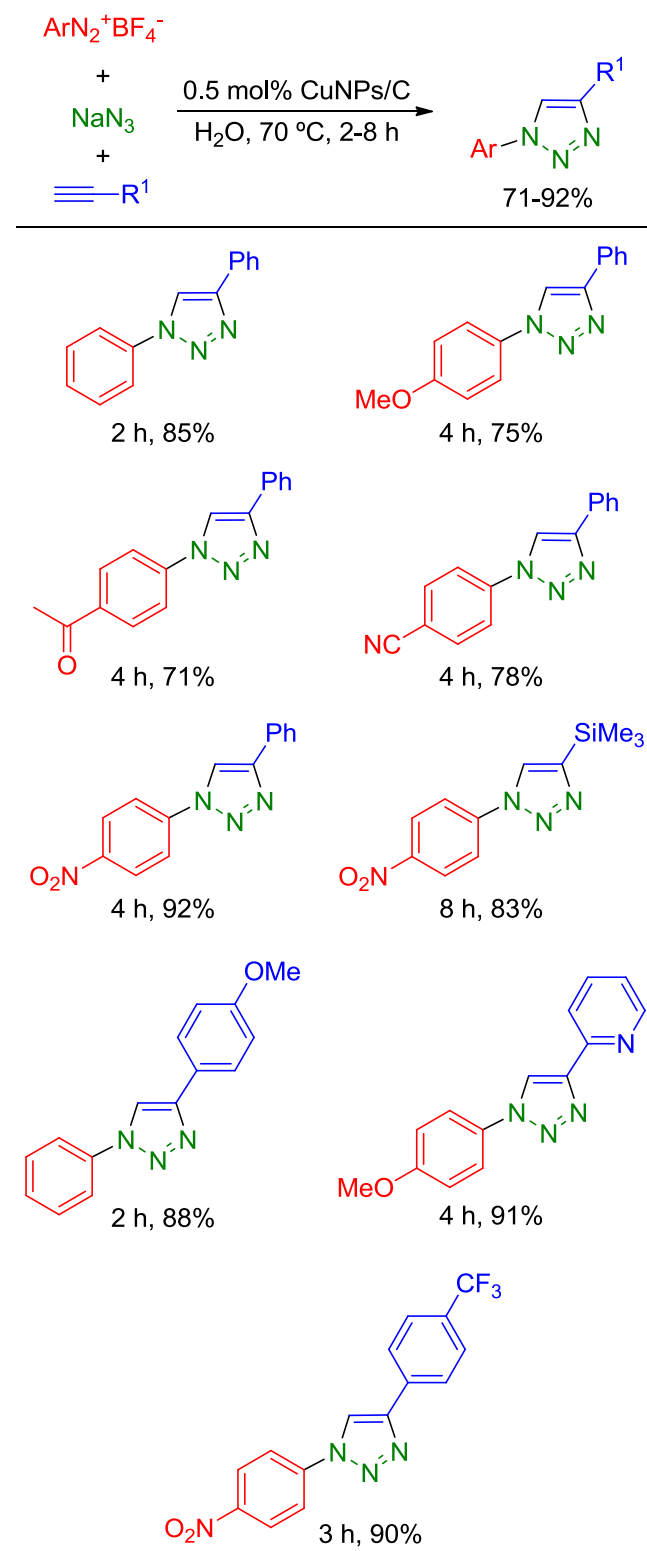
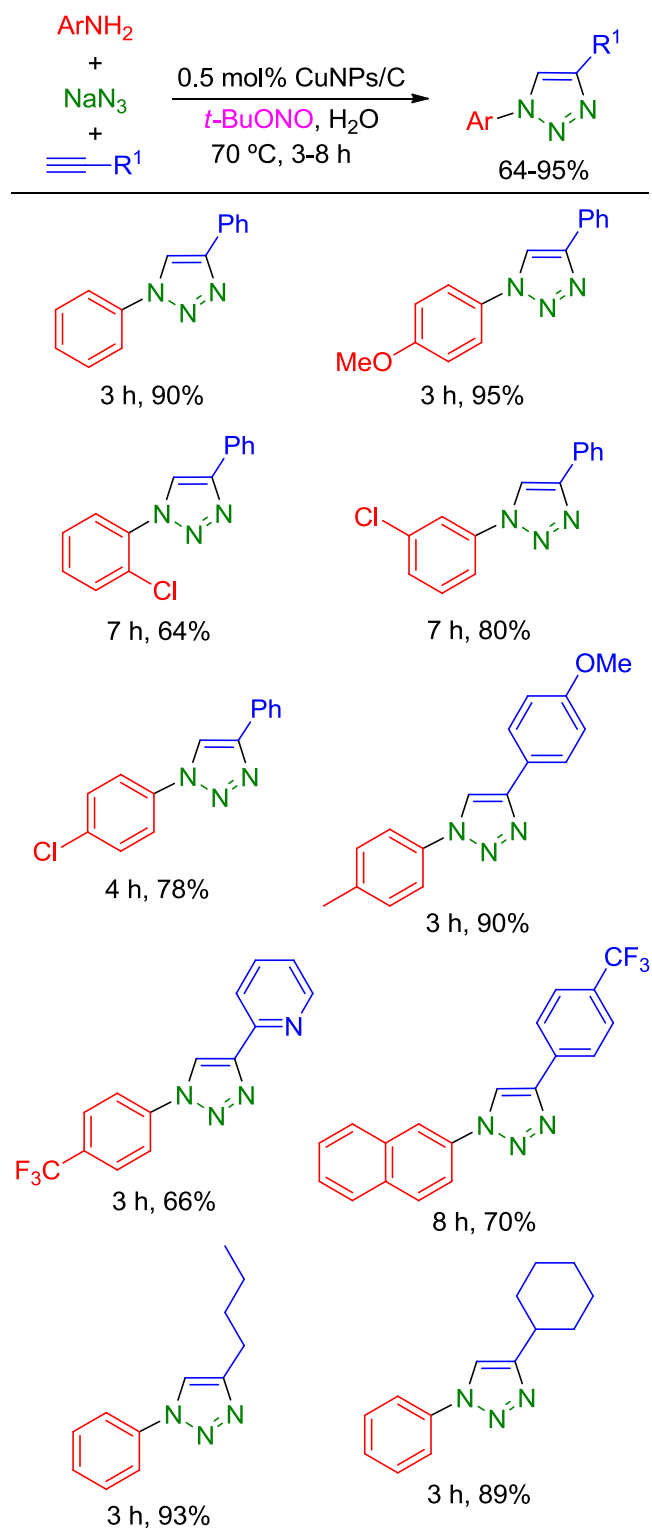


TABLE 6. Three-Component Synthesis of 1,2,3-Triazoles from Anilines as Azido Precursors.

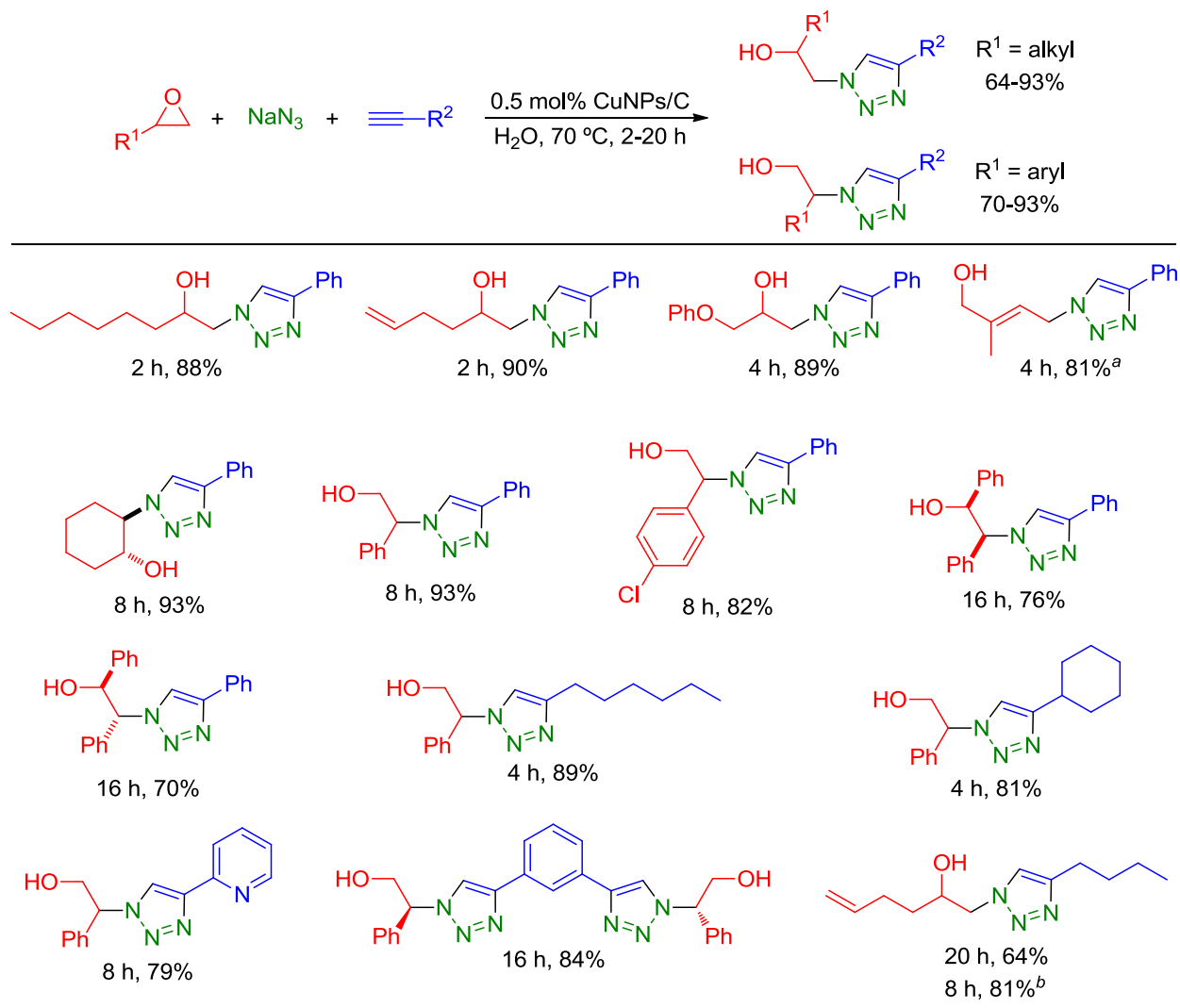


2.2.6. Multicomponent synthesis of 1,2,3-triazoles from epoxides as azido precursors

Strained cycles such as epoxides, aziridines, cyclic sulfates, cyclic sulfamidates, aziridinium ions, and episulfonium ions can experience nucleophilic ring opening in a reliable, stereospecific, often highly regioselective and nearly quantitative manner. These attributes justify the inclusion of this nucleophilic attack into the elite catalogue of click reactions.¹ The azidolysis of epoxides³² and the CuAAC share some intrinsic characteristics which utterly adapt the set of strict bases demanded for Click Chemistry.¹ This is the reason why the synthesis of 1,2,3-triazoles through the *in-situ* generation of azidoalcohols and further cycloaddition with alkynes has gained increasing attention.³³ Although the reactions were carried out in one pot, some of the processes were sequential; hence, monitoring of the azidoalcohol formation was necessary prior to the alkyne addition.

It was demonstrated that CuNPs can catalyze the multicomponent synthesis of 1,2,3-triazoles from epoxides as azido precursors.³⁴ An array of β -hydroxytriazoles was synthesized from epoxides, sodium azide, and terminal alkynes in water under the same conditions as above (*i.e.*, 0.5 mol% CuNPs/C, 70 °C) (Table 7). This double-click methodology was regioselective with respect to both the azidolysis of the epoxide and the 1,3-dipolar cycloaddition as follows: “(a) monoalkyl-substituted oxiranes gave rise to secondary β -hydroxytriazoles; (b) an S_N2' mechanism governed the regiochemistry for vinyl epoxides; (c) monoaryl-substituted oxiranes lead to primary β -hydroxytriazoles with inversion of the configuration; and (d) 1,4-disubstituted triazoles were solely formed”. The regio- and stereochemistry of the products was unequivocally established on the basis of X-ray crystallographic analyses, and proved that the regiochemistry of the products had been wrongly assigned in three of the six publications dealing with this topic.

TABLE 7. Three-Component Synthesis of β -Hydroxy-1,2,3-Triazoles from Epoxides as Azido Precursors.



^a From 2-methyl-2-vinylloxirane. ^b Reaction at 100 °C.

A simple ¹H NMR experiment in CD₃CN was devised to ascertain, quickly and unequivocally, the regiochemistry of this sort of reactions.³⁴ Moreover, the catalyst could be reused with insignificant leaching (80 ppb) over four runs, affording the product in excellent-to-good yields (93–70%). The supported nanoparticulate catalyst was found to perform better than some

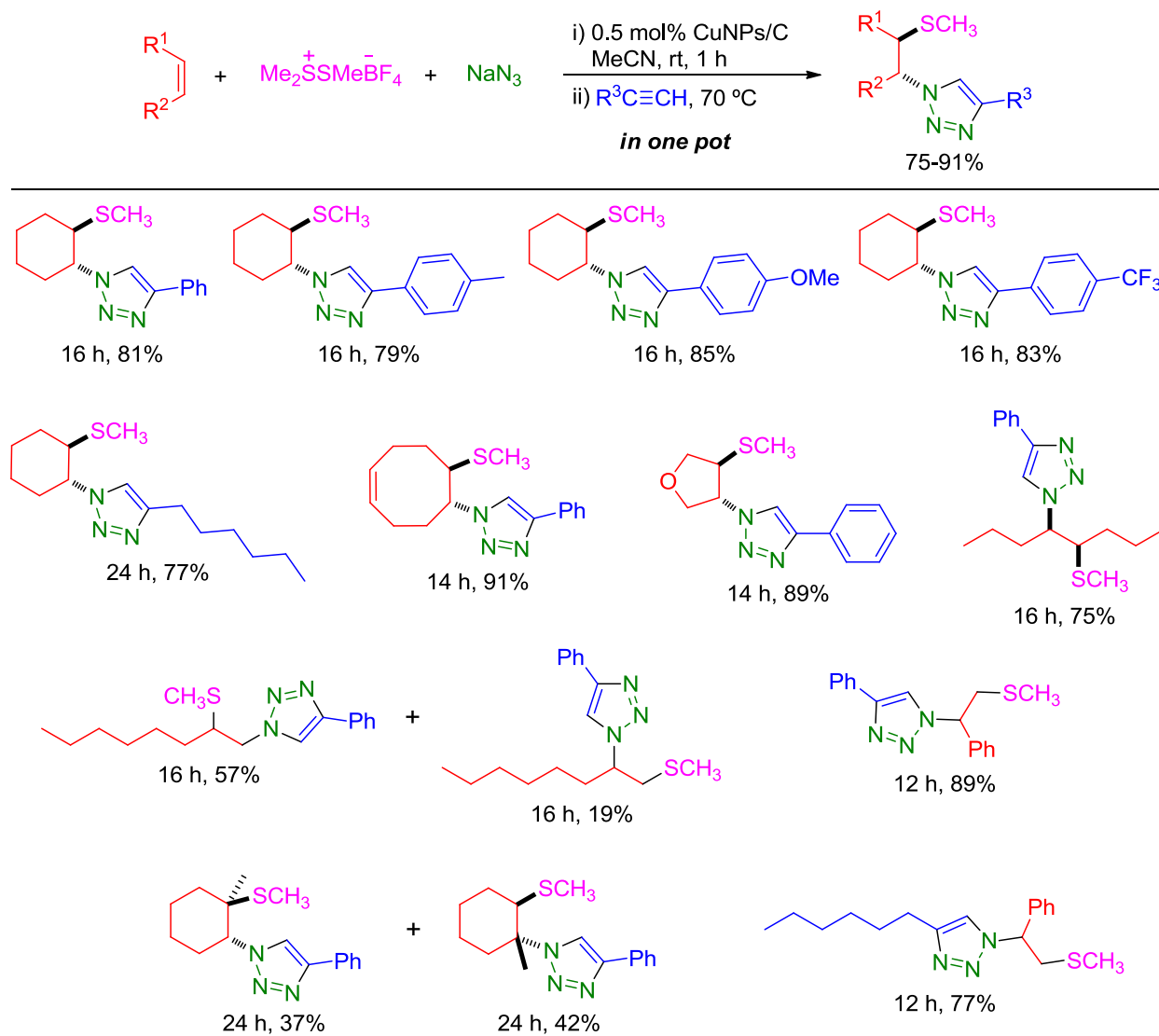
commercial catalysts as regards the metal loading, reaction time and yield. Deuterium labeling essays disclosed the function of the CuNPs, *i.e.* to augment the acidity of the terminal alkyne (in water and in the absence of base) for acetylide formation. These experiments also indicated the very probable participation of other intermediates, such as copper(I) triazolides.

2.2.7. Multicomponent synthesis of 1,2,3-triazoles from alkenes as azido precursors

Olefins can be considered the most accessible raw materials which can yield a carbon skeleton. The azasulfenylation of olefins developed by Trost *et al.* in 1982³⁵ was used as source of inspiration to potentially transform alkenes into triazoles. In Trost's report, treatment of an alkene with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF), was followed by the addition of a nitrogen nucleophile and stirring at ambient temperature for 1–4 days. A more convenient variation of this method was discovered by directly mixing the alkene with CuNPs/C, DMTSF, and NaN₃ in MeCN, whereby the corresponding methylsulfanyl azide was produced in only 1 h at room temperature.

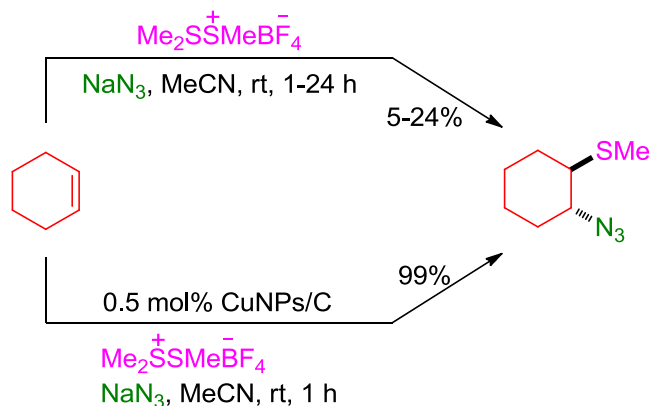
1,2,3-Triazoles were synthesized in one-pot from inactivated alkenes by means of a sequence comprised of two click steps catalyzed by CuNPs/C: the alkene azidosulfenylation and the reaction of the *in-situ* generated organic azide with the terminal alkyne.³⁶ The resulting β -methylsulfanyl triazoles were obtained regio- and diastereoselectively in 75–91% yield (Table 8). The regioselectivity observed followed the same trend as in the domino azidolysis-CuAAC of epoxides, albeit the azidolysis of oct-1-ene oxide³⁴ was more regioselective than the azidosulfenylation of oct-1-ene. The fact that CuNPs/C could have a catalytic role in the first synthetic step was undoubtedly evidenced by effecting two tests (Scheme 4): (a) the reaction of cyclohexene with DMTSF and NaN₃ in MeCN at rt (1–24 h) gave multiple products and only

TABLE 8. Three-Component Synthesis of β -Methylsulfanyl-1,2,3-Triazoles from Alkenes as Azido Precursors.

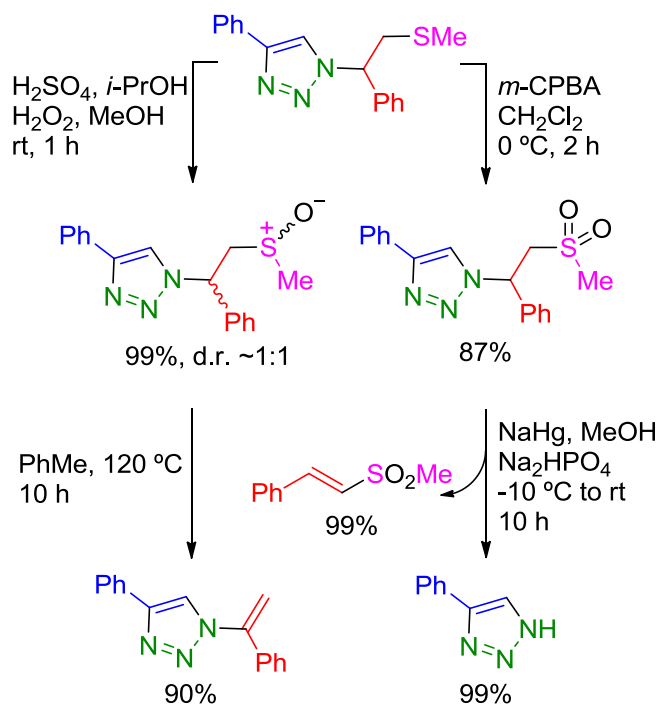


5–24% of the expected azide; (b) under the same conditions but in the presence of 0.5 mol% CuNPs/C, that azide was formed quantitatively in only 1 h. Even though catalyst reutilization was inefficient in this case, very probably due to poisoning by sulfur, the catalytic activity of the nanocatalyst was greater than that of some commercially accessible copper sources in the bulk

SCHEME 4. Catalytic Role of CuNPs/C in the Azidosulfenylation of Cyclohexene.



SCHEME 5. Synthetic Transformations of a β -Methylsulfanyl-1,2,3-Triazole.



form, which failed in the azidosulfenylation step. Additionally, 1-vinyl-4-substituted- or 4-monosubstituted-1,2,3-triazoles were efficiently made by the subsequent application of simple and quantitative oxidation-elimination procedures (Scheme 5).

2.2.8. Unsupported versus supported CuNPs

The catalytic systems and methodologies described herein for the CuAAC based on supported CuNPs are distinctly more advantageous than those based on unsupported CuNPs. In fact, the former meet most of the ideals of Green Chemistry⁸ and foundations of Click Chemistry,¹ namely: (a) waste is reduced to a sodium-salt aqueous solution as the azides are generated *in situ*; (b) all the experiments were safe and no explosion occurred; (c) three or four materials are integrated into the final triazole, hence, with high atom economy; (d) the manipulation of potentially explosive organic azides is circumvented; (e) neat water or ethanol-water are used as solvents (except in the alkene azidosulfenylation-CuAAC); (e) the preparation of the catalyst is simple and conducted at room temperature; (f) derivatization is also minimized; (g) the metal load is low and the catalyst is recyclable; (h) the progress of the reaction can be checked visually; (j) the methodology is versatile as a single catalyst can be applied to a variety of starting materials in the same medium; (k) reactions are of wide scope and high yielding; (l) all the necessary chemicals are commercially or readily available; (m) simple reaction conditions are practiced and compatible with the presence of oxygen and water (except in the alkene azidosulfenylation-CuAAC); (n) both the nucleophilic opening of strained rings and the formation of 1,4-disubstituted-1,2,3-triazoles are highly regioselective; (o) products are, generally, easily isolated or do not need purification.

3. CONCLUSION

We have summarized the application of easily-prepared unsupported and supported CuNPs to the CuAAC. The unsupported catalyst, Cu(0)NPs in tetrahydrofuran, allowed the fast reaction of terminal alkynes with pre-formed azides in the presence of triethylamine as a base; nanoparticle

dissolution under these conditions, however, prevented the catalyst recovery. The catalysts composed of oxidized CuNPs on activated carbon (CuNPs/C) or silica-coated maghemite nanoparticles (CuNPs/MagSilica) were endowed with salient features which made the click reaction much more efficient and sustainable than with the unsupported counterpart, namely: (a) the three-component version of the CuAAC was applied, (b) reactions were conducted in neat water, (c) with low metal loading, and (d) with easy recovery and reuse of the catalyst. In particular, CuNPs/C displayed high versatility because, using the same conditions in every case, 1,4-disubstituted-1,2,3-triazoles were effectively synthesized from terminal alkynes, sodium azide and different azido precursors, including organic halides, diazonium salts, anilines and epoxides. A one-pot protocol was also developed with this catalyst whereby inactivated alkenes could be utilized as azido precursors in the click reaction. Moreover, in all the above reactions practiced, the performance of CuNPs/C was above that of commercial bulk copper catalysts, once more bolstering the catalytic advantages of nanostructured materials. Further research must be devoted to the design of durable heterogeneous nanocatalysts, which enable click chemistry to be exploited competently at a large scale with negligible copper contamination of the products.

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