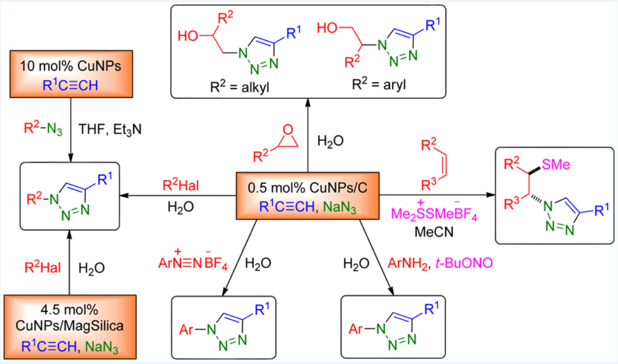
ACCOUNTS
of chemical research

Copper Nanoparticles in Click Chemistry

Francisco Alonso,*[†] Yanina Moglie,[‡] and Gabriel Radivoy[‡]

[†]Instituto de Síntesis Orgánica (ISO) and Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

[‡]Departamento de Química, Instituto de Química del Sur (INQUISUR-CONICET), Universidad Nacional del Sur, Avenida Alem 1253, 8000 Bahía Blanca, Argentina



CONSPECTUS: The challenges of the 21st century demand scientific and technological achievements that 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 that help to safeguard the health of our planet against negligent and uncontrolled production. 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 that can increase the inherent effectiveness of CuAAC because of the enhanced catalytic activity of nanostructured metals and their plausible reutilization capability as heterogeneous catalysts.

This Account describes our contribution to click chemistry 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 CuAAC could be applied; (b) the metal loading could be substantially decreased; (c) reactions could be conducted in neat water; and (d) the catalyst could be recovered easily and reutilized. In particular, the catalyst composed of oxidized CuNPs (Cu_2O/CuO, 6.0 ± 2.0 nm) supported on carbon (CuNPs/C) 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) supported on MagSilica could be alternatively used for the same purpose under similar conditions. Incorporation of an aromatic substituent at the 1-position of the triazole could be accomplished using the same CuNPs/C catalytic system starting from aryldiazonium 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 types of reaction studied, CuNPs/C exhibited better behavior than some commercial copper catalysts with regard to the metal loading, reaction time, yield, and recyclability. Therefore, the results of this study also highlight the utility of nanosized copper in click chemistry compared with bulk copper sources.

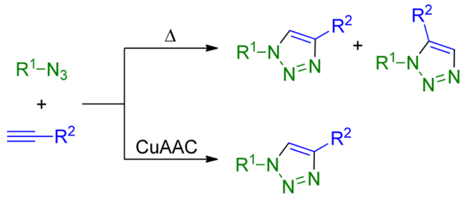
1. INTRODUCTION

Click chemistry is a conception of organic synthesis that is of paramount importance in modern chemistry.[1] To paraphrase Sharpless and co-workers, 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". Copper-catalyzed azide−alkyne cycloaddition (CuAAC) stands out among this group of select reactions since the capital discovery by the teams of Meldal[2] and Sharpless[3] in the dawn of the 21st century, namely, the dramatic acceleration of the Huisgen[4] 1,3-dipolar cycloaddition reaction of organic azides and alkynes under copper(I) catalysis and mild conditions, together with high regioselectivity toward the 1,4-regioisomer of the triazole (Scheme 1).[5] The first decade of click chemistry has recently been commemorated;[6] throughout this time, an increasing number of disciplines[7] have taken advantage of the unique benefits offered by CuAAC, the click reaction *par antonomasia*.

Received: April 27, 2015
Published: September 2, 2015

DOI: 10.1021/acs.accounts.5b00293
Acc. Chem. Res. 2015, 48, 2516−2528

Scheme 1. Huisgen and CuAAC Syntheses of 1,2,3-Triazoles



Green chemistry[8] shares with click chemistry some of the aforementioned stringent criteria, by 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 alternative to traditional catalysis because of the high surface-to-volume ratio of the nanoparticles, which hightens their activity and selectivity, preserving the inherent characteristics of a heterogeneous catalyst.[9] Particularly, inorganic supports with high surface area can be used to immobilize metal nanoparticles and obtain specially active and recyclable catalysts as a result of 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.

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]

As a result of our interest in metal colloids[14] and initial studies on active copper [produced by reduction of copper(II) chloride dihydrate with lithium metal and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) in tetrahydrofuran (THF)],[15] the formation of CuNPs from either $CuCl_2 \cdot 2H_2O$ or anhydrous $CuCl_2$ was discovered under the above-mentioned conditions. Herein we present our contribution to the field of click chemistry by means of both unsupported and supported CuNPs catalysts. Preformed 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 although this Account is focused on heterogeneous catalysis, the fundamental contribution of homogeneous catalysis to the advance of click chemistry must not be disregarded; speeding up the CuAAC reaction at room temperature and decreasing the amounts of copper to levels of a few parts per million are some praiseworthy achievements of homogeneous CuAAC.[16]

2. DISCUSSION

2.1. Unsupported CuNPs in Click Chemistry

Unsupported CuNPs have been scarcely studied in CuAAC compared with the supported counterparts; the inherent tendency toward 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 poly(vinylpyrrolidone)-stabilized CuNPs,[17d] all of which catalyzed the reaction of preformed azides and terminal alkynes.

Our group prepared Cu(0)NPs by fast chemical reduction of anhydrous copper(II) chloride with lithium metal and a catalytic amount of DTBB as an electron carrier in THF at room temperature under argon, in the absence of any added nucleation or antiagglomeration agent (Figure 1); the chloride anion (accompanied by its Li counteranion, derived from the reductant)[18a] and, to a lesser extent, the solvent (THF)[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 analysis (EDX), and selected-area electron diffraction (SAED) brought into view spherical face-centered-cubic copper(0) nanoparticles with a particle size distribution of ca. 3.0 ± 1.5 nm.[19]

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.

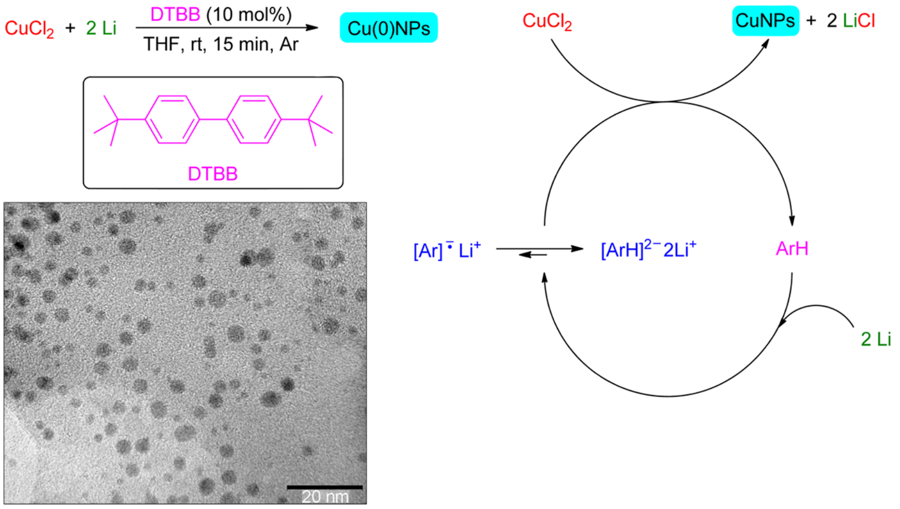
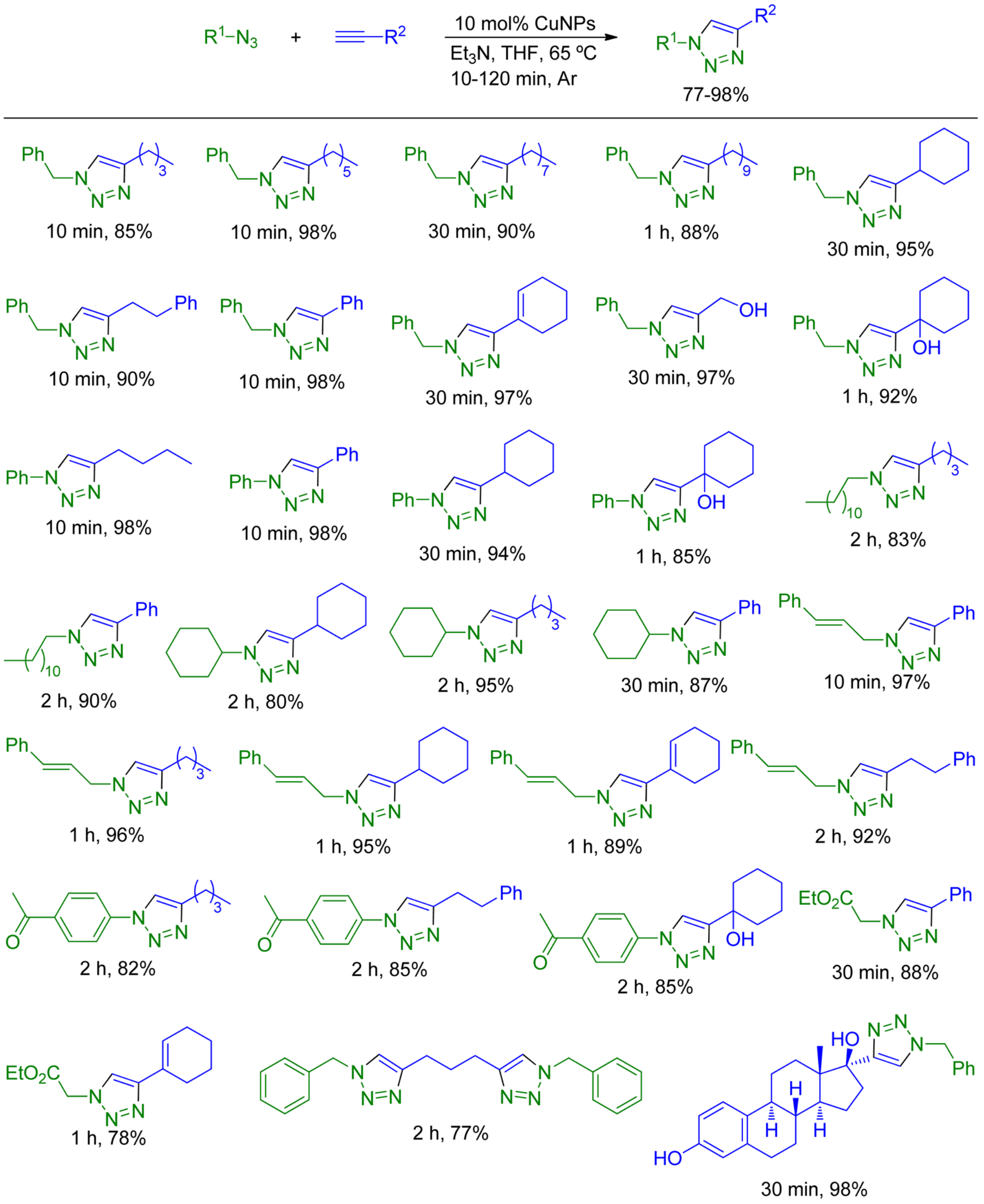


Figure 1. Synthesis and TEM micrograph of the CuNPs. The TEM micrograph is reproduced with permission from ref 19a. Copyright 2009 Elsevier.

Table 1. Azide-Akyne Cycloaddition (AAC) Catalyzed by Unsupported CuNPs



Notably, all of the 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 workup 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.

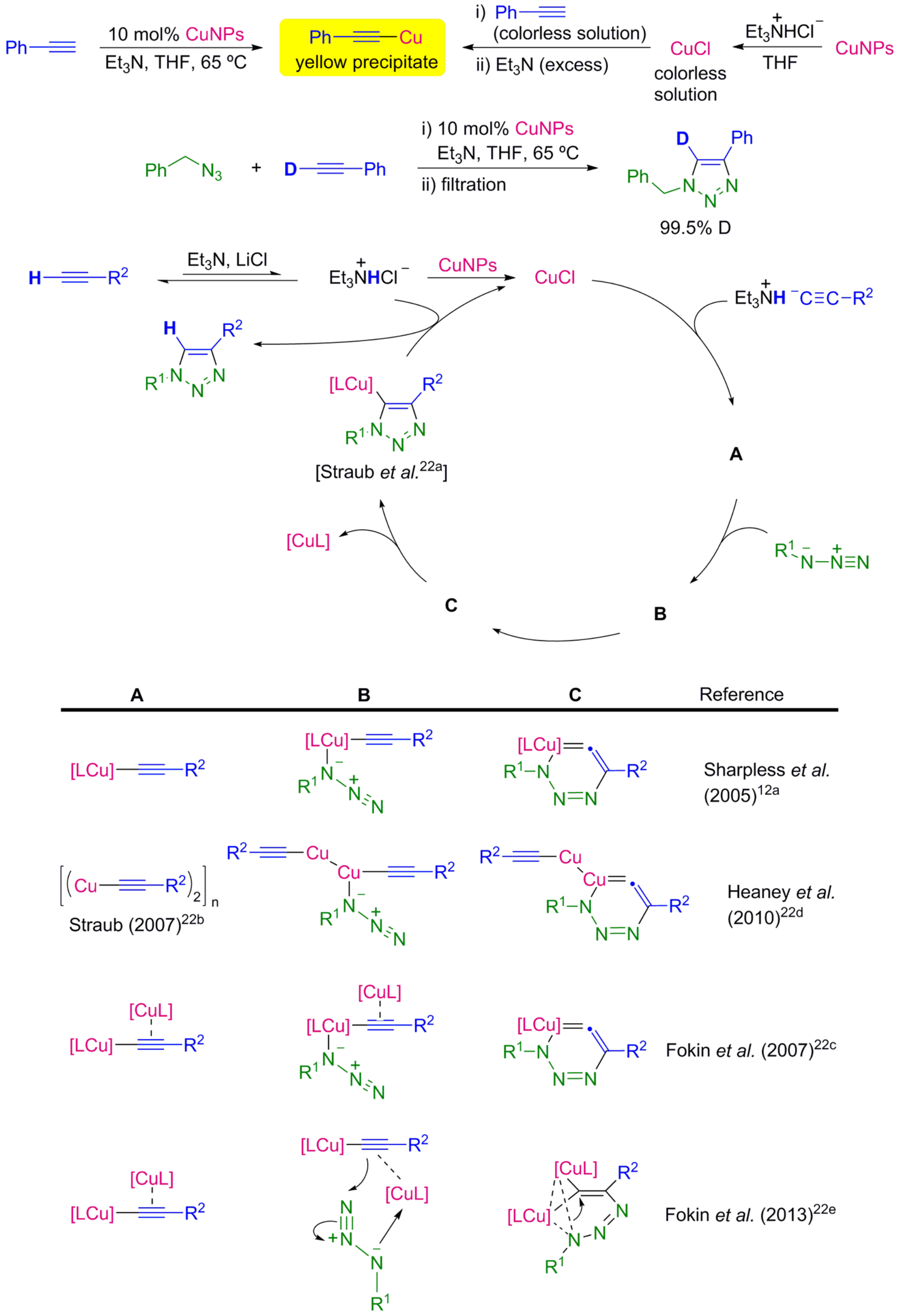
Much debate has arisen concerning the mechanism of CuAAC.[21] On the basis of different experiments,[19b] a reaction mechanism was proposed wherein copper(I) acetylides appeared as the true intermediate species (Scheme 2). In this mechanism, the in situ generation of CuCl was postulated, after acetylene 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 of the recent one disclosed by Fokin and co-workers 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 regeneration of CuCl.

2.2. Supported CuNPs in Click Chemistry

2.2.1. Introduction.

Many procedures have been put into practice in order to expand the possibilities to apply CuAAC and increase its efficiency. Among them, those involving three key features in modern synthetic organic chemistry are considered of special interest: (a) multicomponent reactions, in which isolation and manipulation of the organic azides is unnecessary since they are produced in situ, thereby

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



diminishing risks, shortening reaction times, and reducing waste; (b) heterogeneous catalysis, above all nanocatalysis, which is favorable with respect to the homogeneous analogue because the catalyst is more stable and can be often recovered and reused; and (c) the use of aqueous media, which has a beneficial effect on the economy and safety of production as well as in the environment.

In this sense, various articles on heterogeneous CuAAC have appeared in the literature.[23] Catalysts based on copper(I) immobilized on different supports, such as charcoal,[23a] zeolites,[23b] ionic polymers,[23c] aluminum oxyhydroxide fibers,[23d] and Amberlyst A-21,[23e] are advantageous because of their easy recovery and reutilization potential. All of these examples, however, involved preformed organic azides.

The one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from in situ-generated azides was originally developed by Fokin and co-workers.[24] Later on, silica[25a] and zeolites[25b] were used as supports for the copper-catalyzed heterogeneous version of the one-pot synthesis. In regard to the latter heterogeneous multicomponent approach but using nanocatalysis, CuNPs supported on Al_2O_3 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 pretreated activated carbon was successfully applied to the three-

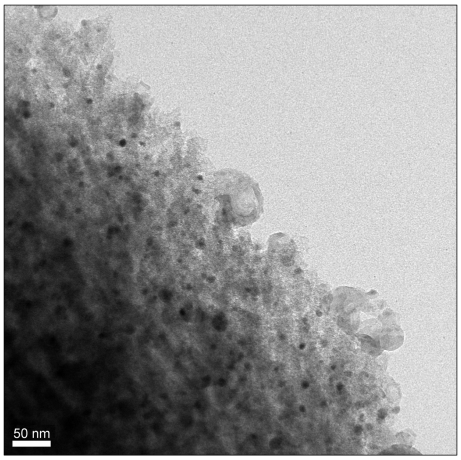


Figure 2. TEM micrograph of CuNPs/C. Reproduced with permission from ref 27a. Copyright 2010 John Wiley & Sons.

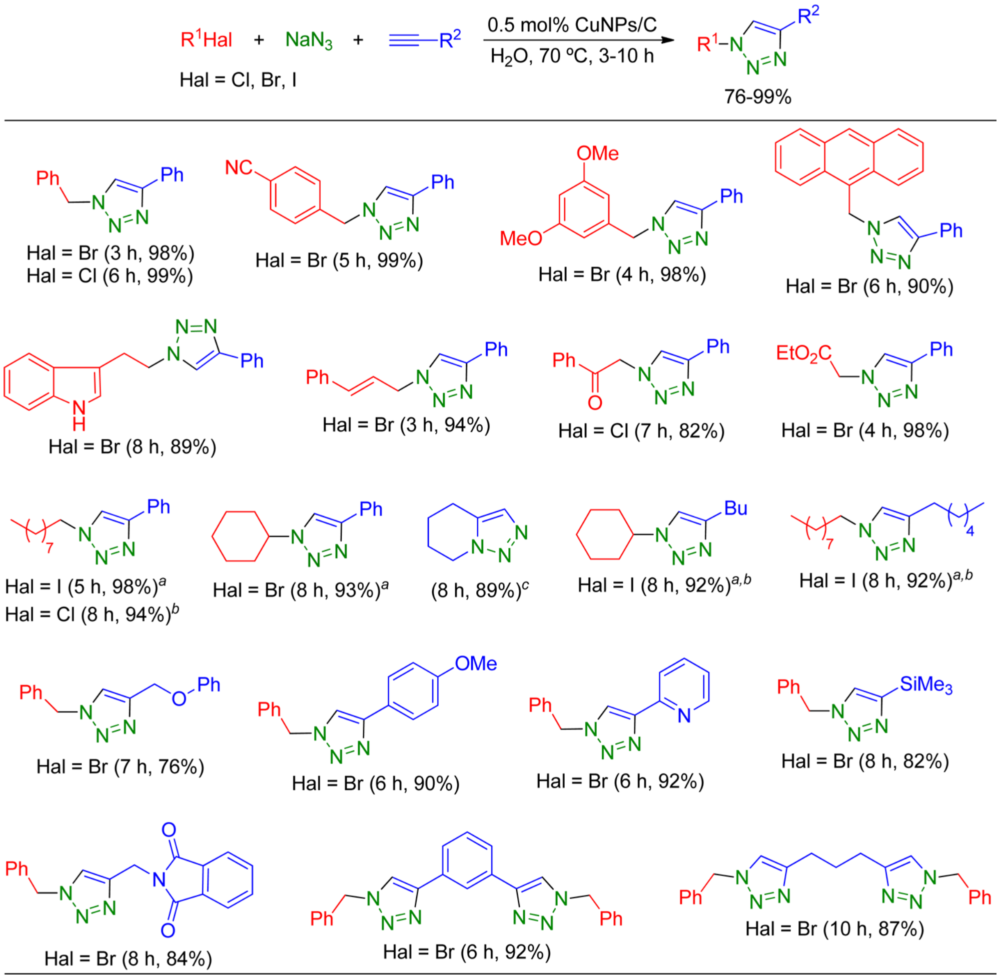
component reaction of activated organic halides in water at 100 °C.[26b]

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 nonrecyclability shortcoming, a variety of supported copper catalysts were 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 reaction as prepared, with CuNPs supported on carbon (CuNPs/C) being the most efficient.[27] Analysis by TEM, EDX, XPS, and SAED unveiled the presence of spherical Cu_2O/CuO NPs dispersed on the active carbon support with an average size of ca. 6.0 ± 2.0 nm (Figure 2).

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 multicomponent CuAAC in water at 70 °C (Table 2). A wide range of triazoles, including one bicyclic triazole and bistriazoles, were synthesized from activated or nonactivated organic halides (chlorides, bromides, and iodides) and different terminal alkynes. Deactivated alkyl halides worked better in a 1:1 H_2O/EtOH solvent system, whereas the combination of deactivated alkyl halides and aliphatic alkynes was found to be more reluctant to react. To the best of our knowledge, this was the first report describing the use of oxidized CuNPs in the multicomponent variant of the click reaction.

Furthermore, this method was found to be equally effectual and straightforward for the preparation of some potentially

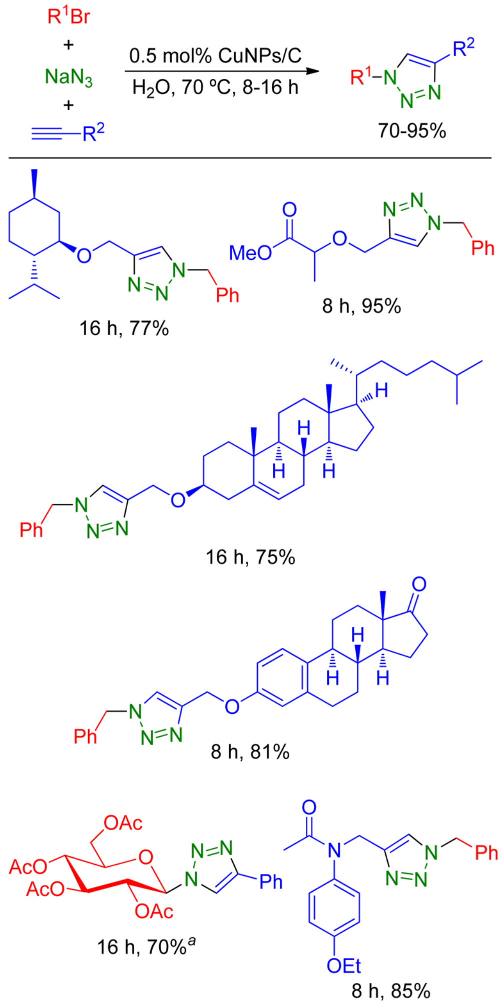
Table 2. Three-Component CuAAC from Organic Halides as Azido Precursors with CuNPs/C as Catalyst



[a] Reaction in 1:1 H_2O/EtOH. [b] Reaction at 100 °C. [c] From 6-chlorohex-1-yne.

DOI: 10.1021/acs.accounts.5b00293
Acc. Chem. Res. 2015, 48, 2516−2528

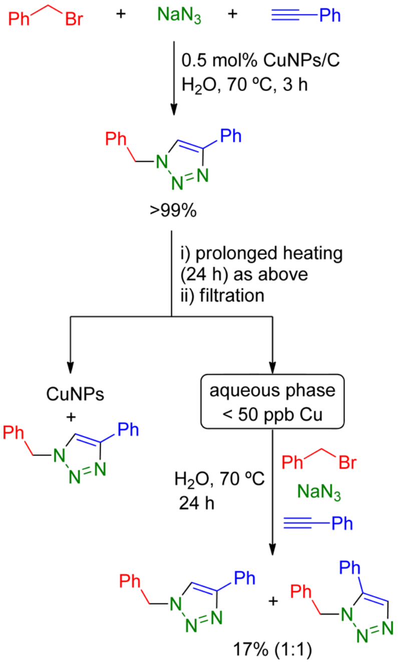
Table 3. Synthesis of Potentially Biologically Active Triazoles



[a]Reaction at 100 °C.

Figure 3. Triazole products covered with CuNPs/C [ca. 8 mm (left) and 10 mm (right)]. Reproduced with permission from ref 27b. Copyright 2011 The Royal Society of Chemistry.

Scheme 3. Experiments on the Nature of the Catalysis



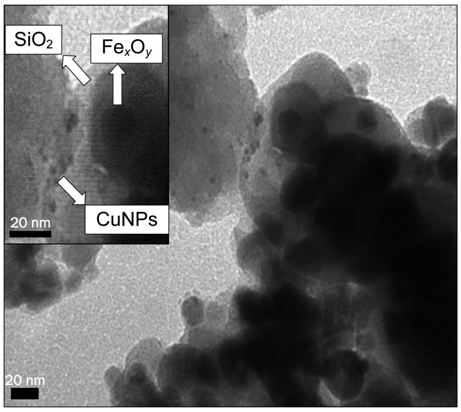


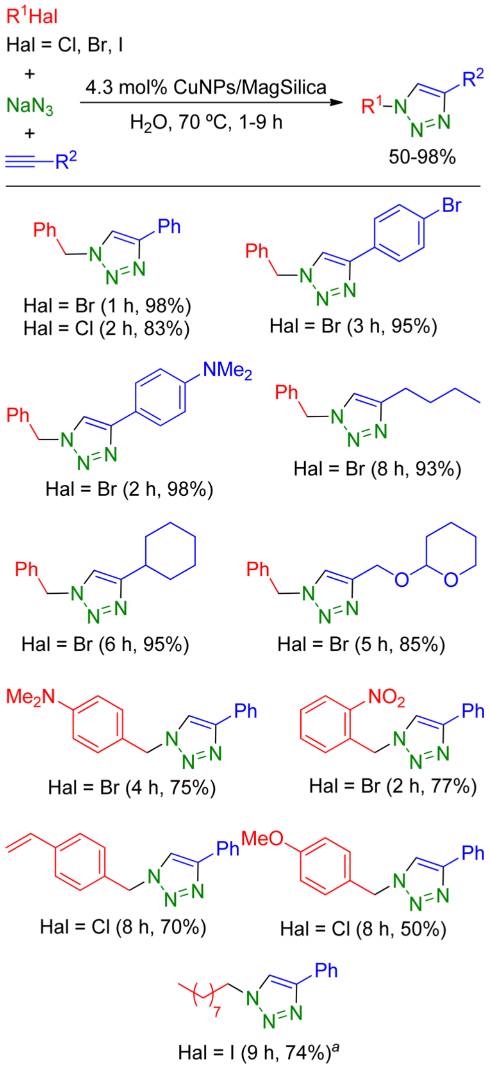
Figure 4. TEM micrograph of CuNPs/MagSilica. Reproduced with permission from ref 30. Copyright 2013 Elsevier.

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).

2.2.3. Nature of the CuNPs/C Catalyst.[27b] It is worth 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 comprising 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 had a contour reminiscent 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.

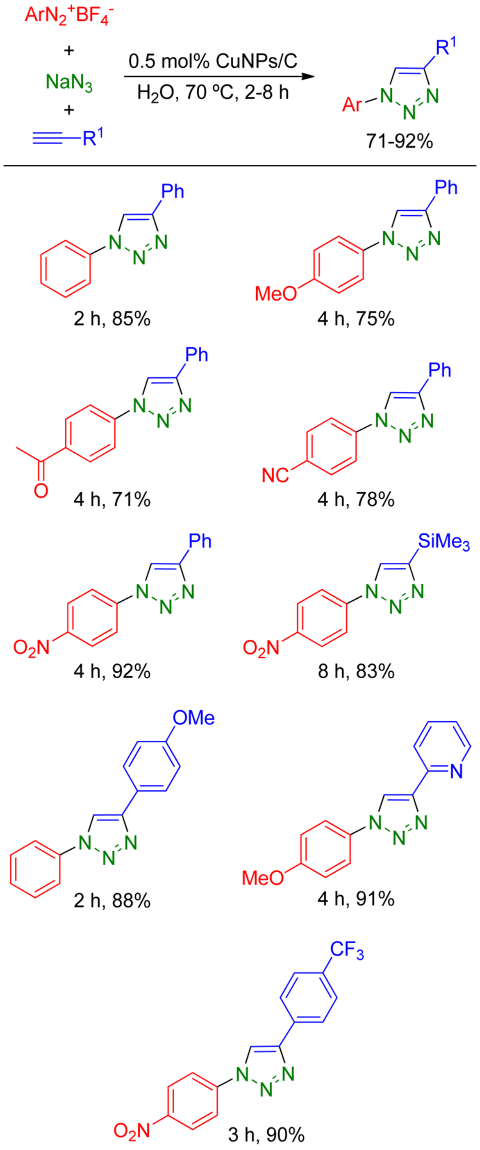
Even though the amount of catalyst deployed in these reactions was small, it could be retrieved by simple filtration and reutilized, leading to outstanding yields of the triazole product in five consecutive runs (98–90%) with undetectable copper leaching. In order to unveil the nature of the catalysis, the following protocol was carried out: the mixture resulting from a standard reaction, which contained the 1,2,3-triazole, was further warmed for 24 h with the aim of leaching 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

Table 4. Three-Component CuAAC from Organic Halides as Azido Precursors with CuNPs/MagSilica as Catalyst



[a] Reaction at 100 °C.

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



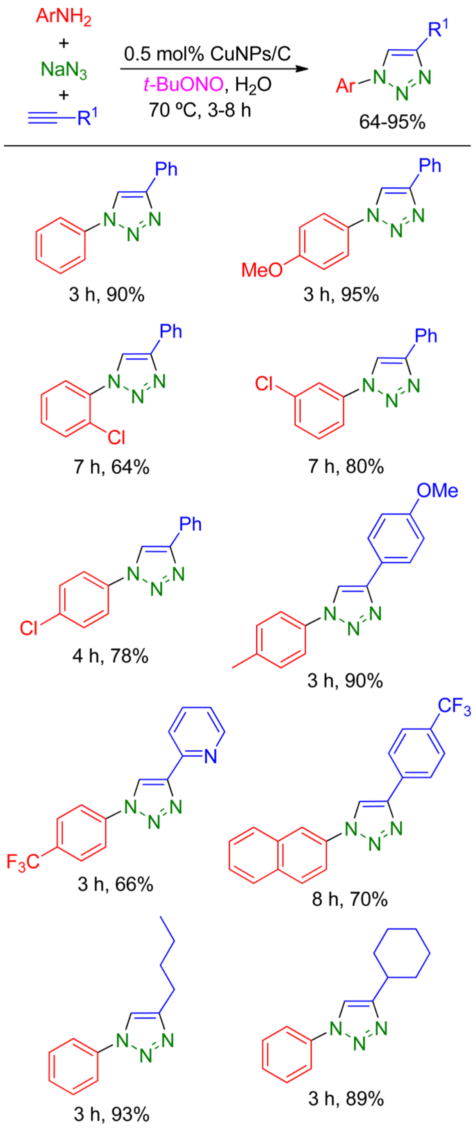
°C for 24 h, the 1,2,3-triazole was obtained in 17% conversion as a ca. 1:1 ratio of the 1,4- and 1,5-disubstituted regioisomers. This result proved that the reaction took place under thermal conditions in a noncatalyzed mode, which could be asserted by determining the copper content of the resulting aqueous phase (<50 ppb Cu). Although all of these experiments denote a process that is heterogeneous in nature, the possibility that the catalyst operates as a reservoir for metal species that leach into solution and readsorb cannot be ruled out.[18a] Nevertheless, Scaiano and co-workers recently combined single-molecule spectroscopy with standard bench-scale techniques to examine the CuNP-catalyzed AAC and proved that the catalysis occurs at the surface of the CuNPs.[29]

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 a 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 that were oxidized and well-dispersed on the magnetic support (Figure 4).

The CuNPs/MagSilica catalyst manifested good performance in the three-component CuAAC reaction from organic halides using 4.3 mol % Cu in water at 70 °C. This procedure was successfully applied to electronically different arylacetylenes as well as to aliphatic alkynes, though the latter 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 below the detection level of atomic absorption spectroscopy.

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 preformed azides or the more appropriate azides generated in situ 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

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



regard, the versatility of the CuNPs/C catalyst was broadened by investigating some alternative azide precursors other than organic halides that might be suitable to react 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 practiced for organic halides (0.5 mol % CuNPs/C, water, 70 °C). In this way, aromatic substituents bearing electronically different groups could be incorporated at the 1-position of the triazole in good yields and relatively short reaction times (Table 5).[27b]

The direct use of anilines as azido precursors was first described by Moses and co-workers in 2007. The reaction of anilines with *t*-BuONO and trimethylsilyl azide in CH_3CN 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, because the entire process was sequential, monitoring of the azide formation before the cycloaddition step was indispensable. It was found that anilines could be directly converted into 1,2,3-triazoles with *t*-BuONO and NaN_3 under the catalysis of CuNPs/C in aqueous media (Table 6).[27b] This multicomponent reaction was more convenient since NaN_3 is cheaper than trimethylsilyl azide, the reaction was 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.

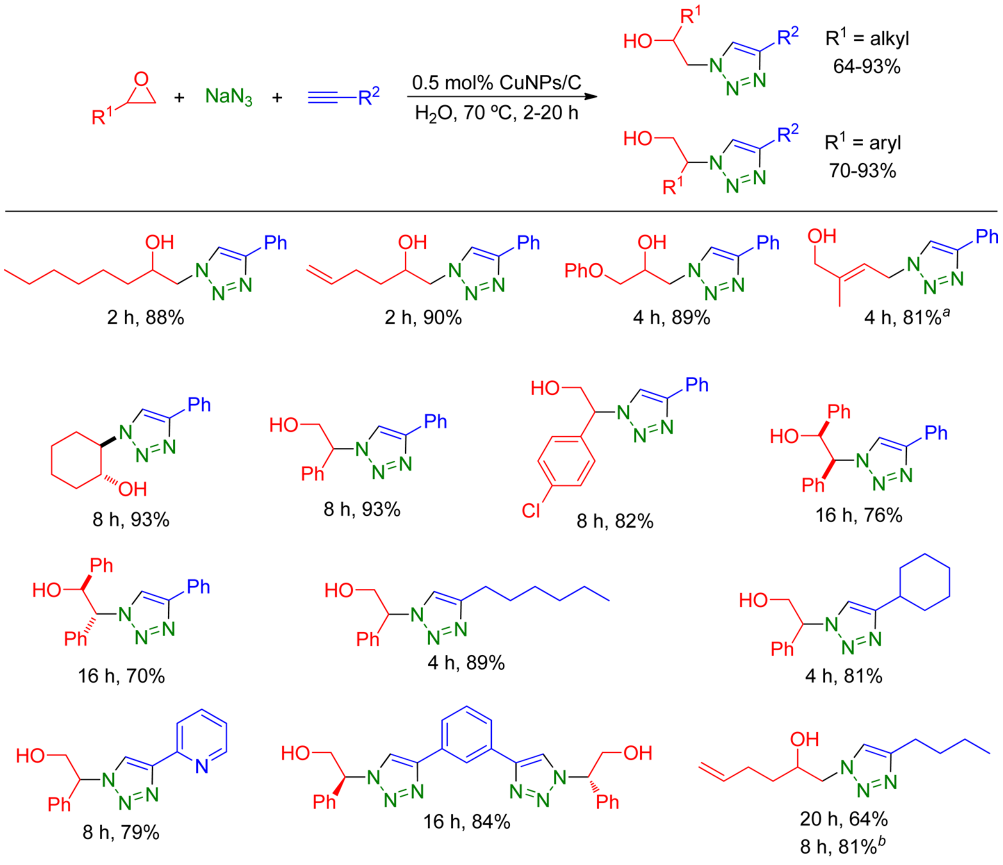
2.2.6. Multicomponent Synthesis of 1,2,3-Triazoles from Epoxides as Azido Precursors. Strained cycles such as epoxides, aziridines, cyclic sulfates, cyclic sulfamidates, aziridinium ions, and episulfonium ions can experience nucleophilic ring opening in a reliable, stereospecific, often highly regioselective, and nearly quantitative manner. These attributes justify the inclusion of this nucleophilic attack into the elite catalogue of click reactions.[1] Azidolysis of epoxides[32] and CuAAC share some intrinsic characteristics that utterly adapt the set of strict bases demanded for click chemistry.[1] For this reason, the synthesis of 1,2,3-triazoles through in situ generation of azido alcohols 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 azido alcohol 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 is regiospecific 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 it was proved that the regiochemistry of the products had been wrongly assigned in three of the six publications dealing with this topic.

A simple ^1H NMR experiment in CD_3CN was devised to ascertain the regiochemistry of this sort of reaction quickly and unequivocally.[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 with regard to 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 that can yield a carbon skeleton. The azasulfenylation of olefins developed by Trost and Shibata in 1982[35] was used as a source of inspiration to potentially transform alkenes into triazoles. In their 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

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



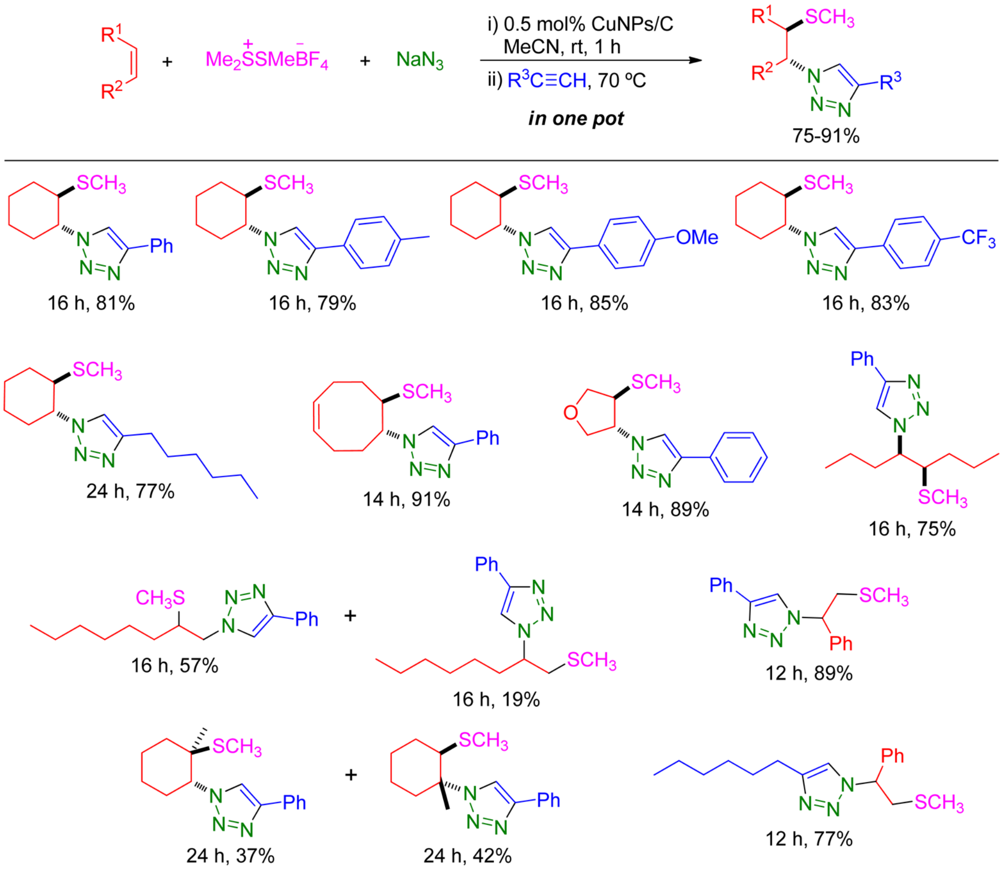
[a]From 2-methyl-2-vinyloxirane. [b]Reaction at 100 °C.

1–4 days. A more convenient variation of this method was discovered by directly mixing the alkene with CuNPs/C, DMTSF, and NaN_3 in MeCN, whereby the corresponding methylsulfanyl azide was produced in only 1 h at room temperature.

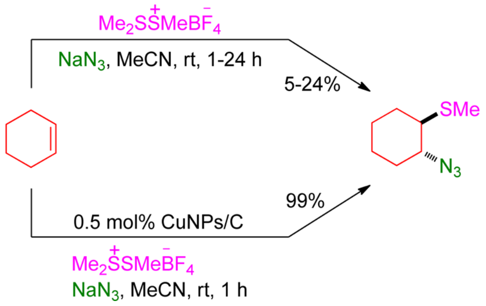
1,2,3-Triazoles were synthesized in one pot from inactivated alkenes by means of a sequence comprising two click steps catalyzed by CuNPs/C: the alkene azidosulfenylation and the reaction of the in situ-generated organic azide with the terminal alkyne.[36] The resulting β-methylsulfanyl-1,2,3-triazoles 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, although the azidolysis of oct-1-ene oxide[34] 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 NaN_3 in MeCN at rt (1–24 h) gave multiple products and only a 5–24% yield 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 because of poisoning by sulfur, the catalytic activity of the nanocatalyst was greater than that of some commercially accessible copper sources in bulk 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 CuAAC using supported CuNPs are distinctly more advantageous than those based on unsupported CuNPs. In fact, the former meet most of the ideals of green chemistry[8] and foundations of click chemistry:[1] (a) waste is reduced to a sodium salt aqueous solution, as the azides are generated in situ; (b) all of the experiments were safe, and no explosion occurred; (c) three or four materials are integrated into the final triazole, hence providing 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 sequence); (e) the preparation of the catalyst is simple and conducted at room temperature; (f) derivatization is 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 of the necessary chemicals are commercially or readily available; (m) simple reaction conditions are employed that are compatible with the presence of oxygen and water (except in the alkene azidosulfenylation–CuAAC sequence); (n) both the nucleophilic opening of strained rings and the formation of 1,4-disubstituted 1,2,3-triazoles are highly regioselective; and (o) the products generally are easily isolated or do not need purification.

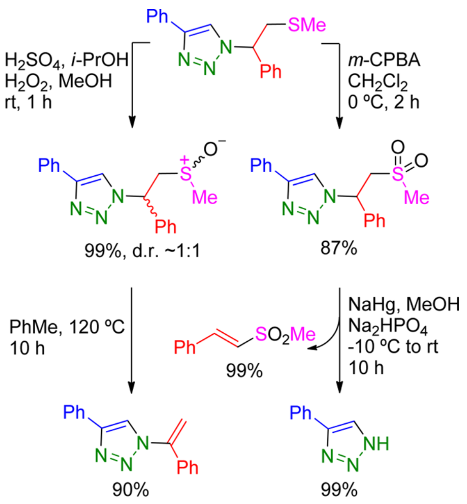
Table 8. Three-Component Synthesis of *β*-Methylsulfanyl-1,2,3-triazoles from Alkenes as Azido Precursors



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



Scheme 5. Synthetic Transformations of a *β*-Methylsulfanyl-1,2,3-triazole



3. CONCLUSION

We have summarized the application of easily prepared unsupported and supported CuNPs to CuAAC. The unsupported catalyst, Cu(0)NPs in tetrahydrofuran, allowed the fast reaction of terminal alkynes with preformed azides in the presence of triethylamine as a base; however, nanoparticle dissolution under these conditions prevented recovery of the catalyst. The catalysts composed of oxidized CuNPs on activated carbon (CuNPs/C) or silica-coated maghemite nanoparticles (CuNPs/MagSilica) were endowed with salient features that 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) low metal loading was used; and (d) the catalyst could be easily recovered and reused. 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 of the above reactions, 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 that enables click chemistry to be exploited competently on a large scale with negligible copper contamination of the products.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: falonso@ua.es.

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

Biographies

Francisco Alonso received his B.Sc. (1986), M.Sc. (1988), and Ph.D. (1991) in Chemistry from the University of Alicante. He was a postdoctoral Fleming Fellow (1992−1994) at the University of Oxford and became an Associate Professor in 1998 at the University of Alicante. His research focuses on the development of new synthetic methodologies involving transition-metal nanoparticles and the application of organometallic intermediates to the synthesis of naturally occurring molecular structures. He is the Director of the Instituto de Síntesis Orgánica and cofounder of Medalchemy S. L.

Yanina Moglie received her B.Sc. (2004) and Ph.D. (2009) in Chemistry from the Universidad Nacional del Sur (UNS) (Bahía Blanca, Argentina). After a postdoctoral stay at the University of Alicante (2010−2013), in 2014 she became a CONICET Associate Researcher of the Instituto de Química del Sur (INQUISUR, Bahía Blanca). Her research focuses on supported metal nanoparticles and their application in organic synthesis.

Gabriel Radivoy received his B.Sc. (1990) and Ph.D. (1996) in Chemistry from the UNS. After a three-year postdoctoral stay (1998−2001) at the University of Alicante, he moved back to the UNS, where he became an Associate Professor in 2009. His research is focused on new synthetic methodologies based on metal nanoparticles as catalysts. He is an Independent Researcher at CONICET and a member of the board of INQUISUR (CONICET-UNS).

■ ACKNOWLEDGMENTS

This work was supported by the Spanish Ministerio de Economía y Competitividad, the Generalitat Valenciana, Fondo Europeo de Desarrollo Regional, the Argentinian Consejo Nacional de Investigaciones Científicas y Técnicas and Agencia Nacional de Promoción Científica Tecnológica, and the Instituto de Síntesis Orgánica (Universidad de Alicante).

■ REFERENCES

(1) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.

(2) (a) Tornøe, C. W.; Meldal, M. Peptidotriazoles: Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions on Solid-Phase. In *The Wave of the Future*; Lebl, M., Houghten, R. A., Eds.; American Peptide Society and Kluwer Academic Publishers: San Diego, 2001; pp 263−264. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem.* **2002**, *67*, 3057−3064.

(3) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(4) Huisgen, R.; Knorr, R.; Möbius, L.; Szeimies, G. 1.3-Dipolare Cycloadditionen, XXIII. Einige Beobachtungen zur Addition Organischer Azide an CC-Dreifachbindungen. *Chem. Ber.* **1965**, *98*, 4014−4021.

(5) (a) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. Cu^I-Catalyzed Alkyne-Azide "Click" Cycloadditions from a Mechanistic and Synthetic Perspective. *Eur. J. Org. Chem.* **2006**, 51−68. (b) Meldal, M.; Tornøe, C. W. Cu-Catalyzed Azide-Alkyne Cycloaddition. *Chem. Rev.* **2008**, *108*, 2952−3015. (c) Fokin, V. V. CuAAC: The Quintessential Click Reaction. In *Organic Chemistry—Breakthroughs and Perspectives*, 1st ed.; Ding, K., Dai, L.-X., Eds.; Wiley-VCH: Weinheim, Germany, 2012; Chapter 7, pp 247−277.

(6) (a) Wang, Q.; Hawker, C. Toward a Few Good Reactions: Celebrating Click Chemistry's First Decade. *Chem. - Asian J.* **2011**, *6*, 2568−2569. (b) For a special issue, see: *Chem. - Asian J.* **2011**, *6*, 2565−2847.

(7) (a) *Click Chemistry for Biotechnology and Materials Science*; Lahann, J., Ed.; Wiley: Chichester, U.K., 2009. (b) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. Click Chemistry for Drug Development and Diverse Chemical-Biology Applications. *Chem. Rev.* **2013**, *113*, 4905−4979.

(8) Anastas, P.; Eghbali, N. Green Chemistry: Principles and Practice. *Chem. Soc. Rev.* **2010**, *39*, 301−312.

(9) (a) *Nanoparticles and Catalysis*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2008. (b) *Selective Nanocatalysts and Nanoscience*, 1st ed.; Zecchina, A., Bordiga, S., Groppo, E., Eds.; Wiley-VCH: Weinheim, Germany, 2011. (c) *Nanomaterials in Catalysis*; Serp, P., Philippot, K., Eds.; Wiley-VCH: Weinheim, Germany, 2013. (d) For a special issue, see: Nanoparticles for Catalysis. *Acc. Chem. Res.* **2013**, *46*, 1671−1910. (e) *Metal Nanoparticles for Catalysis: Advances and Applications*; Tao, F., Ed.; Royal Society of Chemistry: Cambridge, U.K., 2014.

(10) For a review, see: Campelo, J. M.; Luna, D.; Luque, R.; Marinas, J. M.; Romero, A. A. Sustainable Preparation of Supported Metal Nanoparticles and their Applications in Catalysis. *ChemSusChem* **2009**, *2*, 18−45.

(11) Nasir Baig, R. B.; Varma, R. S. Nanocatalysis in Water. In *Metal-Catalyzed Reactions in Water*; Dixneuf, P. H., Cadierno, V., Eds.; Wiley-VCH: Weinheim, Germany, 2013; Chapter 9, pp 337−394.

(12) (a) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates. *J. Am. Chem. Soc.* **2005**, *127*, 210−216. (b) Gommermann, N.; Gehrig, A.; Knochel, P. Enantioselective Synthesis of Chiral α-Aminoalkyl-1,2,3-triazoles Using a Three-Component Reaction. *Synlett* **2005**, 2796−2798.

(13) For reviews, see: (a) Jin, T.; Yan, M.; Yamamoto, Y. Click Chemistry of Alkyne-Azide Cycloaddition Using Nanostructured Copper Catalysts. *ChemCatChem* **2012**, *4*, 1217−1229. (b) Woo, H.; Kang, H.; Kim, A.; Jang, S.; Park, J. C.; Park, S.; Kim, B.-S.; Song, H.; Park, K. H. Azide-Alkyne Huisgen [3 + 2] Cycloaddition Using CuO Nanoparticles. *Molecules* **2012**, *17*, 13235−13252.

(14) (a) For the first applications of finally divided metals in organic chemistry, see: Sabatier, P. *La Catalyse en Chimie Organique*; Librairie Polytechnique Ch.Béranger: Paris, 1913. (b) Rieke, R. D. Use of Activated Metals in Organic and Organometallic Synthesis. *Top. Curr. Chem.* **1975**, *59*, 1−31. (c) Fürstner, A. *Active Metals*; Wiley-VCH: Weinheim, Germany, 1996.

(15) (a) Alonso, F.; Vitale, C.; Radivoy, G.; Yus, M. Reduction of Carbonyl Compounds and Imines using the $CuCl_2 \cdot 2H_2O$-Li-DTBB(cat.) Combination. *Synthesis* **2003**, 443−447. (b) Alonso, F.; Moglie, Y.; Radivoy, G.; Vitale, C.; Yus, M. Hydrodehalogenation of Organic Halides using the $CuCl_2 \cdot 2H_2O$-Li-arene(cat.) Combination. *Appl. Catal., A* **2004**, *271*, 171−176. (c) Radivoy, G.; Alonso, F.; Moglie, Y.; Vitale, C.; Yus, M. Reduction of Alkyl and Vinyl Sulfonates Using the

$\text{CuCl}_2\cdot 2\text{H}_2\text{O}$-Li-DTBB(cat.) System. *Tetrahedron* **2005**, *61*, 3859−3864.

(16) (a) Berg, R.; Straub, J.; Schreiner, E.; Mader, S.; Rominger, F.; Straub, B. F. Highly Active Dinuclear Copper Catalysts for Homogeneous Azide-Alkyne Cycloadditions. *Adv. Synth. Catal.* **2012**, *354*, 3445−3450. (b) Deraedt, C.; Pinaud, N.; Astruc, D. Recyclable Catalytic Dendrimer Nanoreactor for Part-Per-Million Cu^{I} Catalysis of "Click" Chemistry in Water. *J. Am. Chem. Soc.* **2014**, *136*, 12092−12098.

(17) (a) Durán Pachón, L.; van Maarseveen, J. H.; Rothenberg, G. Click Chemistry: Copper Clusters Catalyse the Cycloaddition of Azides with Terminal Alkynes. *Adv. Synth. Catal.* **2005**, *347*, 811−815. (b) Orgueira, H. A.; Fokas, D.; Isome, Y.; Chan, P. C.-M.; Baldino, C. M. Regioselective Synthesis of [1,2,3]-Triazoles Catalyzed by Cu(I) Generated in situ from Cu(0) Nanosize Activated Powder and Amine Hydrochloride Salts. *Tetrahedron Lett.* **2005**, *46*, 2911−2914. (c) Molteni, G.; Bianchi, C. L.; Marinoni, G.; Santo, N.; Ponti, A. Cu/Cu-Oxide Nanoparticles as Catalyst in the "Click" Azide-Alkyne Cycloaddition. *New J. Chem.* **2006**, *30*, 1137−1139. (d) Sarkar, A.; Mukherjee, T.; Kapoor, S. PVP-Stabilized Copper Nanoparticles: A Reusable Catalyst for "Click" Reaction between Terminal Alkynes and Azides in Nonaqueous Solvents. *J. Phys. Chem. C* **2008**, *112*, 3334−3340.

(18) (a) Astruc, D.; Lu, F.; Ruiz Aranzaes, J. Nanoparticles as Recyclable Catalysts: The Frontier between Homogeneous and Heterogeneous Catalysis. *Angew. Chem., Int. Ed.* **2005**, *44*, 7852−7872. (b) Franke, R.; Rothe, J.; Pollmann, J.; Hormes, J.; Bönnemann, H.; Brijoux, W.; Hindenburg, T. A Study of the Electronic and Geometric Structure of Colloidal $\text{Ti}^0\cdot 0.5\text{THF}$. *J. Am. Chem. Soc.* **1996**, *118*, 12090−12097.

(19) (a) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. Copper Nanoparticles in Click Chemistry: an Alternative Catalytic System for the Cycloaddition of Terminal Alkynes and Azides. *Tetrahedron Lett.* **2009**, *50*, 2358−2362. (b) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. Unsupported Copper Nanoparticles in the 1,3-Dipolar Cycloaddition of Terminal Alkynes and Azides. *Eur. J. Org. Chem.* **2010**, 1875−1884.

(20) Pérez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asín, J. A.; Isac-García, J.; Santoyo-González, F. Multivalent Neoglycoconjugates by Regiospecific Cycloaddition of Alkynes and Azides Using Organic Soluble Copper Catalysts. *Org. Lett.* **2003**, *5*, 1951−1954.

(21) (a) Hein, J. E.; Fokin, V. V. Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) and Beyond: New Reactivity of Copper(I) Acetylides. *Chem. Soc. Rev.* **2010**, *39*, 1302−1315. (b) Buckley, B. R.; Heaney, H. Mechanistic Investigations of Copper(I)-Catalysed Alkyne-Azide Cycloaddition Reactions. *Top. Heterocycl. Chem.* **2012**, *28*, 1−30.

(22) (a) Nolte, C.; Mayer, P.; Straub, B. F. Isolation of a Copper(I) Triazolide: A "Click" Intermediate. *Angew. Chem., Int. Ed.* **2007**, *46*, 2101−2103. (b) Straub, B. F. μ-Acetylide and μ-Alkenylidene Ligands in "Click" Triazole Syntheses. *Chem. Commun.* **2007**, 3868−3870. (c) Ahlquist, M.; Fokin, V. V. Enhanced Reactivity of Dinuclear Copper(I) Acetylides in Dipolar Cycloadditions. *Organometallics* **2007**, *26*, 4389−4391. (d) Buckley, B. R.; Dann, S. E.; Heaney, H. Experimental Evidence for the Involvement of Dinuclear Alkynylcopper(I) Complexes in Alkyne-Azide Chemistry. *Chem. - Eur. J.* **2010**, *16*, 6278−6284. (e) Worrell, B. T.; Malik, J. A.; Fokin, V. V. Direct Evidence of a Dinuclear Copper Intermediate in Cu(I)-Catalyzed Azide-Alkyne Cycloadditions. *Science* **2013**, *340*, 457−460.

(23) (a) Lipshutz, B. H.; Taft, B. R. Heterogeneous Copper-in-Charcoal-Catalyzed Click Chemistry. *Angew. Chem., Int. Ed.* **2006**, *45*, 8235−8238. (b) Chassaing, S.; Sido, A. S. S.; Alix, A.; Kumarraja, M.; Pale, P.; Sommer, J. "Click Chemistry" in Zeolites: Copper(I) Zeolites as New Heterogeneous and Ligand-Free Catalysts for the Huisgen [3 + 2] Cycloaddition. *Chem. - Eur. J.* **2008**, *14*, 6713−6721. (c) Sirion, U.; Bae, Y. J.; Lee, B. S.; Chi, D. Y. Ionic Polymer Supported Copper(I): A Reusable Catalyst for Huisgen's 1,3-Dipolar Cycloaddition. *Synlett* **2008**, 2326−2330. (d) Park, I. S.; Kwon, M. S.; Kim, Y.; Lee, J. S.; Park, J. Heterogeneous Copper Catalyst for the Cycloaddition of Azides and Alkynes without Additives under Ambient Conditions. *Org. Lett.* **2008**, *10*, 497−500. (e) Smith, C. D.; Baxendale, I. R.; Lanners, S.; Hayward, J. J.; Smith, S. C.; Ley, S. V. [3 + 2] Cycloaddition of Acetylenes with Azides to Give 1,4-Disubstituted 1,2,3-Triazoles in a Modular Flow Reactor. *Org. Biomol. Chem.* **2007**, *5*, 1559−1561. (f) For a minireview of heterogeneous AAC, see: Dervaux, B.; Du Prez, F. E. *Chem. Sci.* **2012**, *3*, 959−966.

(24) (a) Feldman, A. K.; Colasson, B.; Fokin, V. V. One-Pot Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from In Situ Generated Azides. *Org. Lett.* **2004**, *6*, 3897−3899. (b) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. A Microwave-Assisted Click Chemistry Synthesis of 1,4-Disubstituted 1,2,3-Triazoles via a Copper(I)-Catalyzed Three-Component Reaction. *Org. Lett.* **2004**, *6*, 4223−4225.

(25) (a) Miao, T.; Wang, L. Regioselective Synthesis of 1,2,3-Triazoles by Use of Silica-Supported Copper(I) Catalyst. *Synthesis* **2008**, 363−368. (b) Bénéteau, V.; Olmos, A.; Boningari, T.; Sommer, J.; Pale, P. Zeo-Click Synthesis: Cu^{I}-Zeolite-Catalyzed One-Pot Two-Step Synthesis of Triazoles from Halides and Related Compounds. *Tetrahedron Lett.* **2010**, *51*, 3673−3677.

(26) (a) Laksmi Kantam, M.; Swarna Jaya, V.; Sreedhar, B.; Mohan Rao, M.; Choudary, B. M. Preparation of Alumina Supported Copper Nanoparticles and their Application in the Synthesis of 1,2,3-Triazoles. *J. Mol. Catal. A: Chem.* **2006**, *256*, 273−277. (b) Sharghi, H.; Khalifeh, R.; Doroodmand, M. M. Copper Nanoparticles on Charcoal for Multicomponent Catalytic Synthesis of 1,2,3-Triazole Derivatives from Benzyl Halides or Alkyl Halides, Terminal Alkynes and Sodium Azide in Water as a "Green" Solvent. *Adv. Synth. Catal.* **2009**, *351*, 207−218.

(27) (a) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. Multicomponent Synthesis of 1,2,3-Triazoles in Water Catalysed by Copper Nanoparticles on Activated Carbon. *Adv. Synth. Catal.* **2010**, *352*, 3208−3214. (b) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. Click Chemistry from Organic Halides, Diazonium Salts and Anilines in Water Catalysed by Copper Nanoparticles on Activated Carbon. *Org. Biomol. Chem.* **2011**, *9*, 6385−6395.

(28) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. Multicomponent Click Synthesis of Potentially Biologically Active Triazoles Catalysed by Copper Nanoparticles on Activated Carbon in Water. *Heterocycles* **2012**, *84*, 1033−1044.

(29) Decan, M. R.; Impellizzeri, S.; Marin, M. L.; Scaiano, J. C. Copper Nanoparticle Heterogeneous Catalytic "Click" Cycloaddition Confirmed by Single-Molecule Spectroscopy. *Nat. Commun.* **2014**, *5*, 4612.

(30) Nador, F.; Volpe, M. A.; Alonso, F.; Feldhoff, A.; Kirschning, A.; Radivoy, G. Copper Nanoparticles Supported on Silica Coated Maghemite as Versatile, Magnetically Recoverable and Reusable Catalyst for Alkyne Coupling and Cycloaddition Reactions. *Appl. Catal., A* **2013**, *455*, 39−45.

(31) (a) Barral, K.; Moorhouse, A. D.; Moses, J. E. Efficient Conversion of Aromatic Amines into Azides: A One-Pot Synthesis of Triazole Linkages. *Org. Lett.* **2007**, *9*, 1809−1811. (b) Moorhouse, A. D.; Moses, J. E. Microwave Enhancement of a 'One-Pot' Tandem Azidation−'Click' Cycloaddition of Anilines. *Synlett* **2008**, 2089−2092.

(32) Amantini, D.; Fringuelli, F.; Piermatti, O.; Tortoioli, S.; Vaccaro, L. Nucleophilic Ring Opening of 1,2-Epoxides in Aqueous Medium. *ARKIVOC* **2002**, No. xi, 293−311.

(33) (a) Yadav, J. S.; Subba Reddy, B. V.; Madhusudhan Reddy, G.; Narasimha Chary, D. Three Component, Regioselective, One-Pot Synthesis of β-Hydroxytriazoles from Epoxides via 'Click Reactions'. *Tetrahedron Lett.* **2007**, *48*, 8773−8776. (b) Kumaraswamy, G.; Ankamma, K.; Pitchaiah, A. Tandem Epoxide or Aziridine Ring Opening by Azide/Copper Catalyzed [3 + 2] Cycloaddition: Efficient Synthesis of 1,2,3-Triazolo β-Hydroxy or β-Tosylamino Functionality Motif. *J. Org. Chem.* **2007**, *72*, 9822−9825. (c) Rajender Reddy, K.; Uma Maheswari, C.; Rajgopal, K.; Lakshmi Kantam, M. One-Pot Sequential Synthesis of β-Hydroxy-1,4-disubstituted-1,2,3-triazoles from In-Situ Generated β-Azido Alcohol by Click Chemistry. *Synth. Commun.* **2008**, *38*, 2158−2167. (d) Sharghi, H.; Beyzavi, M. H.; Safavi, A.; Doroodmand, M. M.; Khalifeh, R. Immobilization of

Porphyrinatocopper Nanoparticles onto Activated Multi-Walled Carbon Nanotubes and a Study of its Catalytic Activity as an Efficient Heterogeneous Catalyst for a Click Approach to the Three-Component Synthesis of 1,2,3-Triazoles in Water. *Adv. Synth. Catal.* **2009**, *351*, 2391−2410. (e) Sharghi, H.; Hosseini-Sarvari, M.; Moeini, F.; Khalifeh, R.; Beni, A. S. One-Pot, Three-Component Synthesis of 1-(2-Hydroxyethyl)-1*H*-1,2,3-Triazole Derivatives by Copper-Catalyzed 1,3-Dipolar Cycloaddition of 2-Azido Alcohols and Terminal Alkynes under Mild Conditions in Water. *Helv. Chim. Acta* **2010**, *93*, 435−449. (f) Boningari, T.; Olmos, A.; Reddy, B. M.; Sommer, J.; Pale, P. Zeo-Click Chemistry: Copper(I)-Zeolite-Catalyzed Cascade Reaction; One-Pot Epoxide Ring-Opening and Cycloaddition. *Eur. J. Org. Chem.* **2010**, 6338−6347.

(34) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. Multicomponent Click Synthesis of 1,2,3-Triazoles from Epoxides in Water Catalyzed by Copper Nanoparticles on Activated Carbon. *J. Org. Chem.* **2011**, *76*, 8394−8405.

(35) Trost, B. M.; Shibata, T. Nucleophilic Attack on Olefins Initiated by Dimethyl(methylthio)sulfonium Fluoroborate (DMTSF). Azasulfenylation. *J. Am. Chem. Soc.* **1982**, *104*, 3225−3228.

(36) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. Alkenes as Azido Precursors for the One-Pot Synthesis of 1,2,3-Triazoles Catalyzed by Copper Nanoparticles on Activated Carbon. *J. Org. Chem.* **2013**, *78*, 5031−5037.