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PAPER

Click chemistry from organic halides, diazonium salts and anilines in water catalysed by copper nanoparticles on activated carbon†‡

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An easy-to-prepare, reusable and versatile catalyst consisting of oxidised copper nanoparticles on activated carbon has been fully characterised and found to effectively promote the multicomponent synthesis of 1,2,3-triazoles from organic halides, diazonium salts, and aromatic amines in water at a low copper loading.

Introduction

The concepts of click chemistry[1] and green chemistry[2] share a series of stringent criteria in order to design and implement more efficient and environmentally benign processes. In recent years, nano-catalysis has emerged as a sustainable and competitive alternative to conventional catalysis since the metal nanoparticles possess a high surface-to-volume ratio, which enhances their activity and selectivity, while at the same time maintaining the intrinsic features of a heterogeneous catalyst.[3] In particular, the immobilisation of metal nanoparticles on high-surface-area inorganic supports allows a higher stability and dispersity of the particles as well as a further exploitation of the special activity and recycling properties of the catalyst.[4] With these principles in mind, new possibilities arise for the copper-catalysed Huisgen[5] 1,3-dipolar cycloaddition of organic azides and alkynes,[6] the paradigm of a click reaction.

In fact, despite the fact that the aforementioned cycloaddition has been intensively studied, the application of supported copper nanoparticles (CuNPs) to this reaction is scant. For instance, CuNPs immobilised in aluminium oxyhydroxide nanofiber were shown to be highly active in the cycloaddition of azides and alkynes at room temperature in hexane.[7] Very recently, copper nitride nanoparticles supported on a superparamagnetic mesoporous microsphere, $Cu_3N/Fe_3N@SiO_2$, were found to catalyse the click cycloaddition at room temperature in acetonitrile.[8] In this case, the catalyst was reusable but the presence of triethylamine and long reaction times (12 h to 14 d) were mandatory in order to achieve good yields. More advantageous are the methodologies in which the organic azides are generated *in situ* from organic halides (three-component alkyne–azide cycloaddition) since (a) hazards derived from their isolation and handling are minimised, (b) the time consuming and waste generating additional synthetic step is avoided, and (c) the common organic solvents utilised (*e.g.*, dioxane, toluene, DMF, dichloromethane, hexane) can be replaced by neat water. In this vein, CuNPs on alumina catalysed the multicomponent synthesis of 1,2,3-triazoles, in modest to good yields, starting from activated organic halides at room temperature in water.[9] The catalyst was reused for three cycles but its preparation seems rather tedious, through an aerogel method under supercritical conditions using copper(II) acetylacetonate, aluminium isopropoxide, methanol, toluene, and deionised water. CuI/Cu NPs of 80–300 nm were supported on pre-treated activated carbon and the resulting catalyst applied to the three-component reaction of activated organic halides in water at 100 °C.[10]

The above described methods based on supported CuNPs are clearly convenient in the sense that the catalysts can be easily recovered and reused. However, the long and tedious procedures usually required for the heterogenisation of copper and the limited substrate scope can curtail the widespread utilisation of this type of catalyst. Therefore, there is still an upsurge of interest in developing easy-to-prepare and versatile heterogeneous copper catalysts that efficiently enable the synthesis of triazoles in water.

Owing to our dedication to study and understand the reactivity of active metals,[11] we found out that active copper [obtained from $CuCl_2{\cdot}2H_2O$, lithium metal, and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) in THF at room temperature] was able to reduce carbonyl compounds, imines and sulfonates, and promoted the hydrodehalogenation of organic halides under very mild conditions.[12] We also discovered that CuNPs are formed when the active copper is generated from anhydrous $CuCl_2$ under the above mentioned conditions. These unsupported copper nanoparticles (10 mol%) effectively catalysed the 1,3-dipolar cycloaddition of organic azides and terminal alkynes in the presence of triethylamine at 65 °C in THF.[13]

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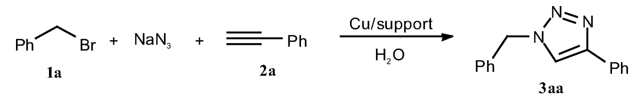
† Dedicated to the memory of Professor Rafael Suau.

‡ Electronic supplementary information (ESI) available: general remarks, XRD spectrum of the catalyst, experimental procedures, and spectroscopic characterisation of new compounds. See DOI: 10.1039/c1ob05735a

Remarkably short reaction times (10–120 min), comparable to those previously reported under microwave heating, were recorded in the absence of any stabilising additive or ligand. Unfortunately, the CuNPs underwent dissolution under the reaction conditions which precluded their reuse. More recently, we introduced a catalyst consisting of oxidized copper nanoparticles on activated carbon, readily prepared under mild conditions, which manifested a high versatility in the multicomponent Huisgen 1,3-dipolar cycloaddition in water.[14] Not only organic halides, but examples of other azide precursors, such as an epoxide, diazonium salt, aniline, and alkene, were successfully transformed into the corresponding 1,2,3-triazoles. We would like to present herein a more complete study on the catalyst and its substrate scope, including diazonium salts and anilines as aryl halide substitutes.

Table 1 Screening of copper catalysts in the three-component azide–alkyne cycloaddition in water[a]



Entry	Support (mol% Cu)[b]	T/°C	Time(h)	Yield(%)[c]
1	SiO_2 (1)	70	4	90 (16)
2	Al_2O_3 (1)	70	9	>99 (13)
3	TiO_2 (1)	70	24	74
4	MgO (1)	70	24	16
5	ZnO_2 (1)	70	24	57
6	Al silicate (1)	70	6	>99 (19)
7	Al (1)	70	24	18
8	MCM-10 (1)	70	24	17
9	magnetite (1)	70	9	>99 (0)
10	graphite (5)	70	14	80
11	graphite (5)[d]	70	24	0
12	graphite (5)	25	24	33
13	graphite (1)	25	24	31
14	graphite (1)	70	7	90
15	MWCNT[e] (5)	70	6	>99 (20)
16	activated carbon (5)	70	7	>99
17	activated carbon (5)[d]	70	24	0
18	activated carbon (5)	25	24	30
19	**activated carbon (1)**	**70**	**3**	>99 (**>99**)
20	activated carbon (0)	70	24	50[f]

[a] Reaction conditions: **1a** (1 mmol), NaN_3 (1.1 mmol), and **2a** (1 mmol) in H_2O. [b] Amount of copper added to the support. [c] GLC yield; the yield after a second cycle is in parenthesis. [d] Solvent-free reaction. [e] Multi-walled carbon nanotube. [f] **3aa** was obtained as a 1 : 1.3 mixture of regioisomers; alkyne 19%; azide 31%.

Catalyst screening

In order to analyse the effect of the support, an array of copper catalysts were prepared by simply adding the support to a suspension of the recently prepared CuNPs. This suspension was readily obtained by mixing anhydrous copper(II) chloride, lithium metal, and a catalytic amount of DTBB (10 mol%) in THF at room temperature. The catalysts were used as prepared without any further pre-treatment. The activity of the different catalysts was tested in the cycloaddition of benzyl bromide (**1a**) and phenylacetylene (**2a**) (Table 1). The best results were obtained with SiO_2 (entry 1), Al_2O_3 (entry 2), Al silicate (entry 6), magnetite (entry 9), graphite (entry 14), MWCNT (entry 15), and activated carbon (entry 19), with the yields being ≥90% in ≤9 h at 70 °C. Among them, activated carbon[15] exhibited the highest activity (>99% yield, 3 h), giving triazole **3aa** in quantitative yield after reuse in a second cycle (entry 19). In a control experiment, the model reaction was carried out with activated carbon, in the absence of copper (entry 20); the reaction yield was much lower (50%) and the process lacked regioselectivity.

Catalyst characterisation

The copper-on-activated-carbon catalyst was fully characterised in order to ascertain its nature and morphology. A copper content in the catalyst of 1.6 wt% was determined by inductively coupled plasma mass spectrometry (ICP-MS). Transmission electron microscopy (TEM) revealed the presence of spherical nanoparticles dispersed on the active carbon support with an average size of *ca.* 6 ± 2 nm (Fig. 1). Energy-dispersive X-ray (EDX) analysis on various regions confirmed the presence of copper on the support, with energy bands of 8.04, 8.90 keV (K lines) and 0.92 keV (L line) (Fig. 2). The XRD diffractogram did not show any significant peak for copper due to the small crystal domains and/or low copper loading weight.[16] The XPS spectrum displays two O (1s) peaks at 532.2 and 534.2 eV (Fig. 3), and three Cu ($2p_{3/2}$) peaks at 934.1, 936.4, and 945.7 eV (Fig. 4). Both the O (1s) and Cu ($2p_{3/2}$) values are abnormally high with respect to those found in the literature for copper-on-carbon catalysts.[17] Since the C (1s) peak (284.4 eV) was used as an internal standard to calibrate the binding energies, we believe that a differential charge phenomenon could occur as a result of the difficulties in differentiating the adventitious carbon from the carbon support by XPS. If we, however, assume that the peak at 936.4 eV corresponds to Cu(II), the typical value of which would be expected at 934.0 eV, a correction could be applied accordingly. Therefore, the corrected values would be: 529.8 and 531.8 eV for O (1s), and 931.7, 934.0 and 943.3 eV for Cu ($2p_{3/2}$). From these results we can deduce that the surface of the copper nanocatalyst is mainly oxidised. The O (1s) peak at 529.8 can be ascribed to the CuO phase, whereas the peak at 531.8 eV is suggested to be associated with species chemisorbed on the carbon.[17] The Cu ($2p_{3/2}$) region might be assigned to Cu_2O (931.7 eV) and CuO (934.0 eV), with the peak at 943.3 eV being a satellite shake-up feature characteristic of Cu(II) species.[18] These data are in agreement with the presence of Cu_2O and CuO detected in the selected-area electron-diffraction pattern (SAED) of the CuNPs (Fig. 5). The application of oxidised CuNPs to the click reaction is a matter of recent discovery.[19] Mixed Cu/Cu-oxide[19a] (mostly composed of Cu_2O and CuO nanoparticles), CuO hollow nanostructures,[19b] and PVP-stabilised Cu_2O nanoparticles[19c] have been found to catalyse the 1,3-dipolar cycloaddition of pre-formed azides and terminal alkynes. To the best of our knowledge, however, this is the first time that oxidised CuNPs have been utilised in the three-component version, *i.e.* the reaction of an organic halide with sodium azide and a terminal alkyne in one pot.

Synthesis of 1,2,3-triazoles from organic halides

With an optimised catalyst and reaction conditions in hand, we first studied the multicomponent click reaction of activated organic halides and phenylacetylene (**2a**) in water at 70 °C, using 0.5 mol% CuNPs/C (Table 2, entries 1–7). Both benzyl bromide and chloride (**1a**) gave triazole **3aa** in excellent yield, although the

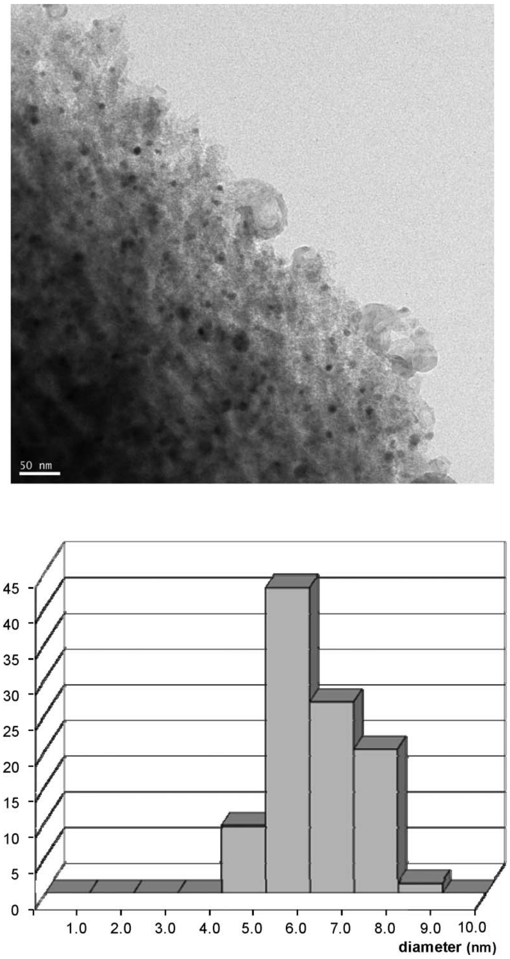


Fig. 1 TEM micrograph and size distribution of CuNPs/C.

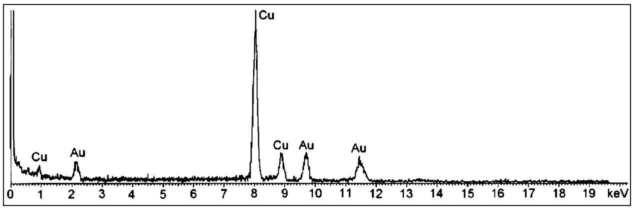


Fig. 2 EDX spectrum of CuNPs/C.

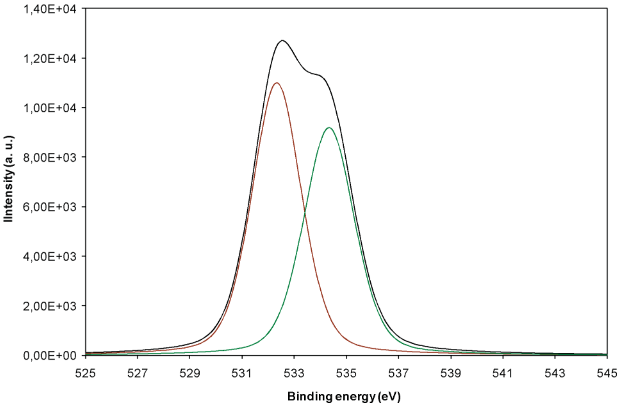


Fig. 3 XPS spectrum of the CuNPs/C at the O (1s) level.

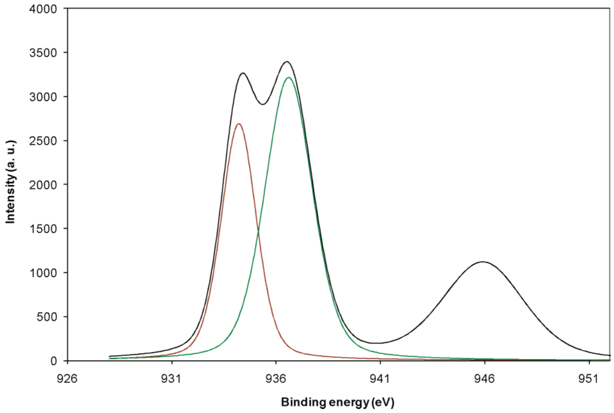


Fig. 4 XPS spectrum of the CuNPs/C at the Cu $2p_{3/2}$ level.

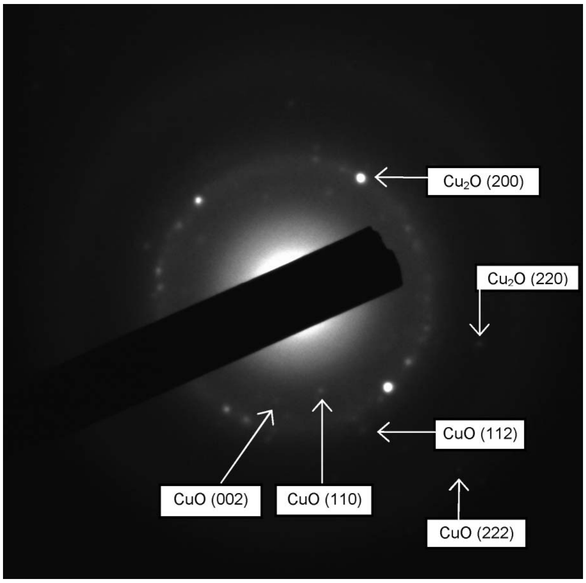
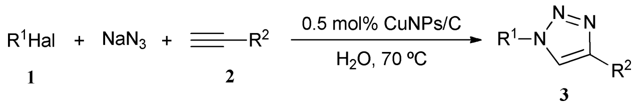


Fig. 5 Selected area electron diffraction (SAED) pattern of the CuNPs/C.

former reacted faster (entry 1). Benzyl bromides bearing either electron-withdrawing (**1b**) or electron-donating groups (**1c**), as well as the more electronically neutral 9-anthryl bromide (**1d**), also reacted nicely (entries 2–4). Cinnamyl bromide (**1f**) yielded a single triazole **3fa** under the reaction conditions, in spite of the fact that allylic azides are prone to undergo a [3,3]-sigmatropic rearrangement leading to mixtures of triazoles (Table 2, entry 5).[20] Some α-halocarbonyl compounds, such as α-chloroacetophenone (**1g**) or ethyl α-bromoacetate (**1h**), were also studied, with the chloride again reacting more sluggishly than the bromide (entries 6 and 7). It is worthy of note that deactivated alkyl halides could be also used as the azide precursors in the reaction with phenylacetylene (entries 8–10), with a solvent system composed of H_2O–EtOH 1 : 1 providing the best results in entries 8 and 9. As expected, the reactivity followed the trend RI > RBr > RCl, with both the iodide (**1i**, X = I) and bromides (**1j**, **1k**) reacting at 70 °C and the chloride (**1i**, X = Cl) at 100 °C. Then, we tested alkynes other than phenylacetylene in the reaction with benzyl bromide (**1a**). Phenyl propargyl ether (**2b**), 4-methoxyphenylacetylene (**2c**), 2-ethynylpyridine (**2d**), and *N*-propargylphthalimide (**2e**) were transformed into the corresponding triazoles in good yields under

Table 2 Three-component 1,3-dipolar azide–alkyne cycloaddition catalysed by CuNPs/C using organic halides as the azide precursors[a]



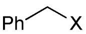
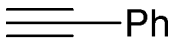
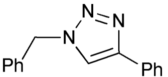
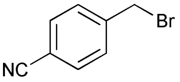
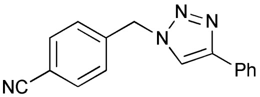
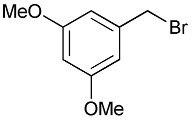
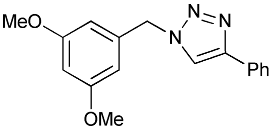
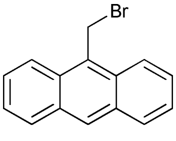
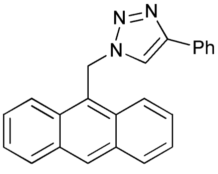
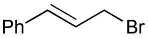
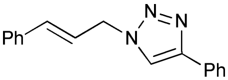
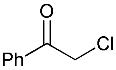
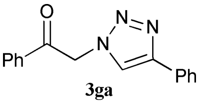
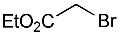
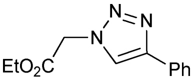
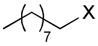
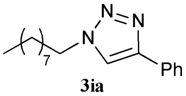
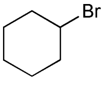
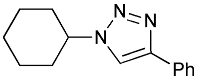
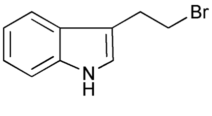
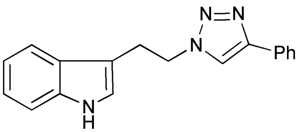
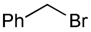
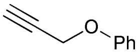
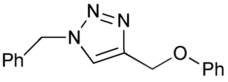
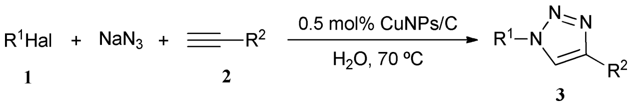
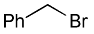
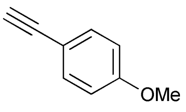
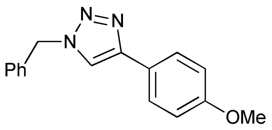
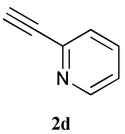
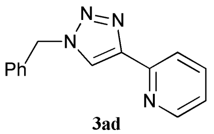
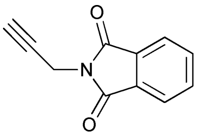
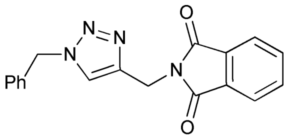
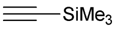
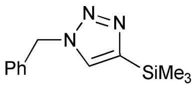
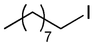
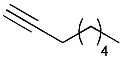
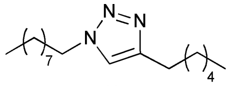
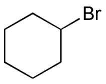
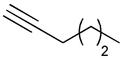
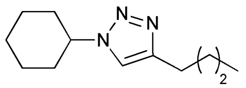
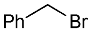
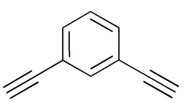
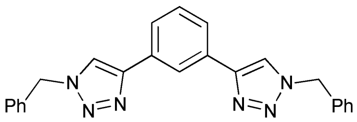
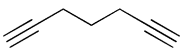
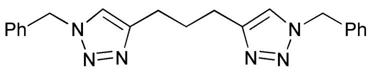
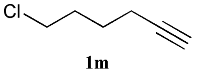
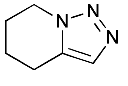
Entry	Organic halide	Alkyne	Time(h)	Triazole	Yield(%)[b]
1	 X = Br X = Cl **1a**	 **2a**	3 6	 **3aa**	98 99
2	 **1b**	**2a**	5	 **3ba**	99
3	 **1c**	**2a**	4	 **3ca**	98
4	 **1d**	**2a**	6	 **3da**	90
5	 **1f**	**2a**	3	 **3fa**	94
6	 **1g**	**2a**	7	 **3ga**	82
7	 **1h**	**2a**	4	 **3ha**	98
8	 X = I X = Cl **1i**	**2a**	5[c] 8[c,d]	 **3ia**	98 94
9	 **1j**	**2a**	8[c]	 **3ja**	93
10	 **1k**	**2a**	8	 **3ka**	89
11	 **1a**	 **2b**	7	 **3ab**	76

Table 2 (*Contd.*)

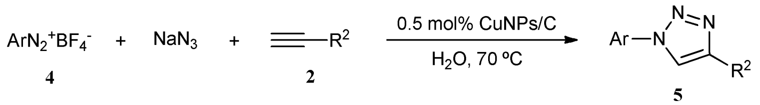


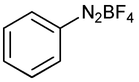
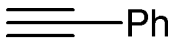
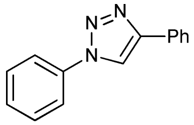
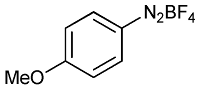
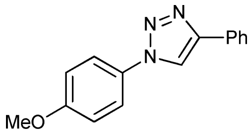
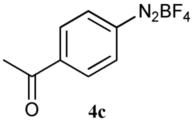
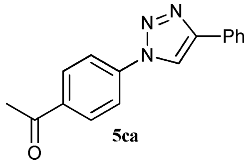
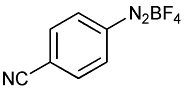
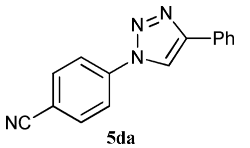
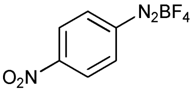
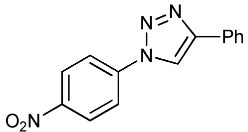
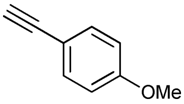
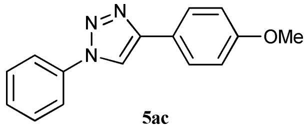
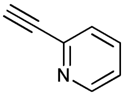
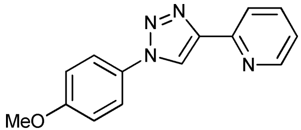
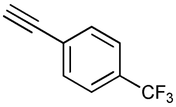
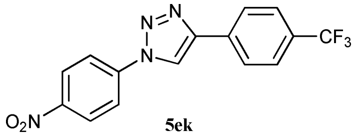
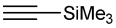
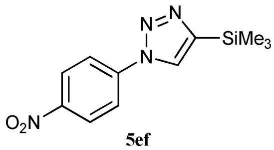
Entry	Organic halide	Alkyne	Time(h)	Triazole	Yield(%)[b]
12	 **1a**	 **2c**	6	 **3ac**	90
13	**1a**	 **2d**	6	 **3ad**	92
14	**1a**	 **2e**	8	 **3ae**	84
15	**1a**	 **2f**	8	 **3af**	82
16	 **1i**	 **2g**	8[c,d]	 **3ig**	92
17	 **1l**	 **2h**	8[c,d]	 **3lh**	89
18	 **1a**	 **2i**	6[e]	 **3ai**	92
19	**1a**	 **2j**	10[e]	 **3aj**	87
20	 **1m**		8	 **3m**	89

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), NaN_3 (1.1 mmol), CuNPs/C (0.5 mol%) in H_2O at 70 °C. [b] Isolated yield. [c] Reaction in H_2O–EtOH 1 : 1. [d] Reaction at 100 °C. [e] 2 mmol of **1a**

the standard reaction conditions (entries 11–14). The successful reaction with trimethylsilylacetylene (**2f**) provides an indirect entry into the 1-monosubstituted triazoles, which could be obtained after proper desilylation, thus making unnecessary the handling of acetylene or acetylene precursors (entry 15).[21] Interestingly, the 1,3-dipolar cycloaddition was also accomplished for the more reluctant to react alkyl-substituted halides and alkynes (**1i** and **1l** with **2g** and **2h**, respectively) (entries 16 and 17). The synthesis of bistriazoles was also readily effected from diynes **2i** and **2j** with two equivalents of benzyl bromide (entries 18 and 19). Moreover,

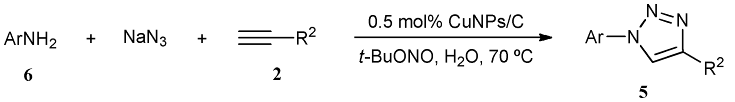
Table 3 Three-component 1,3-dipolar azide–alkyne cycloaddition catalysed by CuNPs/C using diazonium salts as the azide precursors[a]

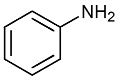
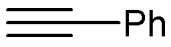
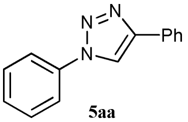
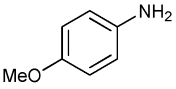
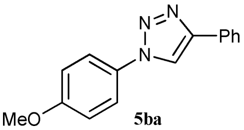
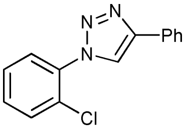
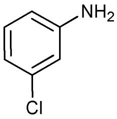
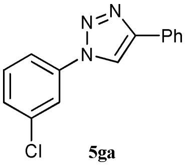
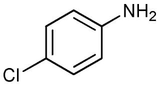
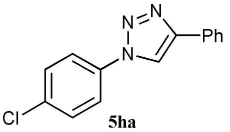
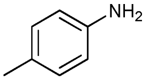
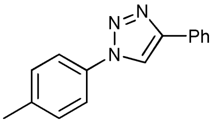
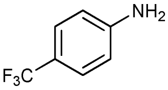
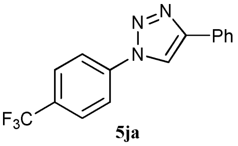
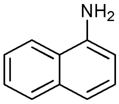
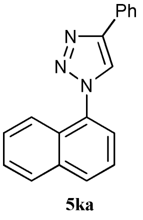
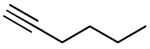
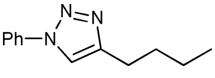
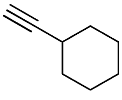
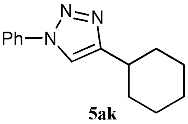


Entry	Diazonium salt	Alkyne	Time(h)	Triazole	Yield(%)[b]
1	 **4a**	 **2a**	2	 **5aa**	85
2	 **4b**	**2a**	4	 **5ba**	75
3	 **4c**	**2a**	4	 **5ca**	71
4	 **4d**	**2a**	4	 **5da**	78
5	 **4e**	**2a**	4	 **5ea**	92
6	**4a**	 **2c**	2	 **5ac**	88
7	**4b**	 **2d**	4	 **5bd**	91
8	**4e**	 **2k**	3	 **5ek**	90
9	**4e**	 **2f**	8	 **5ef**	83

[a] Reaction conditions: **4** (1 mmol), **2** (1 mmol), NaN_3 (1.1 mmol), CuNPs/C (0.5 mol%) in H_2O at 70 °C. [b] Isolated yield.

Table 4 Three-component 1,3-dipolar azide–alkyne cycloaddition catalysed by CuNPs/C using aromatic amines as the azide precursors[a]



Entry	Aromatic amine	Alkyne	Time(h)	Triazole	Yield(%)[b]
1	 **6a**	 **2a**	3	 **5aa**	90
2	 **6b**	**2a**	3	 **5ba**	95
3	 **6f**	**2a**	7	 **5fa**	64
4	 **6g**	**2a**	7	 **5ga**	80
5	 **6h**	**2a**	4	 **5ha**	78
6	 **6i**	**2a**	3	 **5ia**	90
7	 **6j**	**2a**	3	 **5ja**	66
8	 **6k**	**2a**	8	 **5ka**	70
9	**6a**	 **2h**	3	 **5ah**	93
10	**6a**	 **2k**	3	 **5ak**	89

[a] Reaction conditions: **6** (1 mmol), **2** (1 mmol), NaN_3 (1.1 mmol), *t*-BuONO (1.6 mmol), CuNPs/C (0.5 mol%) in H_2O at 70 °C. [b] Isolated yield.

the haloalkyne **1m** was directly converted, for the first time, into the bicyclic triazole **3m**, while other reported procedures involve multistep syntheses.[22]

Synthesis of 1,2,3-triazoles from diazonium salts

Generally, the synthesis of 1,2,3-triazoles through click chemistry involves pre-formed azides or, more desirably, *in situ* generated azides from organic halides. In some cases, however, the substrate availability and functionality hampers this synthesis and a functional group transformation prior to the click reaction is required. In this respect, we explored some alternative substrates to the organic halides as azide precursors which, being compatible with the standard reaction conditions, could expand the versatility of the catalyst. We discovered that diazonium salts are potential substitutes for the less reactive aromatic halides and could be used in the three-component synthesis of 1,2,3-triazoles under the same conditions applied to the organic halides (Table 3).

In a first example, commercially available phenyldiazonium tetrafluoroborate (**4a**) and phenylacetylene (**2a**) gave 1,4-diphenyl-1,2,3-triazole (**5aa**) in 85% yield and relatively short reaction time (entry 1). Isolated yields of around 75% were achieved for diazonium salts with either electron-donating (**4b**) or electron-withdrawing (**4c**, **4d**) substituents at the *para* position (entries 2–4). The reaction with commercial 4-nitrophenyldiazonium tetrafluoroborate (**4e**) led to the expected triazole **5ea** in high yield and the same reaction time as for the substrates **4b**–**4d** (entry 5). The process proved to be less efficient for alkyl-substituted alkynes, with **4a** mainly leading to azobenzene. In contrast, other alkynes with electronically different substituents, such as 4-methoxyphenylacetylene (**2c**), 2-ethynylpyridine (**2d**), 4-trifluoromethylphenylacetylene (**2k**) or trimethylsilylacetylene (**2f**), readily gave the products derived from the diazonium salts **4a**, **4b**, and **4e** (entries 6–9).

Synthesis of 1,2,3-triazoles from aromatic amines

Due to the successful use of diazonium salts in the three-component dipolar cycloaddition, we went one step ahead and implemented a protocol to use anilines as aromatic azide precursors. Among the different methods of synthesis of aromatic azides from anilines, that recently developed by Moses *et al.* is worthy of note.[23] In this article, anilines were reacted with *t*-BuONO and $TMSN_3$ in CH_3CN, with the resulting azides being further subjected to the click reaction in one pot.[23a] The rate of formation of the triazoles was significantly enhanced by using microwave radiation.[23b] The whole process was, however, sequential and, therefore, the course of the azide formation needed monitoring before the cycloaddition. We were delighted to find out that the direct conversion of anilines into 1,2,3-triazoles could be attained with *t*-BuONO and NaN_3 in water under the catalysis of CuNPs/C. This four-component reaction is favourable since cheaper sodium azide is used, it is performed in water, and no monitoring of intermediates is needed.

A variety of electronically different anilines was studied in the reaction with phenylacetylene (**2a**) (Table 4). The triazoles derived from electronically neutral aniline (**6a**) and electronically rich 4-methoxyaniline (**6b**) were obtained in high yields after 3 h (entries 1 and 2). The *meta*- and *para*-chloroanilines (**6g** and **6h**) behaved better than the more sterically demanding *ortho*-chloroaniline (**6f**) (entries 3–5). A lower yield was recorded for 4-(trifluoromethyl)aniline **6j**, with an I(−) inductive effect group, in comparison with 4-methylaniline (**6i**), with an I(+) inductive effect group (entries 6 and 7). Naphthyl-1-amine (**6k**) reacted somewhat more sluggishly giving rise to the expected triazole in 70% isolated yield (entry 8). The methodology was also applicable to the alkyl- and cycloalkyl-substituted alkynes **2h** and **2k**, which when combined with aniline produced **5ah** and **5ak**, respectively, in high yields and relatively quickly (entries 9 and 10).

Stability and recycling of the catalyst

The catalyst was handled in air and all the experiments were carried out without air exclusion; these are advantages that make the process operationally simple. The reaction of benzyl bromide (**1a**) and phenylacetylene (**2a**), when conducted at 0.1 M (1 mmol starting materials, 10 ml H_2O) and 0.01 M (1 mmol starting materials, 100 ml H_2O), also afforded the expected triazoles in high conversions (>99% and 80%, respectively), albeit longer reaction times were required (8 and 24 h, respectively). Furthermore, in most cases the progress of the reaction could be followed visually. The original triphasic reaction was composed of a bottom aqueous phase and a top oily layer, with the latter containing both the catalyst and the starting materials. When the reaction ended, one solid piece at the surface of a transparent and colourless solution was observed, where the triazole was in the core of the solid covered by the catalyst. The black solid was nearly spherical or with a shape which resembled that of a virus or a naval mine (Fig. 6). This shape was the result of the intermolecular forces operating between two hydrophobic components in an aqueous medium. It is worthwhile mentioning that, despite the small amount of catalyst utilised, it could be easily recovered by filtration (after treating with ethyl acetate) and reused, leading to triazole **3aa** in excellent yields along five consecutive cycles (Fig. 7). No detectable leaching of copper was observed after the fifth cycle by ICP-MS.

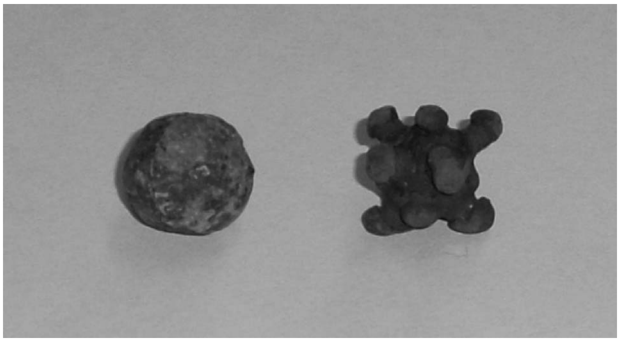


Fig. 6 Images of triazole products covered with the catalyst at the end of the reaction. Approximate size: 8 mm (left), 10 mm (right).

Nature of the catalysis

Copper is an essential nutrient needed to prevent anemia and keep the skeletal, reproductive, and nervous systems healthy. The U.S. National Research Council currently recommends that adults receive 1.5–3.0 mg of copper daily to prevent deficiencies. A

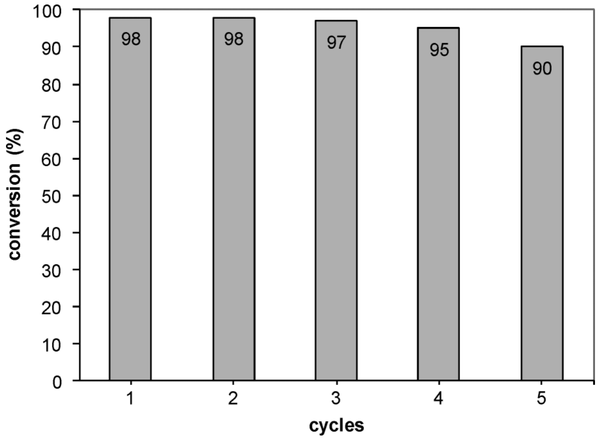


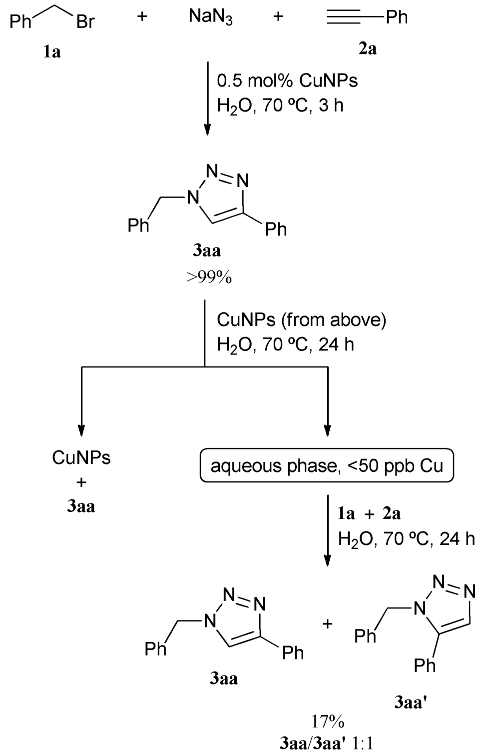
Fig. 7 Recycling of the CuNPs/C in the synthesis of the triazole **3aa**.

study on the response of healthy adults to varying concentrations of copper in drinking water supported the World Health Organization's (WHO) guideline of 2.0 mg L^{-1} as a safe limit.[24] Accumulation of copper in different organs due to a metabolism disorder (Wilson's disease) leads to liver cirrhosis, neurological disturbances and to a complexity of different symptoms.[25] It is also known that an increase in the levels of Cu(I)/Cu(II) in the brain can increase the likelihood of reactive oxygen species being generated inappropriately, leading to the oxidative stress that is observed in neurodegenerative diseases.[26]

According to the above antecedents, to reduce the amounts of copper in solution for click chemistry should be a priority, particularly for biological applications. In this sense, it is important to unveil the nature of the catalysis, with heterogeneous catalysis by supported metals being advantageous over the homogeneous counterpart.[27] For this purpose, benzyl bromide (**1a**) and phenylacetylene (**2a**) were reacted up to a >99% conversion (<3 h) (Scheme 1). Then, the resulting mixture containing the triazole **3aa** was subjected to additional heating, until a total time of 24 h, in order to force any possible copper leaching. The catalyst and the triazole were removed by filtration, the aqueous phase was extracted with ethyl acetate, followed by the addition of fresh **1a** and **2a** to the resulting aqueous phase. The new mixture was allowed to react at 70 °C for 24 h, affording a *ca.* 1 : 1 mixture of the corresponding regioisomeric triazoles in 17% conversion. This result evidenced that the 1,3-dipolar cycloaddition proceeded in a non-catalysed manner under thermal conditions. In fact, this assertion could be corroborated by ICP-MS analyses of the resulting aqueous phase which gave <50 ppb of copper. All these experiments are in agreement with a process of heterogeneous nature.[28]

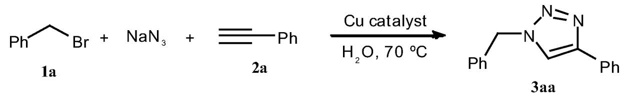
Comparison with other catalysts

In principle, any laboratory-made catalyst should be more efficient than commercially available catalysts used for the same purpose. Otherwise, it is difficult to economically justify the time, materials and human resources employed during its preparation. Taking into account this premise, we undertook a comparative study on the reactivity of the CuNPs/C with the commercially available Cu, Cu_2O, and CuO heterogeneous catalysts. The standard conditions were applied to the reaction of benzyl bromide (**1a**) and phenylacetylene (**2a**) at both 10 and 1 mol% catalyst loadings. Copper metal gave the expected triazole **3aa** in about 50% yield, which remained steady after prolonged heating (Table 5, entry 1). Notably, a maximum 90% yield was observed for 10 mol% Cu_2O catalyst with a similar trend seen for 10 mol% CuO (entries 2 and 3). Some side products (10%) were, however, detected and its recycling furnished triazole **3aa**, in only 20% conversion after 24 h, as a *ca.* 4 : 1 mixture of regioisomers. The conversions dropped when reducing the catalyst loading for both Cu_2O and CuO (entries 4 and 5). Therefore, the nanosized character seems to be decisive in the high performance of our catalyst (entry 6). Very recently, it has been disclosed that defect sites on CuNPs can induce intense dissociation of water to form atomic oxygen,



Scheme 1 Experiments on the nature of the catalysis.

Table 5 Three-component 1,3-dipolar azide–alkyne cycloaddition catalysed by different copper catalysts[a]



Entry	Catalyst	mol (%)	Yield(%)(3 h)[b]	Yield(%)(24 h)[b]
1	Cu	10	52	52
2	Cu_2O	10	90[c]	90[c,d]
3	CuO	10	69	88
4	Cu_2O	1	46	75
5	CuO	1	53	78
6	CuNPs/C	0.5	>99[e]	—

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), NaN_3 (1.1 mmol), catalyst in H_2O at 70 °C. [b] GLC yield. [c] 10% side products were obtained. [d] In a second cycle, the product was obtained in 20% conversion after 24 h as a *ca.* 4 : 1 mixture of regioisomers. [e] Reutilised in five cycles with near quantitative yield of triazole **3aa**.

which might somehow participate in the redox mechanism of the reaction.[29] This fact, together with the large surface-to-volume ratio of the nanocatalyst and its distribution on the support, could account for the behaviour of the CuNPs/C when compared with the commercial bulk catalysts.

Conclusions

We have developed a catalyst consisting of copper nanoparticles supported on activated carbon for the synthesis of 1,4-disubstituted-1,2,3-triazoles through a multicomponent alkyne–azide 1,3-dipolar cycloaddition in water. The catalyst was fully characterised and the copper nanoparticles were determined to mostly be in the oxidised forms of Cu_2O and CuO. A wide range of triazoles has been synthesised from organic chlorides, bromides and iodides, either activated or non-activated, and different terminal alkynes. Two new protocols were devised for the click reaction involving diazonium salts or anilines as aryl azide precursors, with the latter being a tetra-component process. The catalytic system and methodologies described herein follow the majority of the principles[1] of the Green Chemistry framework and the rigorous criteria of click chemistry,[2] namely: (a) waste is minimised to the corresponding sodium salt by-products since the azides are generated *in situ*; (b) the atom economy is high as three or four materials are incorporated into the final product; (c) the handling of potentially hazardous organic azides is prevented; (d) all reactions are performed in neat water or ethanol–water; (e) the catalyst preparation is conducted at ambient temperature and, though heating is necessary in the triazole synthesis, most of the reaction times are relatively short (≤ 5 h); (f) derivatisation is also minimised; (g) the catalyst is used at low copper loading and can be reused; (h) the monitoring of the process can be done visually; (i) all the experiments presented in this article are safe and no explosion occurred by *in situ* generation of the azides; (j) the methodology is modular (applicable to different types of starting materials in the same medium), wide in scope, and high yielding; (k) all starting materials, reagents, and the catalyst are commercially or readily available; (l) the reaction conditions are simple and the process is insensitive to oxygen and water; (m) the process is regioselective, providing exclusively the 1,4-disubstituted-1,2,3-triazoles; (n) the product is easily isolated and does not require purification. In addition, the catalyst is superior to other commercial heterogeneous copper catalysts and seemingly operates under heterogeneous conditions.

Experimental

Typical procedure for the preparation of CuNPs/C

Anhydrous copper(II) chloride (135 mg, 1 mmol) was added to a suspension of lithium (14 mg, 2 mmol) and 4,4′-di-*tert*-butylbiphenyl (DTBB, 27 mg, 0.1 mmol) in THF (2 mL) at room temperature under an argon atmosphere. The reaction mixture, which was initially dark blue, rapidly changed to black, indicating that the suspension of CuNPs was formed. This suspension was diluted with THF (18 mL) followed by the addition of the activated carbon (1.28 g). The resulting mixture was stirred for 1 h at room temperature, filtered, and the solid successively washed with water (20 mL), THF (20 mL) and dried under vacuum.

General procedure for the CuNPs/C-catalysed click reaction in water using organic halides or diazonium salts as the azide precursors

NaN_3 (72 mg, 1.1 mmol), the organic halide or diazonium salt (1 mmol), and the alkyne (1 mmol) were added to a suspension of CuNPs/C (20 mg, 0.5 mol% Cu) in H_2O (2 mL). The reaction mixture was warmed to 70 °C and monitored by TLC and/or GLC until total conversion of the starting materials. Water (30 mL) was added to the resulting mixture, followed by extraction with EtOAc (3×10 mL). The collected organic phases were dried with anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to give the corresponding triazoles **3** or **5**, which did not require any further purification.

General procedure for the CuNPs/C-catalysed click reaction in water using aromatic amines as the azide precursors

NaN_3 (72 mg, 1.1 mmol), aromatic amine (1.0 mmol.), *t*-BuONO (190 μL, 1.6 mmol) and the alkyne (1.0 mmol) were added to a suspension of CuNPs/C (20 mg, 0.5 mol% Cu) in H_2O (2 mL). The reaction mixture was warmed to 70 °C and monitored by TLC until total conversion of the starting materials. Water (30 mL) was added to the resulting mixture, followed by extraction with EtOAc (3×10 mL). The collected organic phases were dried with anhydrous $MgSO_4$, and the solvent was removed *in vacuo* to give the corresponding triazoles **5**, which did not require any further purification.

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