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Carbon nanotube-copper ferrite-catalyzed aqueous 1,3-dipolar cycloaddition of *in situ*-generated organic azides with alkynes

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A novel nanohybrid catalyst was developped by assembling copper ferrite nanoparticles on carbon nanotubes. The supramolecular catalyst was applied to the one pot azidation/1,3-dipolar cycloaddition of various substrates, at room temperature, and in an aqueous medium. The nanohybrid could also be recycled and reused by means of magnetic recovery.

The Huisgen 1,3-dipolar cycloaddition,[1a,b] involving alkyne and azide derivatives, is a widely employed click reaction in research fields as diverse as chemical biology or material chemistry.[1c-e] The reaction classically requires a cuprous salt catalyst to trigger smooth and regioselective transformations.[2] However, copper salts residues are rather toxic and difficult to eliminate from reaction mixtures, thus prompting the search for copper-free alternatives. This led to recent development by Bertozzi and co-workers of strained cyclooctynes[3] which are reactive in the absence of any copper catalyst but are somehow complex to synthesize and lack of chemoselectivity. These shortcomings associated to the 1,3-dipolar cycloaddition of organic azides with alkynes could likely be overcome by heterogenization of the active catalyst as, besides easy removal from the reaction mixture, supporting the metal should also allow for its recycling and reuse, thus contributing to the sustainability and greening of the overall process. As regards the latter point, the replacement of conventional organic solvents with water could also constitute a major improvement. However, the use of water is not always suited due to the insolubility of the reagents which can be circumvented, in some cases, by using surfactant micelles[4] that are acting as dispersant and nano-reactors where the reagents are concentrated.

With these features in mind, we report here, the design and synthesis of a novel heterogeneous catalyst that can efficiently promote the aqueous one-pot condensation/cycloaddition of *in situ* generated organic azides with terminal alkynes. This carbon nanotube-based[5] assembly also incorporates a hemi-micellar domain for concentration of the reagents at the vicinity of the active catalytic copper species.

The supramolecular catalyst was prepared according to a strategy inspired by our previous work on metal nanoparticles (NPs) supported on carbon nanotubes (CNTs).[6-8] The process relies on a layer-by-layer approach using the self-assembly properties of some amphiphiles to provide highly functional nanotubes. In short, multi-walled carbon nanotubes were sonicated in an aqueous solution of amphiphilic units made of a lipophilic diacetylene (DA) chain and a nitrilotriacetate polar head (NTA). The resulting CNT suspension is the upshot of the self-assembly of the amphiphiles at the surface of the nanotubes, giving rise to hemi-micellar structures also referred to as nanorings (Figure 1).

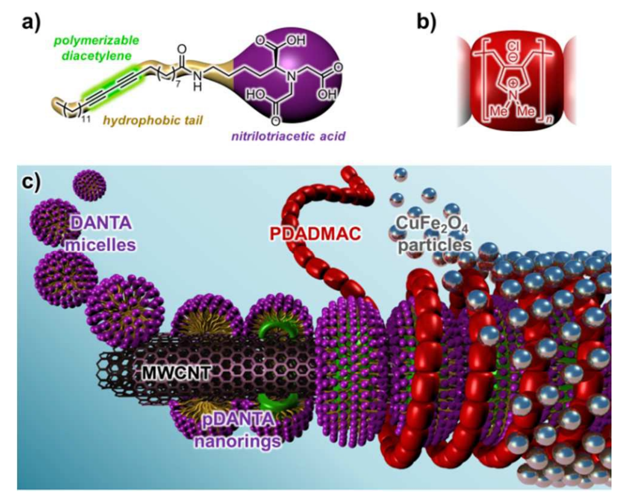

Figure 1. a) Structure of DANTA; b) Structure of PDADMAC; c) Schematic representation of the assembly process.

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Electronic Supplementary Information (ESI) available: assembly procedure of the $CuFe_2O_4$CNT nanohybrid and copies of NMR spectra. See DOI: 10.1039/x0xx00000x

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These structures arise from hydrophobic interactions between the lipidic chains of the amphiphiles and the graphitic surface of the CNTs, while the polar head groups are interfacing with the aqueous environment. The nanorings are then consolidated through a photopolymerization process that involves the diacetylene motifs. In fact, UV irradiation at 254 nm triggers a topochemical 1,4-addition process allowing covalent attachment of neighboring diacetylene groups. The polymerized nanorings located on the CNTs build a continuous domain containing a hydrophobic region that is likely to accommodate organic molecules and behave as nano-reactor. This domain also displays high density of negative charges at its surface. The presence of these charges were thus exploited to electrostatically adsorb a second cationic layer made of poly(diallyldimethyl ammonium chloride) (PDADMAC). The cationic polymer creates a tridimensional network that is adapted to the stabilization and robust anchoring of metal nanoparticles. Hence, a colloid suspension of preformed copper ferrite nanoparticles[9] was added to the doubly-coated carbon nanotubes. This led to dense and homogeneous covering of CNT surface with copper nanoparticles embedded in the polymer layer, as evidenced by transmission electron microscopy (TEM, Figure 2a). The nanoparticles were shown to be of spherical shape with an average diameter of 4.8 nm (see size distribution, Figure 2b). The hybrid catalyst was kept in an aqueous suspension and used as such for further experiments. The copper content of the $CuFe_2O_4$CNT suspension was measured by inductively coupled plasma mass spectroscopy (ICP-MS) which indicated a [Cu] = 0.8 mM. The hybrid was further characterized by X-ray photoelectron spectroscopy (XPS) which confirmed the binary nature of the metal particles (see the Cu2p and Fe2p regions in Figure 2c and 2d, respectively).

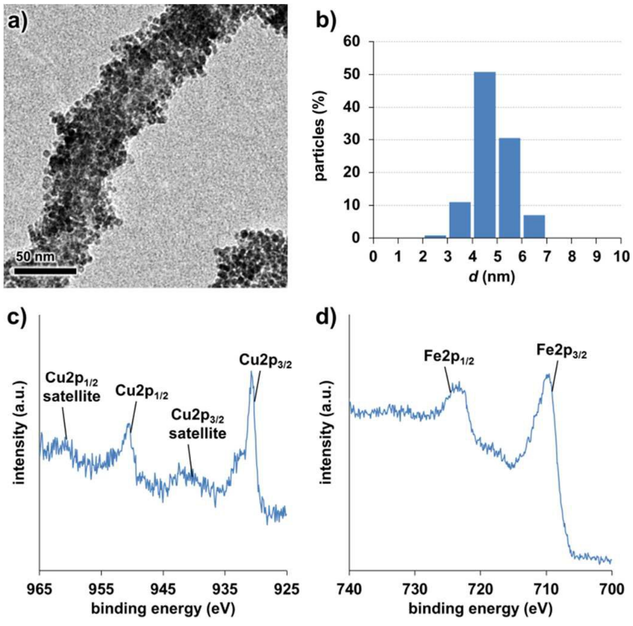

Figure 2. a) TEM image of the final $CuFe_2O_4$CNT hybrid; b) size distribution of the $CuFe_2O_4$ nanoparticles (obtained from the measurement of 250 particles); c) Cu2p region and d) Fe2p region of the XPS spectra of the nanohybrid.

Table 2. Scope of the $CuFe_2O_4$CNT-catalyzed Huisgen reaction of alkynes with bromides.[a]

entry	bromide **1**	alkyne **2**	yield (%)[b]
1	**1a**	**2a**	90
2	**1a**	**2b**	92
3	**1a**	**2c**	82
4	**1a**	**2d**	87
5	**1a**	**2e**	84
6	**1a**	**2f**	65
7	**1b**	**2a**	88
8	**1c**	**2a**	78
9	**1c**	**2d**	84
10	**1d**	**2a**	81
11	**1e**	**2a**	traces

[a] **1** (0.1 mmol), **2** (0.1 mmol), NaN_3 (0.11 mmol), $CuFe_2O_4$CNT (0.4 mol %), H_2O/Ethanol 4:1 (1 mL), room temp., 24 h. [b] Isolated yields.

The newly assembled catalyst was then tested for the promotion of the Huisgen 1,3-cycloaddition through the reaction of terminal alkynes with *in situ* generated organic azide. This one pot sequence (R-X ⟶ $R\text{-}N_3$ ⟶ “click”) offers the advantage of a straightforward process without the need of pre-synthesizing the azido partner, as opposed to most of nanoparticle-catalyzed click reactions.[10] The reaction was carried out at room temperature, under air, using 0.4 mol% of the catalyst and in water/EtOH 4:1.[‡] The catalytic system proved efficient on a variety of substrates (Table 1) and was active on different terminal alkynes such as phenylacetylene derivatives (plain phenylacetylene **2a** – Entry 1, 4-methoxyphenylacetylene **2b** – Entry 2, 3-chlorophenylacetylene **2d** – Entry 4, 4-trifluoromethylphenylacetylene **2e** – Entry 5, phenethylacetylene **2f** – Entry 6), and propargyl alcohol **2c**

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(Entry 3). On the other hand, different brominated counterparts were also successfully employed in the transformation, e.g. fluorinated benzyl bromide derivative **1b** (Entry 7), ethyl bromoacetate **1c** (Entries 8–9), and allyl bromide **1d** (Entry 10), giving rise to the expected triazoles in good to excellent yields (Entries 1–10). However, 1-bromooctane **1e** displayed very poor reactivity under our reaction conditions and only afforded trace amounts of the anticipated cycloaddition product (Entry 11). This lack of reactivity of the aliphatic halide was attributed to the initial nucleophilic displacement of the bromine atom by the azido group which is here the rate limiting step. Indeed, a simple control experiment conducted with authentic 1-azidooctane, 0.4 mol% of $CuFe_2O_4$CNT, and phenylacetylene **2a** led to the clean formation of the expected triazole product **3ea**. It is to be noted that, for all the above examples, the $CuFe_2O_4$CNT-catalyzed [3+2] cycloaddition reaction proceeded in a regioselective fashion affording solely the 1,4-substituted triazole. The system also proved efficient with chlorinated substrates (Table 2). In fact, benzyl chloride **4a** afforded as well the corresponding cycloadducts (triazoles) in satisfactory to good yields upon reaction with NaN_3 and phenylacetylene **2a** (Entry 1), 4-methoxyphenylacetylene **2b** (Entry 2), or 4-trifluoromethylphenylacetylene **2e** (Entry 3). The same comment applies to allyl chloride **4d** which led to triazole **3da** in 76% yield upon reaction with NaN_3 and phenylacetylene **2a** (Entry 4).

One of the key advantages provided by our one-pot nanohybrid-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) is the mildness of the operating conditions. In fact, while other analogous systems require elevated temperatures,[11] high catalytic loadings,[12] pure organic solvents,[13] and/or oxygen free conditions[14] to proceed satisfactorily, our CNT-based nanohybrid operates at room temperature with as little as 0.4 mol% Cu and in a binary aqueous phase.

Table 2. Scope of the $CuFe_2O_4$CNT-catalyzed Huisgen reaction of alkynes with chlorides.[a]

entry	chloride **4**	alkyne **2**	yield (%)[b]
1	**4a**	**2a**	77
2	**4a**	**2b**	57
3	**4a**	**2e**	72
4	**4d**	**2a**	76

[a] **4** (0.1 mmol), **2** (0.1 mmol), NaN_3 (0.11 mmol), $CuFe_2O_4$CNT (0.4 mol %), H_2O/Ethanol 4:1 (1 mL), room temp., 24 h. [b] Isolated yields.

Figure 3. Left: nanohybrid catalyst suspension. Right: magnetic separation of $CuFe_2O_4$CNT (picture taken 15 seconds after the positioning of a permanent magnet).

Table 3. recyclability of the $CuFe_2O_4$CNT catalyst.[a]

entry	catalyst	time (h)	yield (%)[b]
1	fresh	24	90
2	1st reuse	24	89
	2nd reuse	24	85
3	3rd reuse	24	87

[a] **1a** (0.1 mmol), **2a** (0.1 mmol), NaN_3 (0.11 mmol), $CuFe_2O_4$CNT (0.4 mol %), H_2O/Ethanol 4:1 (1 mL), room temp., 24 h. [b] Isolated yields.

A second advantage provided by the $CuFe_2O_4$CNT nanohybrid is the combination of catalytically active copper with magnetically active iron. The latter key feature was exploited for easy magnetic recovery and recycling of the catalyst. In fact, after each cycle, the nanohybrid was separated magnetically from the mixture by use of a permanent magnet that was placed on the walls of the reactor (Figure 3). The product was collected using a pipette, the catalyst rinsed with EtOH and redispersed in liquid media before fresh reagents (benzyl bromide, phenylacetylene and NaN_3) were introduced to the reactor. This process was repeated three times with no significant decrease of the catalytic activity as similar yields of triazole were obtained in each case after 24 h (Table 3). In addition, the mother liquors of each run were analysed by ICP-MS which showed negligible leaching of copper species during the process (< 2 ppm). This recycling experiment suggests no alteration of the active metals and strong interaction with the CNT-based multi-layer assembly.

In conclusion, an efficient and straightforward method for the 1,3-dipolar cycloaddition of *in situ* generated organic azides with alkynes was developed. The process is catalyzed by a newly developed heterogeneous copper catalyst supported on carbon nanotubes which operates in an aqueous solvent system, with low catalytic loadings (0.4 mol%), at room temperature, and under air. The assembly offers three key advantages over known heterogeneous catalysts, *i.e.* i) the presence of a lipophilic domain behaving as a nano-reactor combined with ii) the close vicinity of the active catalytic

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species, and iii) the ease of recycling by simple magnetic recovery of the bimetallic nanohybrid.

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Conflicts of interest

There are no conflicts of interest to declare.

Notes and references

‡ First attempts were carried out in pure water but only led to moderate conversion yields.

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