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Fe/ppm Cu nanoparticles as a recyclable catalyst for click reactions in water at room temperature†

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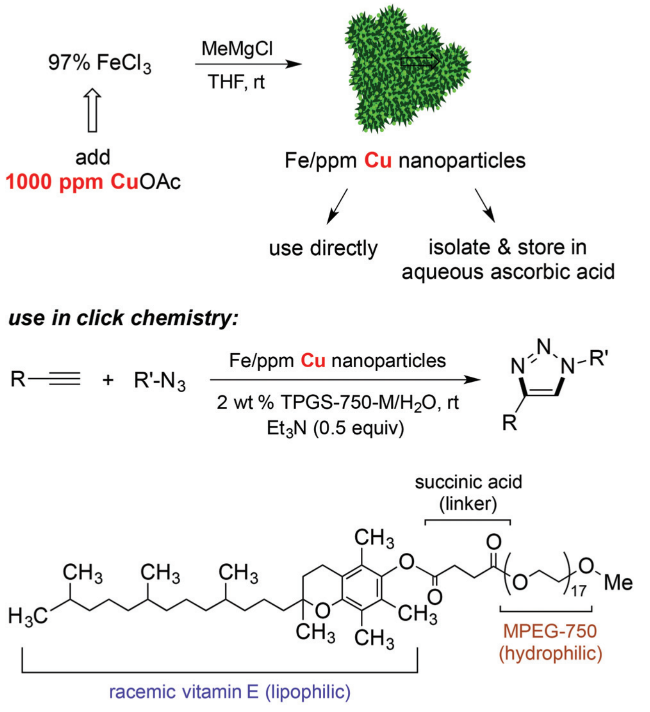
New iron-based nanoparticles doped with ppm levels of CuOAc are capable of catalyzing cycloadditions between alkynes and azides to afford triazole-containing products. These reactions take place in water at ambient temperatures, enabled by the presence of nanomicelles that function as a delivery mechanism. The NPs can be easily recycled within the same reaction vessel. Low levels of residual copper are found in the product.

Copper-based nanoparticles (NPs) continue to be the subject of several recent reports.[1] Much of the driving force behind this popular area of research lies in the base (*i.e.*, inexpensive) metal status of copper for use in catalysis, as well as the accent on heterogeneous reagents that enable facile product isolation and catalyst recycling. Moreover, their application to click chemistry is of value in multiple arenas (*e.g.*, drug discovery,[2] combinatorial chemistry,[3] chemical biology,[4] material science,[5] *etc.*). From the green chemistry perspective, several studies describe reagents that reduce their metal content to ppm levels of copper embedded within NPs.[6–13] Some can be utilized in a purely aqueous setting,[6,13] avoiding in large measure organic solvents and, thereby, minimizing organic waste. While these approaches are meritorious in this regard, those that result in cycloadditions to triazoles at ambient temperatures[7,10] typically require some degree of water solubilization of the educts, and therefore, face obvious limitations. Others involve procedures for reagent preparation that can be lengthy, and/or rely on starting materials that can be costly or esoteric, and the procedures for catalyst recycling can involve several steps.[7,9] Typically, these reports focus heavily on analyses of these newly fashioned NPs (*e.g.*, by SEM, TEM, EDX, *etc.*), and oftentimes are concerned with the extent of copper leaching from the solid support. Few, however, address the key question as to how much residual copper is to be found in the product.[12] In this Letter, we present new NPs that contain ppm levels of copper[13] that are not only trivial to prepare, but can be either used directly in water at room temperature, or can be isolated and stored in an aqueous mixture at room temperature for future use.

Previously, we disclosed new NPs that feature an iron-based platform containing ppm levels of palladium which catalyze Suzuki–Miyaura cross-couplings in water between rt and 45 °C.[14] This technology is enabled by the presence of aqueous nanomicelles derived from TPGS-750-M[15] (**1**, Scheme 1), where the PEG component serves as the delivery mechanism bringing the substrates, housed within, to the metal NP catalyst. This "nano-to-



1; TPGS-750-M

Scheme 1 Preparation of Fe/ppm Cu NPs and their use in click chemistry.

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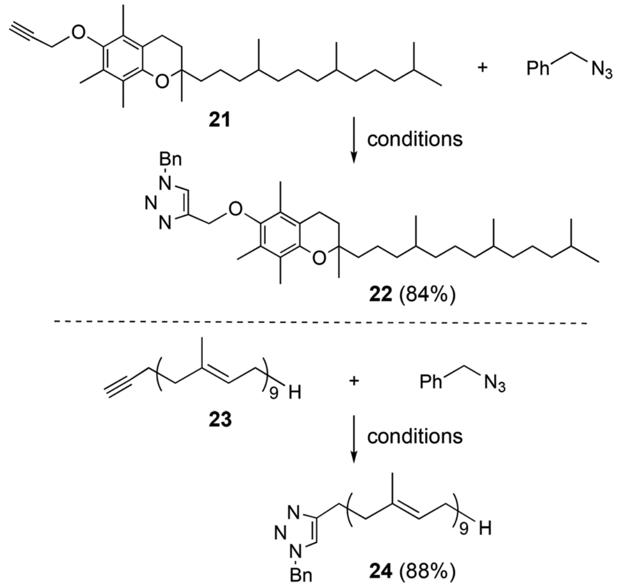
nano" phenomenon[14,16] is non-operative in organic solvents, and is presumably responsible for the mild conditions under which these heterogeneous couplings take place. Replacing the Pd doped into these NPs with copper is especially straightforward; thus, treatment of $FeCl_3$, together with CuOAc (1000 ppm, or 0.1 mol%), in THF with MeMgCl (also in THF; 2.0 equiv.) at room temperature (22 °C) leads to active Fe/ppm Cu NPs. Removal of the THF under vacuum affords the catalyst ready for use in click chemistry. Introduction of an aqueous solution containing two weight percent of **1**, followed by the alkyne, an azide (1.2 equiv.), and Et_3N (0.5 equiv.) leads (with vigorous stirring at room temperature) to the corresponding triazole.

A variety of substrate combinations could be used to arrive at 1,4-disubstituted triazoles. As illustrated in Table 1, alkyl and aryl alkynes readily participated, while benzylic azides serve as excellent reaction partners. Acetylenic derivatives bearing alkyl residues containing free and protected alcohols, as well as a terminal chloride, led to products in good isolated yields, as did a TIPS-protected educt leading to product 7. Aryl alkynes, *e.g.*, those substituted with either electron-withdrawing F or CF_3 moieties, or an electron-donating Me_2N group, were not problematic. Importantly, ICP MS analysis of triazole **2** revealed that <1 ppm of residual copper could be detected, in line with the reduced levels observed previously for both Pd (<10 ppm) and Ni (≤1 ppm).

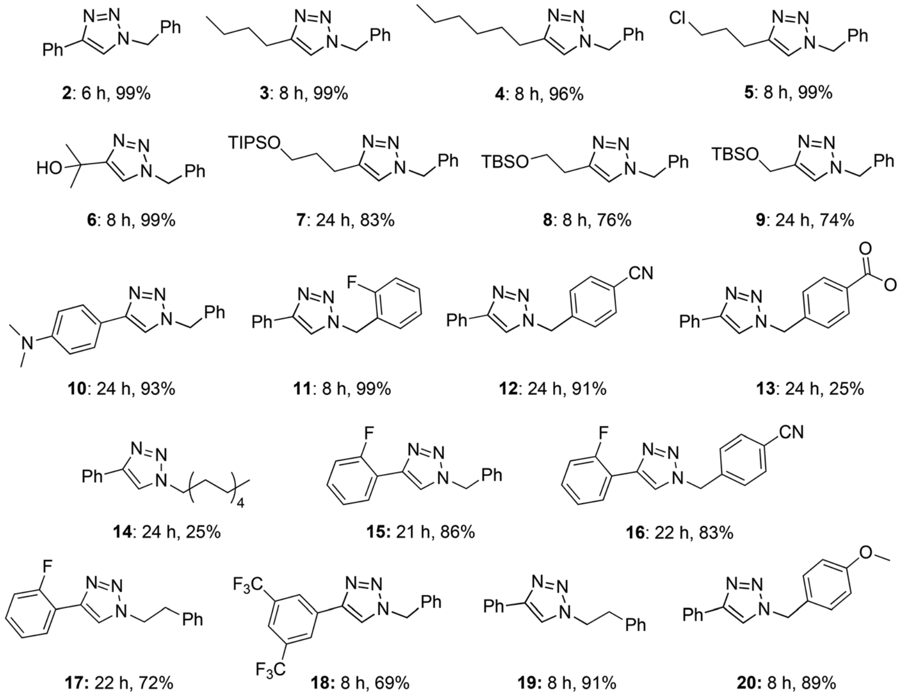
Substrates featuring highly water-insoluble fragments, such as those represented by alkyne **21** derived from vitamin E, and the 48-carbon alkyne **23** prepared from solanesol,[17] were smoothly converted to their corresponding products **22** and **24**, respectively, under these aqueous conditions (Scheme 2). In the absence of TPGS-750-M *en route* to **2** (*i.e.*, "on water"),[18] there was no reaction under otherwise identical conditions.

As an alternative to *in situ* formation and use of these Fe/ppm Cu NPs, removal of the THF *in vacuo* after Grignard addition and trituration with dry pentanes followed by further



Scheme 2 Conditions: Fe/ppm Cu NPs, Et_3N (0.5 equiv.), 2 wt% TPGS-750-M/H_2O, rt.

Table 1 Representative substrates for the Fe/Cu NP-catalyzed click reaction. Conditions: Fe/Cu NPs (1000 ppm Cu), Et_3N (0.5 equiv.), 2 wt% TPGS-750-M/H_2O, rt

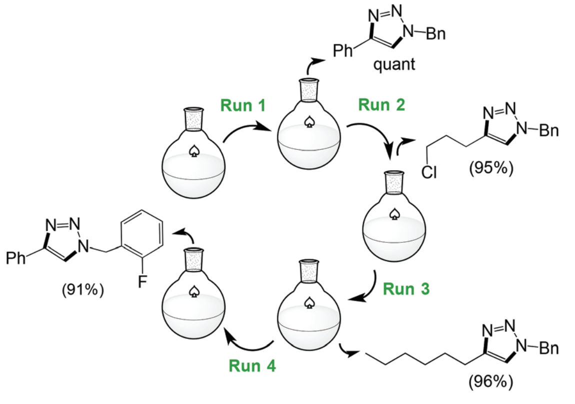


2: 6 h, 99%
3: 8 h, 99%
4: 8 h, 96%
5: 8 h, 99%
6: 8 h, 99%
7: 24 h, 83%
8: 8 h, 76%
9: 24 h, 74%
10: 24 h, 93%
11: 8 h, 99%
12: 24 h, 91%
13: 24 h, 25%
14: 24 h, 25%
15: 21 h, 86%
16: 22 h, 83%
17: 22 h, 72%
18: 8 h, 69%
19: 8 h, 91%
20: 8 h, 89%

drying under high vacuum afforded light brown-colored NPs. This freshly prepared catalyst, stored carefully under argon, could be used with equal effectiveness over a 2–3 day period. However, after a week, it loses much of its activity due to gradual oxidation of copper(I). To maintain these NPs in their active state, storage is best achieved in an aqueous medium containing ascorbic acid[19] (0.10 equiv. *vs.* educt). Click reactions using this catalyst over weeks showed no difference in reaction rates or yields compared to those obtained with freshly made material (see Table 1).

Nano-to-nano technology[14,16] presents opportunities for in-flask processing, and subsequent recycling of the aqueous reaction mixture containing the surfactant and the Fe/ppm Cu NP catalyst. Once a cycloaddition is complete, extraction with minimal amounts of EtOAc ultimately affords the desired cycloadduct. To the remaining mixture, in the presence of added 0.1 equiv. vitamin C, is then introduced an alkyne/azide pair being either the same or different in nature, leading to another click reaction. As shown in Scheme 3, this initial process was repeated three additional times, with each cycle leading to (in this case) a different triazole. The efficiency of cycloaddition remained high throughout. An *E* Factor based on solvent usage, as originated by Sheldon[20] and studied extensively for this micellar technology,[21] was determined to be 4.1, which is *ca.* an order of magnitude below values oftentimes associated with processes in the fine chemicals area.[22]

Analyses by cryo-TEM of isolated Fe/ppm Cu NPs placed in an aqueous medium containing nanomicelles derived from TPGS-750-M provided the appearance, the sizes, and the nano-to-nano state in which this catalyst exists. Fig. 1A confirms the rod-like shape, with sizes that are highly variable (*ca.* 25 nm on average), along with the anticipated association of spherical nanomicelles with the metal NPs. The identical analysis on used NPs (Fig. 1B) showed NPs that had become larger and more fibril-like, while their aggregation with surfactant micelles remains, along with their equivalent activity. An EDX experiment was also run (Fig. 2), and the results, again, are akin to those seen previously with Fe/ppm Pd NPs,[14] where the presence of the ppm metal, copper in this case, was undetectable. Most of the material is composed of Mg and Cl from the



Scheme 3 Recycling of Fe/ppm Cu NPs used in aq. TPGS-750-M.

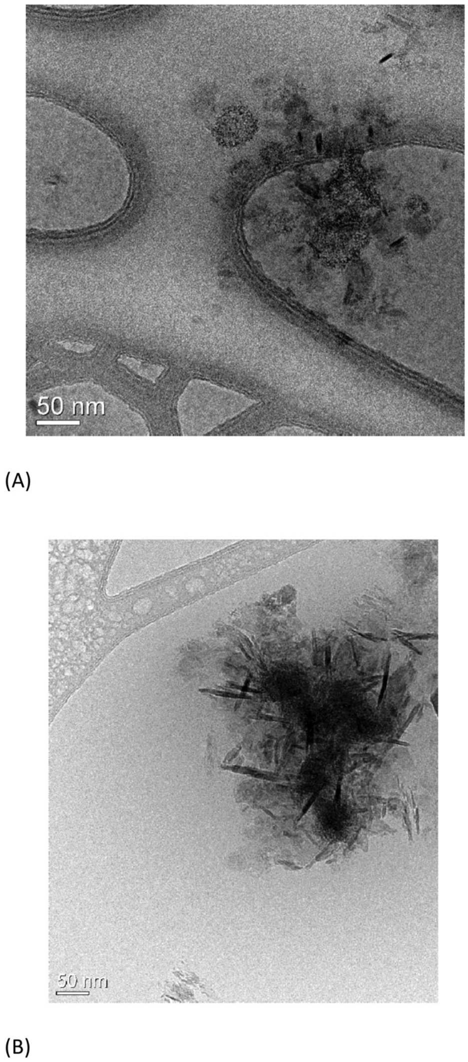


Fig. 1 cryo-TEM data on Fe/ppm Cu NPs in TPGS-750-M/H_2O. (A) Fresh Fe/ppm Cu NPs in 2 wt% TPGS-750-M/H_2O. (B) Used Fe/ppm Cu NPs in 2 wt% TPGS-750-M/H_2O.

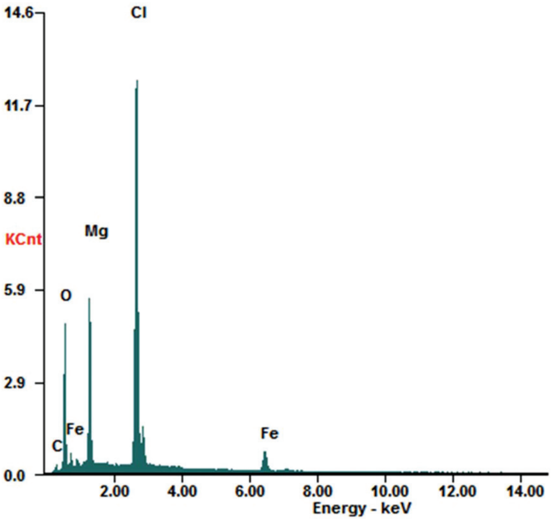


Fig. 2 EDX analysis of Fe/ppm Cu NPs.

Grignard, along with the THF used as solvent; iron constitutes only *ca.* 3% of these NPs.

Conclusion

In summary, an experimentally simple procedure has been developed leading to the formation of nanoparticles containing ppm levels of active Cu(I) that effect click reactions between azides and alkynes in water at ambient temperatures. These [3 + 2]-cycloadditions are enabled by the presence of a surfactant, TPGS-750-M, engineered to maximize reaction efficiency. All ingredients within these aqueous mixtures are recyclable within the same reaction vessel: the water, surfactant, and the catalyst, while the product is easily extracted with minimal amounts of a single organic solvent. Only traces of residual copper are to be expected in the triazole products formed in high yields. Further developments of new catalysts based on Fe/ppm metal NPs containing other base metals (*e.g.*, Ni), as well as precious metals (*e.g.*, Rh and Ir), will be reported in due course.

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