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COMMUNICATION

Magnetic copper–iron nanoparticles as simple heterogeneous catalysts for the azide–alkyne click reaction in water†‡
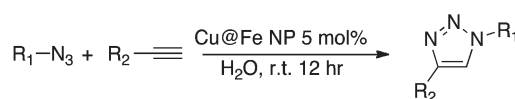
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The development of a novel bimetallic copper–iron nanoparticle synthesis provides a recoverable heterogeneous catalyst for the azide–alkyne "click" reaction in water. The nanoparticles catalyze the production of a diverse range of triazoles, while separation and reuse proved to be easy.

The 2002 development of Cu(I)-catalysed azide–alkyne cycloaddition (AAC) continues to garner much interest today.[1,2] This prototypical "click" reaction offers chemists a highly efficient means for connecting two potentially complex building blocks under mild conditions with high tolerance to other functional groups.[3,4] This reaction has thus been extensively applied to the synthesis of macromolecules[5,6] and the functionalization of biomolecules.[7] The catalysed AAC reaction holds several advantages over the thermal version[8] including regioselectivity, increased reactivity of unactivated alkynes, and high yields even at low concentrations in aqueous media.[9]

Most AAC protocols call for a homogeneous Cu(I) source – either by direct addition of a Cu(I) salt, or *in situ* reduction of Cu(II) by sodium ascorbate.[2,9,10] In an effort to find more reusable catalysts, Cu(I) AAC catalysts have been immobilized onto polymers[11,12] or zeolite.[13] Interestingly, Cu(0) on charcoal,[14] Cu(0) nanoparticles,[15–18] or microwave irradiated Cu turnings,[19,20] as well as CuO nanostructures,[21] have also successfully demonstrated activity for this reaction.

Magnetically recoverable nanoparticles (NPs) represent an easy and environmentally benign means for catalyst recovery,[22] providing catalytic properties intermediate between homogeneous[23] and bulk heterogeneous materials.[24–26] Many schemes exist for using magnetically recoverable catalysts: anchoring homogeneous metal complexes[27–29] or organocatalysts[30] to a magnetic core, plating a catalytically active metal,[31,32] or, more simply, direct use of bare Fe(0)[33–35] or iron oxide NPs.[36,37] Among the strategies recently developed to produce novel magnetic particles, zero-valent Fe NPs (FeNPs) have been used as precursors to seed, reduce and support another metal. By this method, Pd NPs were deposited onto FeNPs and the resulting

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‡ Dedicated to Christian Bruneau, on the occasion of his 60th birthday.

$$R_1-N_3 + R_2\!\!-\!\!\equiv\!\! \xrightarrow[\text{H}_2\text{O, r.t. 12 hr}]{\text{Cu@Fe NP 5 mol\%}}$$

Scheme 1

Table 1 Performance of a series of Cu and Fe based catalysts for the AAC[a]

Entry	Catalyst (loading)	Yield
1	None	<5%
2	$CuFe_2O_4$ NP (5 mol%)	<5%
3	$CuFe_2O_4$ NP + sodium ascorbate (5 mol%)[b]	96%[b]
4	CuI (5 mol%)	99%
5	Cu@FeNP (5 mol%)	93%
6	Cu@FeNP (1 mol%)	81%
7	FeNP (5 mol%)	<5%
8	Cu@FeNP – supernatant[c]	<5%[c]

[a] Reaction conditions: 1 mmol benzyl azide, 1.2 mmol phenylacetylene, 10 mL H_2O, rt, 12 h. [b] Dissolution of nanoparticles observed. [c] Supernatant obtained by subjecting particles to catalytic conditions, removing them, and using supernatant as solvent for reaction.

hybrid NPs were proven to be active and recyclable catalysts for Suzuki coupling.[38]

Herein, we present the synthesis of an active and magnetically recyclable catalyst for the AAC in water (Scheme 1). This catalyst is very simple and produced from exposure to Cu(II) salts of reducing FeNPs seeds in a water–methanol mixture. No ligand or extra reducer is needed.
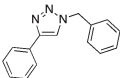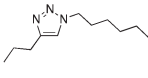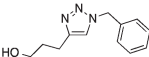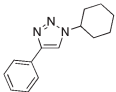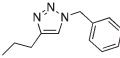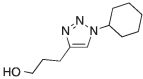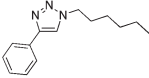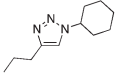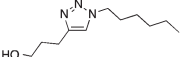
Our initial attempts to perform AAC using magnetically recoverable NPs focused on the use of Cu ferrite ($CuFe_2O_4$). In 2010, Park and coworkers demonstrated that hollow structures of CuO were active catalysts for AAC.[21] However, $CuFe_2O_4$ NPs proved inactive for this transformation (Table 1). In Cu ferrite, Cu is present as Cu(II) in the crystal lattice, while most AAC catalysts are based on Cu(I).[4,10,39] Addition of sodium ascorbate to $CuFe_2O_4$ NPs afforded the expected *in situ* reduction of Cu(II) into Cu(I),[39] and enabled catalysis in yields of 96%. This activity, however, was accompanied by the complete dissolution of the $CuFe_2O_4$ NPs – no solid material could be recovered. These observations suggest that catalysis proceeds through a homogeneous mechanism. To alleviate this limitation, we needed to develop nanocatalysts featuring heterogenized Cu(I)

Table 2 Cu@Fe NP catalyzed azide–alkyne cycloaddition[a]

Entry	Product	Yield	Entry	Product	Yield
1		93%	6		78%
2		89%	7		84%
3		90%	8		67%
4		88%	9		49%
5		91%			

[a] Reaction conditions: 1 mmol azide, 1.2 mmol alkyne, 5 mol% Cu@Fe NP, 10 mL H_2O, rt, 12 h.

species. To this end, we explored other kinds of non-functionalized, bare magnetic NPs. Following a procedure developed with Pd,[38] we plated FeNPs by galvanic reduction of $CuSO_4$. FeNPs are obtained by $NaBH_4$ reduction of $FeSO_4$,[40] before being exposed to $CuSO_4$. The X-ray photoelectron spectroscopy (XPS†) of the resultant nanoparticles indicated the presence of Cu(I) and (II). These results are consistent with the reduction of Cu(II) to Cu(I) by the core of FeNPs.[41] We did not observe evidence of Cu(0) by XPS.

These bi-metallic nanoparticles catalyzed AAC in good yields, in most cases (Table 2). Primary and secondary aliphatic as well as the traditional benzylic azides coupled with aliphatic and aromatic alkynes to generate a range of triazoles. Generally, the more electron-rich azides reacted with the highest efficiency [benzyl (entries 1, 2 and 3) > 2° alkyl (entries 4, 5 and 6) > 1° alkyl (entries 7, 8 and 9)]. Of the alkynes, phenylacetylene reacted best (entries 1, 4, and 7) while simple alkyl substituted alkynes reacted slowest (entries 3, 6 and 9). The system also proved robust toward alcohol-substituted alkynes (entries 2, 5 and 8).

Distinguishing between true heterogeneous and homogeneous catalysis – performed by a leached soluble species – is always critical when using nanoparticulate catalysts.[42] For this reason, the reaction supernatant (in which no soluble copper could be detected by an ICP-OES with a detection limit of 0.001 ppm) was tested for catalytic activity – after the nanoparticles had been magnetically removed and the solution filtered through Celite. The lack of either soluble copper in the reaction mixture or supernatant catalytic activity coupled with the reusability of the catalyst strongly suggest a heterogeneous mechanism. In further support of a heterogeneous mechanism, the nanoparticles could be recovered and reused under stringent inert conditions up to five times with no appreciable decrease in yield (Table 3). However, when the reaction was performed on the bench top in the presence of air, the yield quickly dropped in subsequent recycling runs, most probably caused by an oxidation of Cu(I) into Cu(II).

Table 3 Recycling of Cu@FeNPs catalyst for AAC[a]

Run	Glovebox yield (%)	Benchtop yield (%)
1	93	93
2	93	90
3	92	76
4	93	54
5	91	<5

[a] Reaction conditions: 1 mmol benzyl azide, 1.2 mmol phenylacetylene, 5 mol% catalyst 10 mL H_2O, rt, 12 h.

Conclusions

Herein, we present a bi-metallic copper–iron nanoparticle system for catalysis of the Huigsen 1,3-dipolar, azide–alkyne cycloaddition in water. Interestingly, in this system, the iron(0) core serves a three-fold role. First, it provides a means for magnetic recoverability. Second, it serves as a source of electrons to reduce Cu(II) into Cu(I). Third, it acts as a support for Cu(I) species to prevent their liberation as soluble ions, enabling a heterogeneous mechanism. The synthesis of the catalyst proceeds without the use of reducer, or ligand, making this reaction very atom economical. This work represents the merger of two ubiquitous green chemistry themes: magnetic nanoparticles as easily recoverable catalysts and aqueous "click chemistry". Ongoing studies in our group focus on further characterizing the catalytically active Cu@FeNPs. As this manuscript was in the publication process, another study from the group of Varma was released, describing another highly active and magnetically recoverable nanocatalyst of the AAC reaction.[43]

Experimental section

All reactants were purchased from Sigma Aldrich and used as received. Organic azides were synthesized from the

corresponding bromides *via* a previously reported procedure.[20] All reactions were carried out in an oxygen-free glovebox, except where noted, and all solvents were de-gassed for 20 minutes prior to use. FeNPs were synthesized following a procedure similar to what had been reported before.[40] In MeOH–H_2O (60 mL/140 mL), a solution of $FeSO_4$ (4 g in 200 mL H_2O) was reduced with aqueous $NaBH_4$ (0.8 g in 20 mL H_2O added with a syringe pump at 3 mL min^{-1}) at pH 6 (achieved by addition of 5 mL of 5 N NaOH). Then a $CuSO_4$ solution (8 mg of $CuSO_4$ in 1 mL of H_2O at a rate of 1 mL min^{-1}) was added dropwise to the sonicating solution of FeNPs (28 mg in 9 mL). The resulting slurry was left to sonicate for 30 minutes after addition of $CuSO_4$. These nanoparticles were then washed three times with 10 mL water before being used for catalysis. A typical reaction consisted of resuspension of the nanoparticles in 10 mL water, followed by addition of azide (1 mmol) and alkyne (1.2 mmol), and a magnetic stir bar. The reaction vessel was then capped and left to stir for 12 hours. After each reaction cycle, the nanoparticles stuck to the stir bar when stirring stopped, the solution decanted off, the nanoparticles washed 3 times with acetone, then three times with water with no further purification before reuse. The reaction supernatant and washings were collected together, the solvent evaporated, and the solid product weighed and characterized by NMR spectroscopy on a Mercury 300. The XPS analysis was performed at Ecole Polytechnique Montreal on a VG ESCLAB 3 MKII with a power of 206 W. A surface of 2×3 mm was analysed at a depth of 50–100 Å. ICP-OES was performed on a Trace Scan with a baffled cyclonic spray chamber and mini cross flow nebulizer.

Acknowledgements

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