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# Synthesis of copper catalysts for click chemistry from distillery wastewater using magnetically recoverable bionanoparticles†

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**Copper recovered from a whisky distillery waste stream is shown to be an effective catalyst for a range of azide–alkyne "click" reactions. Biogenic nanomagnetite (BNM), produced under mild conditions, was used to rapidly recover and subsequently support the Cu catalyst which could be separated and recycled easily.**

The uncatalysed Huisgen 1,3-dipolar cycloaddition of organic azides and alkynes is a slow, high temperature process that affords a mixture of 1,4 and 1,5-disubstitution products.[1] In 2002, the groups of Sharpless[2] and Meldal[3] discovered that copper(I) can greatly accelerate the reaction and markedly improve its regioselectivity. Since then, Cu(I)-catalysed azide–alkyne cycloaddition (CuAAC) has become almost synonymous with "click chemistry", with applications in drug discovery,[4,5] bioconjugation,[6,7] materials science,[8] and polymer chemistry.[9] Click chemistry, a concept introduced by Sharpless in 2001, describes a set of highly efficient reactions which are high yielding, wide in scope, use benign solvents, generates only inoffensive byproducts and are regio/stereospecific.[10] Despite the green credentials of click chemistry, the synthesis of CuAAC catalysts often does not follow these same stringent criteria.

There is much interest in the use of supported Cu catalysts due to their increased robustness, ease of recovery and improved reusability, compared to their unsupported counterparts.[11,12] To this end, efforts have been made to immobilize CuAAC catalysts on polymers,[13] zeolites,[14] charcoal,[15,16] graphene,[17,18] and clay.[19] Our previous work demonstrated that under mild aqueous conditions, metal-reducing bacteria can act as both reductant and support for CuAAC catalysts.[20] Producing these catalysts with Cu sourced from waste streams would greatly enhance their green credentials, offering numerous advantages over traditional synthesis using Cu salts. Cu recovery from waste provides a low-cost, renewable source of Cu, minimises or actively reduces waste volumes, and recycles and valorises waste metal into highly useful catalysts.

Magnetic iron nanoparticles offer a promising method for simple recovery of metals from waste solutions.[21,22] In addition, they have gained increased attention as supports for CuAAC catalysts due to their ease of separation, recovery and reuse.[23–25] However, the chemical synthesis of these magnetic nanoparticles often requires high temperature, non-aqueous solvents, stabilizing agents or hazardous chemicals. Microbial metabolism can be harnessed to provide simple, inexpensive, scalable and tunable processes for the synthesis of magnetic nanoparticles under mild conditions.[26,27]

Herein, we present the first synthesis of a CuAAC catalyst using copper recovered from an industrial waste source (Fig. 1). We also demonstrate that the copper can be recovered and subsequently supported using biogenic nanomagnetite (BNM), synthesised under very mild conditions. Due to the magnetic nature of the BNM, the catalyst could easily be separ-

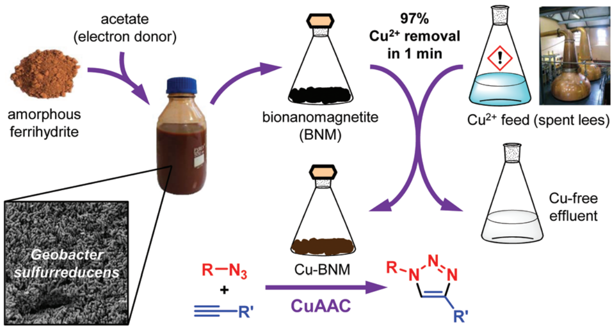

**Fig. 1** Overview of the Cu-BNM catalyst preparation procedure and application to CuAAC.

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ated and reused for up to three cycles. The industrial waste source selected for this study was the spent lees from a whisky distillery located in Scotland. Spent lees are the residues left in the spirit still following the second distillation phase of whisky production, and contain elevated Cu concentrations in addition to a range of fermentation products creating a complex waste source (see ESI†). The lees are normally treated in an effluent plant before being discharged to the environment or applied to land as a soil conditioner. The presence of copper increases the treatment levels required and limits the potential for application to land.

To produce the BNM, cells of the metal-reducing bacterium *Geobacter sulfurreducens* were added to amorphous ferrihydrite and supplied with acetate as an electron donor. The reaction proceeded at 30 °C and the only solvent used was water. After synthesis, the BNM was easily recovered using a magnet and washed 3 times in water to remove residual biomass. Previous characterization revealed an average particle size of 13.3 ± 0.6 nm.[28]

Inductively coupled plasma atomic emission spectroscopy (ICP-AES) confirmed the Cu content in the spent less was 49 mg $L^{-1}$. A BNM concentration of 2.8 mg $mL^{-1}$ spent lees was chosen for Cu recovery and catalyst synthesis in order to provide sufficient $Fe^{2+}$ on the BNM surface for potential $Cu^{2+}$ reduction, and to demonstrate catalytic activity at a relatively low Cu loading. Rapid removal of Cu following BNM addition was confirmed by ICP-AES which revealed >97% of Cu was removed in less than 1 minute. The BNM was then magnetically recovered. Scanning transmission electron microscopy (STEM) and energy-dispersive X-ray spectroscopy (EDX) mapping confirmed the recovered Cu was supported on the BNM ($Cu_{lees}$BNM) with clear evidence of the Cu associated with the Fe signal of the BNM (Fig. 2). Digestion of the recovered $Cu_{lees}$BNM revealed a Cu loading of 2 wt%.

Characterisation of the $Cu_{lees}$BNM was performed using X-ray photoelectron spectroscopy (XPS). Interestingly, XPS analysis of the spent lees suggested the presence of two Cu species. The Cu $2p_{3/2}$ peak at 934.2 eV is characteristic of Cu(II) whereas the peak at 932.8 eV suggests the presence of reduced Cu (Fig. 3a).

However, distinguishing between Cu(I) and Cu(0) is not accurate with this technique.[29] After recovery of the Cu by the BNM, only one peak at 932.7 eV was present, suggesting reduction of the Cu(II) had occurred, most likely mediated by the Fe(II) present within and on the surface of the BNM.[30,31] A catalyst prepared by the addition of reagent grade $CuSO_4$ (dissolved in water) to BNM ($Cu_{salt}$BNM), giving an identical Cu loading of 2 wt%, was also prepared and characterised (Fig. 3b and ESI†). A similar Cu $2p_{3/2}$ peak at 932.8 eV suggested that reduction of Cu(II) by BNM also occurred in the synthesis of the $Cu_{salt}$BNM catalyst (Fig. 3b).

To investigate the potential for using Cu recovered from waste for click reactions, we began by testing the $Cu_{lees}$BNM catalyst in the cycloaddition of benzyl azide **1a** and phenylacetylene **2a** (Table 1). The activity was compared against the $Cu_{salt}$BNM catalyst. When no additional reducing agent was applied, both the $Cu_{lees}$BNM and $Cu_{salt}$BNM were found to be poorly active (Table 1, entries 3 and 4), likely due to the presence of some residual Cu(II) on the surface of the nanomaterial. Addition of ascorbate to the reaction mixture, leading to reduction of Cu(II) to Cu(I), afforded complete conversion to the corresponding 1,2,3-triazole product **3a** (>95%, Table 1, entries 5 and 6). However, ascorbate addition also resulted in dissolution of the $Cu_{lees}$BNM catalyst after prolonged incubation, precluding any potential recyclability, as

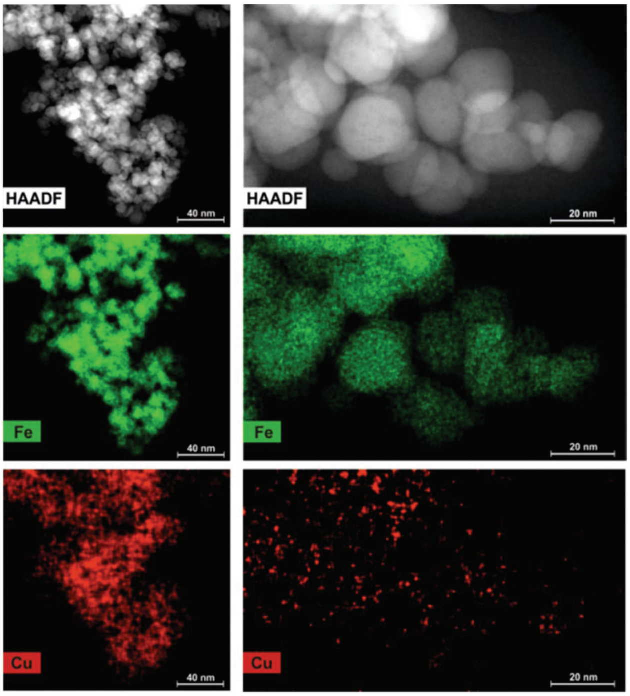


**Fig. 2** High-angle annular dark field (HAADF) images and corresponding elemental maps of Fe and Cu of the $Cu_{lees}$BNM catalyst.

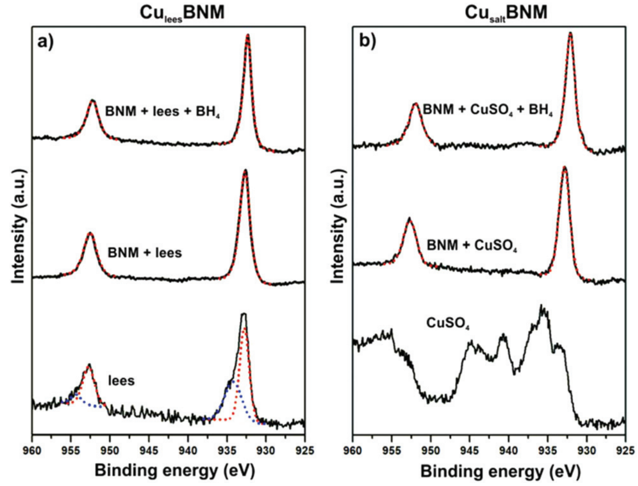
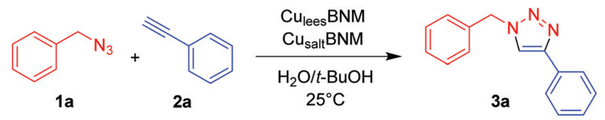


**Fig. 3** XPS surface analysis of (a) $Cu_{lees}$BNM and (b) $Cu_{salt}$BNM catalysts. Data is displayed as black solid lines whilst fits are displayed as red dotted lines.

**Table 1** Performance of Cu$_{\text{lees}}$BNM and Cu$_{\text{salt}}$BNM catalysts for CuAAC[a]



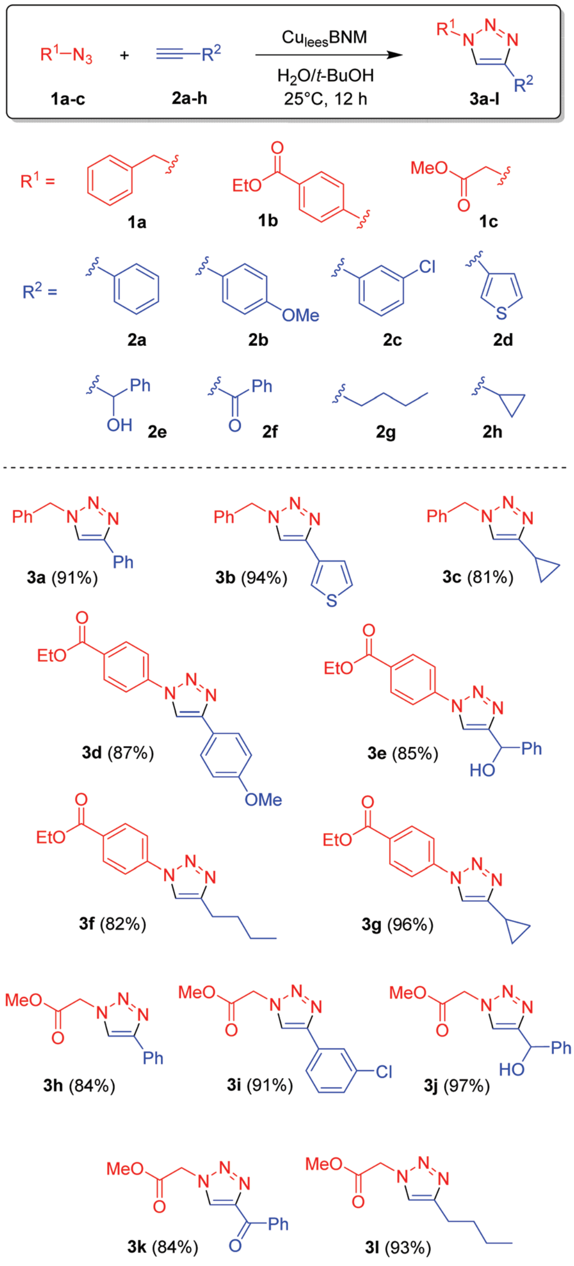
| Entry | Catalyst | Reducing agent | Time [h] | Yield[b] [%] |
|---|---|---|---|---|
| 1 | None | None | 12 | n.d. |
| 2 | BNM | None | 12 | n.d. |
| 3 | Cu$_{\text{salt}}$BNM | None | 12 | 45 |
| 4 | Cu$_{\text{lees}}$BNM | None | 12 | 43 |
| 5 | Cu$_{\text{salt}}$BNM | Ascorbate[c] | 12 | >95 |
| 6 | Cu$_{\text{lees}}$BNM | Ascorbate[c] | 12 | >95 |
| 7 | Cu$_{\text{salt}}$BNM | $NaBH_4$[d] | 5 | 56 |
| 8 | Cu$_{\text{salt}}$BNM | $NaBH_4$[d] | 12 | >95 |
| 9 | Cu$_{\text{lees}}$BNM | $NaBH_4$[d] | 5 | 47 |
| 10 | Cu$_{\text{lees}}$BNM | $NaBH_4$[d] | 12 | >95 |

[a] Reaction conditions: 0.25 mmol **1a**, 0.25 mmol **2a**, 500 μL Cu-BNM suspension, 5 mL $H_2O$/*t*-BuOH (8 : 2), 25 °C. [b] Calculated by $^1$H NMR (n.d. = product not detected). [c] 50 mM sodium ascorbate added to the click reaction mixture. [d] Treatment of the Cu-BNM with 10 mM sodium borohydride prior to click reaction.

has been reported previously.[24] In order to alleviate this issue, the Cu-BNM catalysts were pre-treated with $NaBH_4$ as the reducing agent. This resulted in a shift in the Cu 2p$_{3/2}$ peaks of the nanocatalysts of between 0.4 and 0.8 eV (Fig. 3), likely due to reduction of any residual Cu(II). This enabled excellent catalytic yields whilst also preserving the integrity of the catalyst so that it could be easily separated magnetically for potential reuse. The Cu$_{\text{lees}}$BNM catalyst prepared from the spent lees waste gave complete conversion after 12 hours and was only slightly less efficient over a shorter incubation time compared to the Cu$_{\text{salt}}$BNM catalyst (Table 1, entries 7 and 9). Therefore, all subsequent preparative scale experiments were carried out using the Cu$_{\text{lees}}$BNM catalyst.

We next investigated the CuAAC of an expanded range of azides (**1a–c**) and alkynes (**1a–h**) using the Cu$_{\text{lees}}$BNM catalyst, to produce a variety of 1,2,3-triazole products (Scheme 1). The reactions were conducted on a 5 mL scale, with 0.25 mmol of each reagent and 500 μL of the Cu$_{\text{lees}}$BNM suspension, at 25 °C for 12 h, and the products were isolated by extraction with ethyl acetate. The catalytic system proved very efficient in all cases, affording almost quantitative conversion and very good isolated yields (81–97%) for 12 different triazoles **3a–l**. This also highlights the broad tolerance of this procedure towards different functional groups such as esters, ethers, alcohols, ketones and heterocycles.

Furthermore, the recyclability of the Cu$_{\text{lees}}$BNM was assessed by simple magnetic separation and recovery of the catalyst, before being applied to a new reaction cycle. The recyclability test was performed for the synthesis of **3a**, by extracting the product and/or leftover starting materials with ethyl acetate, magnetically recovering the particles, rinsing them twice with $H_2O$/EtOH 9 : 1, and resuspending them in water for a new reaction cycle (Table 2). The recovered catalyst



**Scheme 1** Preparative scale synthesis of triazoles **3a–l** using the Cu$_{\text{lees}}$BNM catalyst.

**Table 2** Recyclability of the Cu$_{\text{lees}}$BNM catalyst for the synthesis of **3a**[a]

| Cycle | Yield [%] |
|---|---|
| 1 | >95 |
| 2 | 90 |
| 3 | 71 |
| 4 | 27 |
| 5 | <5 |

[a] Reaction conditions for CuAAC: 0.25 mmol **1a**, 0.25 mmol **2a**, 500 μL Cu$_{\text{lees}}$BNM suspension, 5 mL $H_2O$/*t*-BuOH (8 : 2), 25 °C, 12 h.

demonstrated good yields for the first three cycles, before a significant decrease in activity at cycle 4. This highlights the advantage of supporting the copper on a magnetic nanomaterial that can be recovered easily. Further optimisation to improve recyclability is being investigated.

Lastly, in order to prove the scalability of this protocol, a gram-scale synthesis of **3a** from 5 mmol of **1a** and **2a** was performed (employing slightly increased substrate concentrations and decreased catalyst loading, see ESI† for details). Triazole **3a** was obtained in 82% isolated yield after extraction and recrystallisation, demonstrating the usefulness of the $\mathrm{Cu_{lees}}$BNM as a preparative-scale catalyst for CuAAC reactions.

## Conclusions

Herein, we report for the first time CuAAC reactions using copper recovered from an industrial waste stream. In addition, we demonstrate the first use of biogenic magnetic nanoparticles as a simple, green method for recovering and subsequently supporting the CuAAC catalysts. The $\mathrm{Cu_{lees}}$BNM catalysts could be reused for up to three cycles following magnetic separation. Conversion of a pre-existing waste into a useful resource for synthetic applications reduces the additional raw resources and associated costs needed for catalyst preparation, demonstrating a previously unexplored opportunity for sustainable CuAAC. The efficient biological synthesis of the magnetic nanoparticles under mild conditions provides additional green benefits by avoiding the need for reducing agents, non-aqueous solvents, high temperatures or hazardous chemicals for producing the catalyst support. Production of BNM from waste iron oxides could further enhance the green credentials of this CuAAC catalyst synthesis method.[32] The ability of the BNM to act as both the initial recovery agent and subsequent support for the Cu improves the atom efficiency of the process and reduces the number of steps required for catalyst synthesis. Simple magnetic separation and recovery of the $\mathrm{Cu_{lees}}$BNM following the CuAAC adds to the benefits of heterogeneous catalysis. Lastly, the broad applicability of this catalytic system for click reactions has been demonstrated with the synthesis of a panel of 12 different triazoles bearing various functional groups, on preparative scale up to gram-quantities of product. Further work into the physical characterisation of the material and elucidation of the catalytic mechanism is ongoing, in addition to investigating the viability of recovery of Cu and other metals from different waste streams.

## Conflicts of interest

There are no conflicts to declare.

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