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New routes to Cu(I)/Cu nanocatalysts for the multicomponent click synthesis of 1,2,3-triazoles

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Sub-10 nm Cu and CuZn nanoparticles have been prepared and the efficient catalysis of azide–alkyne 1,3-dipolar cycloaddition demonstrated, with triazoles synthesized quantitatively at room temperature using catalyst loadings of 0.03 mol% metal.

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PAPER

New routes to Cu(I)/Cu nanocatalysts for the multicomponent click synthesis of 1,2,3-triazoles†

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An array of copper and copper–zinc based nanoparticles (NPs) have been fabricated employing a variety of polymeric capping agents. Analysis by TEM, XRPD and XPS suggests that by manipulating reagent, reductant and solvent conditions it is possible to achieve materials that are mono-/narrowly dispersed with mean particle sizes in the ≤ 10 nm regime. Oxidative stability in air is achieved for monometallic NPs using poly(methyl methacrylate) (PMMA) anti-agglomerant in conjunction with a variety of reducing conditions. In contrast, those encapsulated by either poly(1-vinylpyrrolidin-2-one) (PVP) or poly(4-vinylpyridine) (PVPy) rapidly show Cu₂O formation, with all data suggesting progressive oxidation from Cu to Cu@Cu₂O core-shell structure and finally Cu₂O. Bimetallic copper–zinc systems, reveal metal segregation and the formation of Cu₂O and ZnO. Catalysts have been screened in the synthesis of 1,2,3-triazoles through multicomponent azide–alkyne 1,3-dipolar cycloaddition. Whereas PMMA- and PVPy-coating results in reduced catalytic activity, those protected by PVP are highly active, with quantitative triazole syntheses achieved at room temperature and with catalyst loadings of 0.03 mol% metal for Cu and CuZn systems prepared using NaH₂PO₂, N₂H₄ or NaBH₄ reductants.

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Introduction

Copper has been used as a catalyst in organic synthesis at the molecular level for many decades.^{1–4} However, whereas the use of nanocatalysts offers enhancements in terms of more economic and sustainable processes where homogeneously catalyzed reactions presently suffer from major drawbacks,^{5–9} the susceptibility of nanoparticulate copper to oxidation^{10,11} has previously limited applications. In spite of this, processing costs and the search for new combinations of beneficial properties have led to continued interest in the replacement of established noble metal nanocatalysts with those of relatively inexpensive metals.¹² In this vein, nanoparticulate copper has recently been deployed in various chemical syntheses, this having been enabled by the development of routes to the preparation of the copper-based nanomaterials Cu(0),^{13–16} CuO and Cu₂O.^{17,18} As a result, copper nanoparticles (Cu NPs) have found many applications in, amongst other reactions, the reduction of functional groups,¹⁹ the formation of carbon–carbon and carbon–nitrogen

bonds,²⁰ and in so-called “click” chemistry.^{21,22} Our own groups have been especially concerned with the development of novel Cu NP catalysts and their application in click chemistry in particular. In this context, we have previously shown that Cu NPs could be formed either from CuCl₂·2H₂O or anhydrous CuCl₂ and elemental lithium in the presence of catalytic 4,4'-di-*tert*-butylbiphenyl (DTBB) in THF at room temperature.^{13,19} These Cu NPs effectively catalysed the 1,3-dipolar cycloaddition of organic azides and terminal alkynes in remarkably short reaction times (10–120 min).^{13,23} Notwithstanding the superior catalytic activity observed when we compared these systems with other commercially available copper sources, the Cu NPs underwent dissolution under reaction conditions (Et₃N, THF, 65 °C) and could not be reused. In order to overcome this problem, we introduced a catalyst consisting of oxidized copper nanoparticles immobilized on activated carbon. These could be readily prepared under mild conditions and proved extremely versatile catalysts for the multicomponent Huisgen 1,3-dipolar cycloaddition in water. Not only organic halides, but some other azide precursors, such as aryldiazonium salts, anilines, and epoxides were shown to be appropriate substrates in this process.^{24–27} Ullmann-type amination is another process in which we have been interested. In this context, we have recently fabricated Cu NPs capped by PVP40 [poly(1-vinylpyrrolidin-2-one), $M_{av} = 40\,000$] that enabled the efficient synthesis of 4-phenoxypyridine using multimode microwave heating in a microfluidic device.²⁸ Kinetic studies have also sought to understand the processes at work during heterogeneously

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catalyzed reactions and, in particular, the differing affinities of reagents and products for the Cu NP surface.²⁹ This work acted as precursor to the synthesis of bimetallic CuZn NPs that achieved enhanced yields for the same transformation under more facile reaction conditions.³⁰ These bimetallic systems have recently been deployed in etherification chemistry with the presence of zinc used to explain the resistance of the system to copper oxide formation.³¹

Whereas the investigation of nanostructured copper-based bimetallic systems has yielded efficient catalysts for industrially relevant processes,^{32,33} bimetallic CuM NPs^{34,35} have previously been found to deactivate on account of metal segregation and selective oxidation.³⁶ In the case of monometallic Cu NPs, the prevailing structure-type noted has hitherto been Cu(core)@CuO/Cu₂O(shell),³⁷ with efforts to control the formation of an oxide shell predicated on the use of capping agents that inhibit molecular access to the particle surface.^{38–40} More recently, it has been shown that the use of polymeric capping agents may enhance the oxidative stability of NPs whilst permitting substrate access and efficient catalysis.⁴¹ Moreover, the range of polymers available for stabilizing highly reactive main group nanomaterials has also very recently been extended through the use of poly(methyl methacrylate) (PMMA) to protect Mg nanocomposites.⁴² The response of Cu-based nanomaterials to this capping agent is, so far as we are aware, yet to be reported.

In the present study, we describe recent work aimed at systematically extending the chemical reduction methods that we have previously used to fabricate a range of Cu-based nanoparticles.⁴¹ Efforts focus on understanding the influence of (i) different steric capping agents, (ii) the choice of metal substrate and reducing agent, (iii) the presence or not of water during the synthesis, and (iv) reagent concentrations and reaction temperature. We report on whether the resulting Cu-based NPs undergo the formation of an oxide coat and on the long-term resistance of these materials to oxidation upon air exposure. Applications in the multicomponent click synthesis of model 1,2,3-triazoles are tested (Scheme 1), with an array of Cu-based nanomaterials screened for activity, selectivity and longevity under different conditions.

Results and discussion

Catalyst preparation and structure

Initial particle preparations sought to extend our former work on PVP-capped Cu^{28,41} and CuZn³⁰ systems using the general route outlined in Scheme 2. The effects of varying polymer chain length were probed, with monometallic Cu fabricated in the presence both of PVP40 and PVP29 (average M_w = 40 000 and 29 000, respectively) by reducing CuSO₄·5H₂O with sodium hypophosphite hydrate, NaH₂PO₂·H₂O, before modulating the pH with aqueous NaOH. The resulting narrow-disperse particles

Scheme 2 Representative conditions for Cu and CuZn NP synthesis.

showed mean particle sizes of 7.23 ± 2.81 and 5.19 ± 1.02 nm, respectively (Table 1, samples 1 and 3, see also Fig. 1 for the latter). The fabrication of Cu using PVP29 made monometallic work consistent with that previously reported for PVP29-coated CuZn systems (also see below). However, for both samples 1 and 3, XRPD analysis demonstrated lines clearly corresponding to oxide formation.

Subsequent work sought to replicate the synthesis of samples 1 and 3 in the absence of water in the expectation of achieving greater control over particle size distribution and/or stability, with solvents being distilled and degassed with argon immediately prior to use and NaOH being added as a solution in the reaction solvent. CuSO₄ was reduced using two eq. NaH₂PO₂ in the presence of 10 eq. PVP following the synthetic procedure described in Scheme 2 (samples 2 and 4, see Fig. 1 for the latter). Similar particle size distributions were observed and XRPD revealed that any enhancement in oxidative stability was modest, with Cu, Cu₂O and CuO all being observed (see ESI†). This led to the conclusion that the elimination of water from the synthesis had not resulted in particles with a long-term resistance to oxidation. Overall, particles synthesized under strictly anhydrous conditions closely resembled those prepared in the

Table 1 Summary of synthetic parameters for and results of syntheses of Cu-based catalysts 1–21

Sample	Cu reagent	Polymer	Solvent–reductant	Mean size (nm)
1	CuSO ₄ ·5H ₂ O	PVP40 ^a	EG ^b –NaH ₂ PO ₂ ·H ₂ O	7.23 ± 2.81
2	CuSO ₄	PVP40	EG–NaH ₂ PO ₂	7.03 ± 1.91
3	CuSO ₄ ·5H ₂ O	PVP29 ^c	EG–NaH ₂ PO ₂ ·H ₂ O	5.19 ± 1.02
4	CuSO ₄	PVP29	EG–NaH ₂ PO ₂	5.02 ± 0.99
5	CuSO ₄	PVP29	EtOH ^d –NaBH ₄	4.42 ± 0.99
6	CuSO ₄	PVP29	EtOH–NaBH ₄	8.91 ± 3.41
7	Cu(OAc) ₂	PVP29	EtOH–NaBH ₄	2.50 ± 0.54
8	Cu(OAc) ₂	PVP29	EtOH ^d –NaBH ₄	3.19 ± 0.86
9	Cu(OAc) ₂	PVP29	THF–N ₂ H ₄	4.14 ± 0.77
10	CuCl ₂	PVP29	EtOH ^d –NaBH ₄	3.35 ± 0.92
11	CuCl ₂	PVP29	THF–N ₂ H ₄	5.02 ± 0.86
12	CuSO ₄	PVPy60 ^e	EG–NaH ₂ PO ₂	2.58 ± 0.60
13	Cu(OAc) ₂	PMMA120 ^f	THF ^d –NaBH ₄ (in EtOH)	2.42 ± 0.48
14	Cu(OAc) ₂	PMMA120	1 : 1 THF : EtOH ^d –NaBH ₄	4.34 ± 0.68
15	Cu(OAc) ₂	PMMA120	THF–NaBH ₄ (in EtOH)	2.48 ± 0.40
16	Cu(OAc) ₂	PMMA120	THF ^d –N ₂ H ₄	8.03 ± 1.34
17	Cu(OAc) ₂	PMMA120	THF–N ₂ H ₄	2.97 ± 0.78
18	CuCl ₂	PMMA120	THF ^d –NaBH ₄ (in EtOH)	3.01 ± 0.34
19	CuCl ₂	PMMA120	1 : 1 THF : EtOH ^d –NaBH ₄	3.96 ± 0.56
20	CuCl ₂	PMMA120	THF ^d –N ₂ H ₄	8.94 ± 1.45
21	CuSO ₄	PMMA120	THF ^d –NaBH ₄ (in EtOH)	3.54 ± 0.74

^a av. M_w = 40 000. ^b Ethylene glycol. ^c av. M_w = 29 000. ^d Heat to reflux. ^e av. M_w = 60 000. ^f av. M_w = 120 000.

Scheme 1 Representative multicomponent synthesis of 1,2,3-triazoles.

Fig. 1 Representative HRTEM images and particle size distributions for Cu catalyst samples 3 (top) and 4 (bottom) at $\times 300k$ magnification. Samples prepared by the NaH_2PO_2 reduction of CuSO_4 in the presence of PVP29 under hydrous and anhydrous conditions, respectively.

presence of water in terms of both morphology and mean particle size and distribution.

Initial attempts at using reducing agents other than hypophosphite for Cu systems failed to afford NPs that were observable by HRTEM. This was independent of Cu(II) sources tested but was particularly pronounced for any synthetic schemes involving water. However, by imposing anhydrous conditions (*vide supra*) and dissolving NaBH_4 and NaOH in either ethylene glycol or EtOH it was possible to obtain a black/brown nanoparticle dispersion amenable to HRTEM analysis. In this way anhydrous CuSO_4 was reduced using 2 eq. NaBH_4 (an effective eight-fold excess of reducing agent) in the presence of 6 eq. PVP29 (samples 5 and 6). Analysis revealed that the use of elevated temperature gave a smaller mean particle size (sample 5) and that sample 6 was composed of NPs that were both significantly larger and had a greater than hoped for size dispersion. Mean particle size was lowered most effectively by varying Cu(II) source, with both $\text{Cu}(\text{OAc})_2$ and CuCl_2 yielding narrow disperse NPs using NaBH_4 (samples 7, 8 and 10). However, for both of these substrates, the alternative use of

hydrazine as reductant gave a slight increase in mean particle size (samples 9 and 11). In each case, TEM images revealed lattice spacings attributable to metallic Cu, with XRPD on samples 7–10 showing progressive oxidation (see ESI†). In particular, sample 7 provided interesting new insights into the process by which particle oxidation had occurred (Fig. 2). Cu NPs have previously been shown to decompose to $\text{Cu}(\text{core})@ \text{CuO}/\text{Cu}_2\text{O}(\text{shell})$ structures.³⁷ Fringe analysis suggests that this process was not uniform in the present work. Hence, for example, the analysis of sample 7 suggests the co-existence of Cu, Cu_2O and $\text{Cu}@ \text{Cu}_2\text{O}$ NPs.

Remaining with anhydrous preparations, the use of more aggressive anti-agglomerant was investigated whilst employing conditions otherwise similar to those used to synthesize sample 4.

A reduction in mean particle size along with a proportionately slightly raised particle size distribution was noted when using PVPy60 [poly(4-vinylpyridine), average $M_w = 60\,000$] capping agent (Table 1), with Cu NPs of 2.58 ± 0.60 nm seen (sample 12, cf. 5.02 ± 0.99 nm for sample 4).

We next sought to extend the idea that variations in Cu(II) reagent and reductant influence both mean particle size and dispersion, whilst recognizing that PVP(y) capping agents were unlikely to yield particles with extensive oxidative stability. We therefore sought to develop a remarkable recent study in which Mg nanocomposites were successfully passivated with respect to oxidation.⁴² In a typical experiment a Cu(II) solution was pretreated with PMMA120 [poly(methyl methacrylate); average $M_w = 120\,000$] before being stirred at 40°C under Ar. The addition of reducing agent resulted in a colour change to dark brown/black. Having allowed the reaction to complete (1.5–2.5 h), purification was achieved by precipitating the sample using ethanol (samples 13–21; Table 1). The reduction of CuSO_4 , $\text{Cu}(\text{OAc})_2$ and CuCl_2 was investigated using N_2H_4 and NaBH_4 reductants. In almost all cases, mono- or narrow-disperse sub-5 nm particles were obtained. The presence of a higher proportion of EtOH favoured agglomeration upon NaBH_4 reduction (cf. samples 13, 14 and also 18, 19). Reduction by N_2H_4 at ambient temperature afforded similarly small NPs (sample 17; Fig. 3),

Fig. 2 HRTEM analysis of sample 7 suggests the presence of Cu (top), $\text{Cu}@ \text{Cu}_2\text{O}$ (centre) and Cu_2O (bottom) particles.

Fig. 3 Analytical data for a representative PMMA120-coated sample of Cu NPs. Sample 17 was prepared using $\text{Cu}(\text{OAc})_2$ and N_2H_4 under anhydrous conditions at room temperature (Table 1). HRTEM reveals monodisperse behaviour (top right) while XPS shows oxidative stability by analysis of the Cu $2p_{3/2}$ region (top right). This is retained after 2 weeks according to XRPD (bottom).

though the use of elevated temperatures led to narrowly dispersed, but significantly agglomerated particles (samples 16, 20). All samples fabricated in the presence of PMMA120 demonstrated excellent oxidative stability, undergoing no visible changes according to XRPD over a period of 2 weeks in the open laboratory (Fig. 3).

Moving to the preparation of bimetallic systems by the introduction of ZnCl_2 into the synthesis, EDS revealed the presence of $K\alpha_1$ emission lines corresponding to Cu and Zn for systems 22–24 (Scheme 2 and Table 2), with the ratio of peak intensities varying in nominal accordance with reaction stoichiometry when EDS was conducted with a broad beam-width

(see ESI†). However, narrow beam EDS plainly revealed that these bimetallic samples were, in fact, comprised of Cu-rich and Zn-rich phases, arguing against individually bimetallic nanoparticles and consistent with the known ability of such systems to undergo dynamic segregation of the metals.³⁶

In line with EDS observations, the XRPD analysis of sample 23 revealed both Cu_2O and ZnO . These last data are supported by the diffraction patterns obtained for this sample by the FFT of representative HRTEM images. Lattice spacings observed in different particles corresponded most closely to either Cu_2O or ZnO . Taken together, these observations suggest the formation of segregated regions of either oxide. ICP-OES (see ESI†) demonstrated that the reaction stoichiometry was well reflected in the product composition for Cu rich syntheses, with samples 24, 27, 30 revealing 70.6–78.0 mol% Cu. However, attempts to incorporate equimolar Cu and Zn (samples 23, 26, 29) resulted in an excess of the latter element (27.1–42.9 mol% Cu). Attempts to fabricate Zn-rich NPs led to the observation of significant levels of zinc, in particular when PVP capping agent was used.

Adjusting the ratios of CuSO_4 and ZnCl_2 in anhydrous preparations whilst maintaining a constant total metal content : polymer : reducing agent ratio yielded CuZn NPs (samples 25–27) that were similar in nature to samples 22–24 – that is, revealing the same tendency for metal segregation and ZnO formation (see ESI†).

HRTEM analysis revealed particles with essentially equivalent size distributions of 5.02 ± 0.99 , 4.97 ± 0.96 , 4.88 ± 1.07 , and 5.10 ± 1.38 nm for PVP-capped samples 4, 25–27. In contrast, PVPy-capped samples 12, 28–30 increased in mean particle size from 2.58 ± 0.60 to 4.21 ± 1.57 nm as a function of Zn contribution to reaction stoichiometry. However, an analysis of particle size histograms showed that for reactions containing more Zn an increasingly bimodal particle size distribution resulted. This was most clear for sample 28 (Fig. 4), for which EDS detected that regions dominated by smaller particles (*ca.* 3 nm wide) were Cu-rich and regions dominated by larger particles (*ca.* 7 nm wide) were Zn-rich. The view that the latter in fact constitute ZnO was reinforced by the observation of lattice spacings corresponding to the oxide. Overall, these data suggest

Table 2 Summary of synthetic parameters for and results of syntheses of Cu-based samples 3, 4 and 12 and their CuZn-based analogues

Sample	Composition ^a (mol%)	Cu reagent	Polymer	Solvent-reductant	Mean size (nm)
3	100 Cu	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$	PVP29	$\text{EG}-\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$	5.19 ± 1.02
22	25 : 75 CuZn	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$	PVP29	$\text{EG}-\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$	6.11 ± 1.66
23	50 : 50 CuZn	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$	PVP29	$\text{EG}-\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$	4.66 ± 0.69
24	75 : 25 CuZn	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$	PVP29	$\text{EG}-\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$	4.55 ± 1.09
4	100 Cu	CuSO_4	PVP29	$\text{EG}-\text{NaH}_2\text{PO}_2$	5.02 ± 0.99
25	25 : 75 CuZn	CuSO_4	PVP29	$\text{EG}-\text{NaH}_2\text{PO}_2$	4.97 ± 0.96
26	50 : 50 CuZn	CuSO_4	PVP29	$\text{EG}-\text{NaH}_2\text{PO}_2$	4.88 ± 1.07
27	75 : 25 CuZn	CuSO_4	PVP29	$\text{EG}-\text{NaH}_2\text{PO}_2$	5.10 ± 1.38
12	100 Cu	CuSO_4	PVPy60	$\text{EG}-\text{NaH}_2\text{PO}_2$	2.58 ± 0.60
28	25 : 75 CuZn	CuSO_4	PVPy60	$\text{EG}-\text{NaH}_2\text{PO}_2$	4.21 ± 1.57
29	50 : 50 CuZn	CuSO_4	PVPy60	$\text{EG}-\text{NaH}_2\text{PO}_2$	3.95 ± 2.06
30	75 : 25 CuZn	CuSO_4	PVPy60	$\text{EG}-\text{NaH}_2\text{PO}_2$	2.91 ± 1.36

^a By reaction stoichiometry.

Fig. 4 Representative FFTs of $\times 800k$ magnification TEM images of individual NPs (left: average $d = 2.47$ Å, Cu_2O (111); right: average $d = 2.81$ Å, ZnO (100)) and the size distribution for CuZn catalyst 28 (prepared from $\text{CuSO}_4\text{-ZnCl}_2$ with dry NaH_2PO_2) suggest that the metals have segregated.

that in each of samples 28–30, Cu-based NPs accounted for the smaller particles observed and were relatively unchanged in each case, while larger ZnO agglomerates had come to dominate in Zn-rich reactions.

Catalyst screening

The multicomponent 1,3-dipolar cycloaddition of terminal alkynes and azides (generated *in situ* from alkyl halides and NaN_3) was chosen as a route for catalyst screening (Scheme 3 and Table 3), utilizing aliquots of as-prepared catalyst MeOH dispersions of known concentration. The reaction with activated benzyl (Bn) bromide **1** was found to be significantly promoted by dispersions of both mono- and bimetallic catalysts without the need for high temperatures and using substantially lower loadings than have previously proved effective for such transformations (0.03 mol% metal *vs.* 1–10 mol% previously).^{43–51} Accordingly, Cu (samples 1 and 2; entries 1 and 2 in Table 3) as well as 50 : 50 CuZn (samples 23 and 26; entries 22 and 25), and 75 : 25 CuZn (sample 24; entry 23) gave yields of **3** that were good-to-quantitative even at room temperature. However, attempts to generate 25 : 75 CuZn catalysts led to NPs with a very low Cu content (see ESI† and *vide supra*), and this was reflected in the poor activity of catalyst 25 (entry 24).

Consistent with PVP-coated NPs demonstrating Cu(I) oxide formation (*vide supra*) there is a difference observed between catalyst reactivities under atmospheres of air or Ar. Hence, sample 4 gave rather lower yields of **3** when used under Ar (compare entries 5 and 6 with entries 3 and 4). The generally lower efficiency of this catalyst under either atmosphere may be interpreted in terms of the inclusion of sulfur in the NP

Scheme 3 Conditions for the multicomponent 1,3-dipolar cycloaddition of terminal alkynes and *in situ* generated azides.

Table 3 Summary of results for the screening of catalysts in the multicomponent synthesis of 1,2,3-triazoles according to Scheme 3. Reactions conducted under air unless otherwise stated

Entry	Catalyst	T ($^{\circ}\text{C}$)	t (h)	3 ^a (%)	5 ^a (%)
1	1	rt	7	94	—
2	2	rt	10	81 ^b	—
3	4	rt	7	60	—
4	4	rt	24	80	—
5	4	rt ^c	7	46	—
6	4	rt ^c	24	48	—
7	7	rt	7	56	—
8	7	rt	24	100 (98)	—
9	7	rt ^c	24	94	—
10	9	rt	24	100 (98)	—
11	9	rt ^c	24	96	—
12	9	rt	18	—	0
13	9	Reflux	6	—	100 (98)
14	12	rt	7	16	—
15	12	Reflux	2	100	—
16	15	rt	24	0	—
17	15	Reflux	24	100	—
18	15	rt ^c	24	0	—
19	17	rt	24	0	—
20	17	Reflux	24	60	—
21	17	rt ^c	24	0	—
22	23	rt	7	98	—
23	24	rt	7	91	—
24	25	rt	7	19	—
25	26	rt	7	100 (99)	—
26	26	rt	16	—	10
27	26	Reflux	6	—	100 (98)
28	28	rt	24	14	—
29	28	Reflux	7	100	—
30	29	rt	7	3	—
31	29	Reflux	2	100	—
32	30	rt	7	5	—
33	30	Reflux	2	100	—

^a Determined from the GLC peak area, isolated yields in parentheses.

^b 19% alkyne homocoupling also observed. ^c Ar atmosphere.

preparation, though it is of interest to note that CuZn systems 24 and 26 resisted comparable deactivation. The possibility of sulfur inhibiting the action of Cu NPs was overcome in catalyst samples 7 and 9, which were sourced from $\text{Cu}(\text{OAc})_2$ (entries 7–11). These catalysts revealed enhanced yields of **3** after 24 h at room temperature under air (entries 8 and 10) and, in fact, returned only small losses of yield under Ar (entries 9 and 11). The temperature responses of the most successful catalyst systems (samples 9 and 26) were further studied in 1,2,3-triazole synthesis using the less reactive, non-activated alkyl halide *n*-nonyl iodide (Scheme 3), with the yield of **5** found to be quantitative under reflux conditions (entries 12, 13, 26 and 27). As with PVP-coated catalysts, PVPy-coated systems revealed oxide formation (*vide supra*). However, inferior reactivity was noted at room temperature for both Cu (catalyst sample 12) and CuZn (samples 28–30) based systems coated with the more aggressive anti-agglomerant. Hence, while each of these samples gave quantitative click conversions under reflux conditions, room temperature reactions revealed yields in the range 3–16%

Scheme 4 Domino multicomponent 1,2,3-triazole synthesis/triazole alkylation.

(entries 14, 15, 28–33). Structural studies showed that PMMA-coated Cu NPs resist oxidation even after sustained air exposure. Both PMMA-coated samples 15 and 17 were found to be completely inactive with respect to triazole synthesis at room temperature under either air or Ar atmospheres (entries 16, 18, 19 and 21) but active when heated to reflux in an aerobic environment (entries 17 and 20). Taken together with the catalytic data for PVPy-capped samples these data suggest that catalytic inactivity cannot be attributed to NP resistance to Cu(I) formation alone, but that reagent access to the catalyst surface is also significant.

During the screening of Cu based nanocatalysts in the click synthesis of 1,2,3-triazoles a remarkable observation was made concerning the ability of air-exposed catalysts to promote the alkylation of triazoles (Scheme 4). To the best of our knowledge, the synthesis of 5-alkynyl 1,2,3-triazoles⁵² following a similar approach has been accomplished only by Porco's group.⁵³

In that report, organic azides and terminal alkynes reacted in a system comprised of $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$, N,N,N' -trimethylethylenediamine as ligand, Hünig's base, molecular oxygen, and 4-methylmorpholine N -oxide as co-oxidant in dichloromethane. Presently, both Cu (sample 1) and 50 : 50 CuZn NPs (sample 23) yielded not only triazole 3 upon treatment with BnBr, NaN_3 and $\text{PhC}\equiv\text{CH}$, but also C-alkynylated heterocycle 6 and BnN_3 7 (Table 4, entries 1 and 3). The selectivity towards 6 was found to be considerably enhanced by either using catalyst sample 2 (entry 2) which, unlike catalyst 1, was fabricated under anhydrous conditions, or by omitting the 12 h pre-treatment but conducting the reaction in an aerobic atmosphere for sample 1 (entry 4). Conversely, bimetallic catalyst 23 was found to be inactive towards alkylation (entry 5) except when air exposure was extended (entry 3), suggesting that the preferential oxidation of Zn rendered the need for an air pre-treatment more important. Failure to expose pure Cu nanocatalyst to air either before or during reaction resulted in the enhanced formation of 3 and a lower level of alkylation (compare entries 2 and 6), with the subsequent addition of phenylacetylene 2 to the reaction in entry 6 yielding even more 3.

The employment of 2 eq. 2 at the outset of a triazole synthesis reaction failed to have a positive effect on the yield of alkylation product at either room temperature or reflux and instead led to enhanced yields of 3 (entries 7–9 and 11–13). It was also generally clear that alkylation was deleteriously affected at higher temperature (*e.g.* compare entries 12 and 13). Taken together, these data suggest that the alkylation of triazoles is best promoted by catalysts rich in Cu_2O , but that

Table 4 Screening of catalyst samples 1, 2 (Cu) and 23 (50 : 50 CuZn) in multicomponent 1,2,3-triazole synthesis/triazole alkylation to give 6

Entry	Sample	Conditions	T ($^{\circ}\text{C}$)	t (h)	3 (%)	6 (%)	7 (%)	8 (%)
1	1	Catalyst stirred in air for 12 h prior to reaction	rt	24	34	32	34	—
2	2	in air	rt	24	13	77	10	—
3	23		rt	24	39	33	26	—
4	1	Reaction in air	rt	24	10	81	9	—
5	23		rt	24	40	—	—	—
6	2	Reaction under Ar	rt	16	63 (77) ^a	23	14	—
7	2	Reaction in air ^b	rt	24	—	—	—	—
8	2	Catalyst stirred in air for 2 h prior to reaction in air ^b	rt	24	32	57	—	3
9	2		Reflux	24	32	57	—	3
10	2	Catalyst stirred in air for 1 h prior to reaction in air	Reflux	24	88	10	—	2
11	2	Catalyst stirred in air for 1 h prior to reaction in air ^b	Reflux	24	72	16	—	—
12	1	Reaction in air ^b	rt	24	29	58	—	—
13	1		Reflux	24	79	5	—	—

^a Yield of 3 after subsequent addition of 1 mmol 2 (1 mmol = 1 eq. wrt BnBr) given in parentheses. ^b Use 2 eq. 2.

catalysts that are excessively exposed to oxygen or that have a lower copper content (e.g. bimetallic catalysts) give less alkylation. The suggestion is that the formation of **6** is strongly dependent on the level of Cu oxidation manifest and that it is inhibited by the presence of less active CuO (e.g. sample 1 after an extended pre-treatment in air) or by the resistance of Cu to oxidation by the sacrificial formation of ZnO (e.g. sample 23). This last point is of particular interest, with Zn having a clear effect on catalytic activity in spite of evidence (*vide supra*) for metal segregation.

In seeking to better understand whether the alkylation process occurred in tandem with triazole formation, catalyst sample 2 was treated with a mixture of **2** and **3** under various conditions. In agreement with Porco's observations,⁵³ the failure to note any detectable reaction argues strongly against C–H activation in pre-formed **3** facilitating alkylation by **2**. Similarly, the treatment of a pre-formed mixture of **3**, **6** and **7** with phenylacetylene yielded no **6** and only a small amount of **8**. Lastly, the failure of a mixture of **1**, NaN₃ and **8** to undergo detectable reaction in the presence of catalyst 2 suggested that **6** is not formed by the click reaction of diyne **8**.

Conclusion

In summary, the fabrication of a variety of Cu-based NPs in the 3–9 nm regime has been allowed by the use different reducing agents (NaH₂PO₂·H₂O, N₂H₄, NaBH₄) and polymeric capping agents. The exclusion of water from NP synthesis was found to have a limited beneficial effect on stability of the resulting NPs. Electron microscopy suggested that samples incorporating either PVP or PVPy anti-agglomerants rapidly underwent oxidation to give Cu@Cu₂O NPs alongside unoxidized Cu NPs, and also the segregation and preferential oxidation of Zn for bimetallic systems. Meanwhile, the use of PMMA capping agent gave oxidatively stable Cu(0) NPs as evidenced by XPS and XRPD.

A selection of as-prepared NPs were screened in the multi-component 1,3-dipolar synthesis of 1,2,3-triazoles using *in situ* generated organic azides. PVPy- and PMMA-coated NPs were found to be inactive at room temperature, suggesting that these polymers represent a barrier against substrate access to the catalyst surface. However, NPs coated with PVP were found to be highly active, producing quantitative yields of triazoles from benzyl bromide at room temperature and from the less reactive *n*-nonyl iodide at reflux. Unprecedentedly low catalyst loadings could be used and alkylation of the triazole C-5 position was also recorded under conditions that promoted limited catalyst oxidation.

Studies will now seek to develop a more detailed understanding of specific triazole syntheses using the most promising catalysts identified. Efforts will focus on extending the range of azide precursors, with anilines, aryldiazonium salts and epoxides all being tested, and of alkynes, including aliphatic alkynes. Zinc-containing catalysts will be studied with a view to developing systems that are active for both terminal and internal alkynes.⁵⁴ Moreover, the presence of Zn clearly influences the resistance of Cu to oxidation and also plays a role in

controlling the formation of alkynylated triazoles. In order to develop catalyst reusability, we are also initiating studies that marry azide-alkyne 1,3-dipolar cycloaddition catalysis with our own recent work on the immobilization of Cu-based NPs.³¹

Experimental

General synthetic and analytical details

Chemicals, including hydrazine (1 M in THF), were purchased from Sigma-Aldrich (reagents: analytical grade; solvents: HPLC grade) and used without further purification. Aqueous solutions were prepared using deionized water (Millipore, specific resistivity ≥ 18.2 M Ω cm). Ethanol was distilled immediately before use. Prior to synthesis, flasks were flushed and all solutions were degassed with argon.

Catalyst preparation

Cu NPs. For specific preparations see ESI.† Copper precursor and capping agent were dissolved in ethylene glycol or EtOH under an Ar atmosphere and the resulting mixture was stirred for 2 h at 0–40 °C in order to pre-coordinate the copper precursor with the ligand. Subsequently, solutions incorporating PVP(y) were cooled to 0 °C to inhibit uncontrolled reduction and the pH modulated to *ca.* 10 by adding NaOH (1 M in either aqueous solution or reaction solvent) as necessary. The mixture was stirred for 15 min after which reducing agent was added (see Table 1). Reactions were stirred at between 25 °C and refluxing conditions for 90–150 min to yield crude NP suspensions, aliquots of which were purified for analysis by extraction using excess acetone or ethanol with maximum exposure times of 90 min and 12 h, respectively. After sedimentation of the particles, the supernatant was decanted and the remaining suspension centrifuged. Upon removal of the acetone/ethanol layer, the colloidal precipitate was resuspended in methanol.

CuZn NPs. For specific preparations see ESI.† CuZn NPs were prepared as for Cu NPs (*vide supra*) except that a solution of zinc chloride in water/ethylene glycol was added to the pre-coordinated Cu precursor after it had been stirred for 2 h at 0–40 °C.

Catalyst characterization

HIGH-RESOLUTION TRANSMISSION ELECTRON MICROSCOPY (HRTEM). Analysis on a JEOL JEM-3011 high-resolution transmission electron microscope required preparation by droplet coating of MeOH suspensions on carbon coated Ni grids (Agar Scientific, 300 mesh). Electron optical parameters: $C_s = 0.6$ mm, $C_c = 1.2$ mm, electron energy spread = 1.5 eV, beam divergence semi-angle = 1 mrad. Elemental analysis was by energy dispersive X-ray spectroscopy (EDS). In this work, narrow beam EDS is defined as using a 7 nm beam diameter (note that this does not reflect the true area over which data was collected due to secondary effects). Broad beam EDS is defined as using a 50 nm beam diameter. A PGT prism Si/Li detector and an Avalon 2000 analytical system were employed. Observed NiK α and K β emission lines were attributed to scattered electrons impinging on the bars of the nickel support grid. Any minor FeK α or CoK α

emission lines were due to parasitic scattering from the lens pole-piece. Some significant $\text{CuK}\alpha$ and $\text{K}\beta$ x-rays were generated from stray electrons impinging on the specimen holder itself. Allowance for this was made by examining a specimen of CeO_2 nanoparticles of similar dimensions (3–10 nm) on a nickel grid in both the standard specimen holder used in this work and also a specially manufactured titanium holder. From the latter, the $\text{NiK}\alpha/\text{NiK}\beta$ intensity ratio was determined to be 6.7 ± 0.1 . This knowledge enabled calculation of the mean value of the $\text{CuK}\alpha$ contribution to the combined $\text{CuK}\alpha + \text{NiK}\beta$ peak recorded in the standard specimen holder. The resulting value was approximately 40% of the observed $\text{NiK}\alpha$ signal. This correction for the contribution from the specimen holder has been made to EDS analyses of CuZn samples (see ESI†).

Samples analyzed on an image aberration corrected FEI Titan 80–300 operated at 300 kV providing an information limit of 0.08 nm in TEM mode were prepared by dropping a suspension of the NPs in MeOH onto carbon-coated Ni grids (Quantifoil). Scanning transmission electron microscopy (STEM) was performed using a high-angle annular dark-field (HAADF) detector with a nominal spot size of 0.14 nm. For spectroscopy, a nominal spot size of ~ 0.5 nm was used in STEM mode with a Gatan Tridiem image filter for electron energy loss spectroscopy (EELS) and an EDAX S-UTW EDS detector.

Particle sizes were analysed using Macnification 2.0.1 by counting the diameters of 100 particles in lower magnification images,⁵⁵ defining size intervals of 0.2 nm between $d_{\min} \leq d \leq d_{\max}$ and counting the number of particles falling into these intervals. The data were then used to construct particle size distributions using DataGraph 3.0.

The detailed analysis of particle morphology was done using Digital Micrograph 3.6.5. The values of average d -spacing were obtained from Fourier transforms of high magnification images ($\times 800k$, $\times 1M$, $\times 1.2M$) using the expression $d = D/20$ where D is the diameter (nm) of rings obtained. The average d -spacing was then verified using the profile tool in Digital Micrograph counting at least 10 d -spacings. To determine the error in the value of d -spacing thus obtained, detailed TEM examination of CeO_2 and Au nanoparticles was undertaken. The relationship between the diameter of the FT rings and the DV value (a measure of the objective lens focusing voltage) was established for DV values between -6 and $+6$ and the value of standard deviation in d -spacing was established to be 10% when compared to literature values. Where oxidation state was determined based on d -spacings obtained by TEM measurements, values within 1 standard deviation ($\pm 5\%$) of literature values were used.

POWDER X-RAY DIFFRACTION (XRPD). XRPD data were collected on a Roentgen PW3040/60 XPert PRO powder X-ray diffractometer with a high resolution PW3373/00 Cu LFF (unmonochromated) tube at $\lambda = 1.5404 \text{ \AA}$ ($\text{CuK}\alpha$). Sample preparation was by solvent evaporation from colloidal suspensions deposited on the 0.5 mm deep ground area of a glass flatplate sample holder using a microscope slide to ensure that the powder sample was smooth, flat and flush with the sample holder surface. The holder was inserted onto the sample stage (PW3071/60 Bracket) such that the sample was just free of the reference plane of the sample stage.

X-RAY PHOTOELECTRON SPECTROSCOPY (XPS). XPS spectra were measured on a Kratos Axis Ultra DLD XPS System using a dual Al–Mg X-ray anode with a circular spatial resolution of 15 μm . Samples were prepared by droplet coating of the methanol dispersed NPs on Si wafers under an atmosphere of air.

INDUCTIVELY COUPLED PLASMA-OPTICAL EMISSION SPECTROSCOPY (ICP-OES). ICP-OES was carried out using a Perkin-Elmer 7300DV spectrometer at an RF power of 1300 W. Gas flows (l min^{-1}) were: 15 (plasma), 0.2 (auxiliary), 0.85 (nebulizer).

Multicomponent synthesis of 1,2,3-triazoles

NaN_3 (72 mg, 1.1 mmol), organic halide [benzyl bromide (119 μl , 1 mmol) or 1-iodononane (197 μl , 1 mmol)], and phenylacetylene (110 μl , 1 mmol or 220 μl , 2 mmol) were added to a suspension of Cu NPs or CuZn NPs in MeOH (2 ml; the metal content of which had been determined by ICP-OES prior to dilution to a known concentration) under an atmosphere of air or argon (see Tables 3 and 4). The reaction mixture was maintained at room temperature or at reflux for a specified time, with the progress being monitored by TLC. Water (30 ml) was added and the mixture extracted with EtOAc ($3 \times 10 \text{ ml}$). The organic phase was dried with anhydrous MgSO_4 , and the solvent removed *in vacuo* to give crude material. This was analyzed by GLC and did not require any further purification when high conversions into the triazoles **3**, **5** and **6** were reached. Triazoles **3**,²³ **5**²⁵ and **6**⁵⁶ were characterized by comparison of their physical and spectroscopic data with those described in the literature.

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