Cu/Cu-oxide nanoparticles as catalyst in the "click" azide–alkyne cycloaddition†

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Mixed Cu/Cu-oxide nanoparticles are an effective catalyst for the "click" 1,3-dipolar cycloaddition between azides and terminal alkynes, featuring short reaction times, soft reaction conditions and full regioselectivity.

The development of nanometre-sized metal and metal oxide particles is intensively pursued because of their importance for both fundamental science and advanced technology. Despite nanoparticles (NP) being objects of chemical nature, most of their applications appear in the materials and biomedical fields.

Since we were intrigued by the possibility of exploring the potential of NP-based products as reagents for organic synthesis, and since transition metal clusters and colloids have found wide application as homogeneous catalysts,[1,2] we decided to use mixed Cu/Cu-oxide NPs as a catalyst for the Cu^I-catalysed "click" azide–alkyne cycloaddition.[3] The uncatalysed reaction between aryl azides and monosubstituted alkynes is a thermally-allowed [3 + 2] cycloaddition which gives mixtures of regioisomeric 1,2,3-triazoles.[4] Conversely, high selectivity towards 4-substituted 1,2,3-triazoles has been achieved when Cu^I is present.[5] Reaction products, namely 1,2,3-triazoles, not only display a wide range of biological activities[6] but are prone to more or less facile transformations depending on the substitution pattern.[7] Cycloaddition of azides to terminal alkynes catalysed by copper clusters has been reported recently.[8] In this paper, we substantially broaden the scope of the investigation by isolating and thoroughly characterising the NPs (including behaviour to air). Moreover, the set of reacting substrates (3 aryl azides and 10 internal and terminal alkynes) has been enlarged to span a wide range of functional groups featuring largely different electronic demand.

Decomposition of copper(II) acetylacetonate in neat oleylamine at 230 °C yields copper metal NPs, which are readily oxidised by air.[2,9,10] To assess the possibility of protecting the NPs against oxidation by simple means, the isolation and characterisation of the NPs has been carried out either in air or by deaerating all solvents and vessels with argon. NPs are precipitated from the reaction crude by adding ethanol. Treatment of the precipitate with toluene yields a minor insoluble residue and a clear, brown dispersion.

Transmission electron microscopy (TEM, Fig. 1) shows that the brown dispersion contains NPs with mean diameter = 14 nm (diameter standard deviation = 3.5 nm) irrespective of deaeration.[2] Air-protected NPs appear homogeneous without discernible internal structure. Conversely, many air-exposed NPs have an internal void and shell–yolk structures are observed.[11] The insoluble residue consists of nanorods longer and nanopolyhedra larger than 100 nm.[9,12,13] Electron diffraction of air-protected NPs shows rings from Cu metal and Cu_2O. X-Ray powder diffraction (XRD) data provided identification (Fig. 2) and quantification (see Table 1) of the crystalline phases, along with a measure of the crystallite size. In air-protected NPs, only metallic Cu and Cu_2O were detected, with $Cu^0:Cu^I \cong 2$. The size of Cu and Cu_2O crystallites is 9.8 ± 0.6 and 3.8 ± 0.6 nm, respectively. Air-exposed NPs consist mostly of Cu_2O and CuO in similar (atomic) amounts. The crystallite size is 7.1 ± 0.4 nm for Cu and 4.3 ± 0.1 nm for Cu_2O and CuO. X-Ray photoelectron spectroscopy (XPS) provided the composition of the NP surfaces (probed layer thickness ~4 nm, *i.e.*, ~2 nm of oleylamine monolayer and ~2 nm of inorganic core), which are reported in Table 1. Air-protected NPs still contain Cu at the surface, along with Cu_2O and CuO. The surface of air-exposed NPs is made of copper oxides only, with a $Cu^I:Cu^{II}$ ratio close to 3 : 1.

From the above data, one can draw the following conclusions. Air-protected NPs consist of a monocrystalline copper core with diameter ≅10 nm and a polycrystalline, mixed coating of copper metal and copper oxides about 4 nm thick. Air-protected NPs might have a core–shell structure: assuming spherical shape, the 68 : 32 $Cu^0:Cu^I$ atomic ratio would correspond to a 11 nm copper core and a 3 nm thick Cu_2O shell, values close to the observed ones. NPs exposed to air are mostly polycrystalline and consist of Cu_2O and CuO crystallites with diameter ≅4 nm. Some NP still contain a 7-nm metallic core.

In order to gain novel insight about the scope and limitations of catalyzed azide–alkyne cycloadditions, we performed

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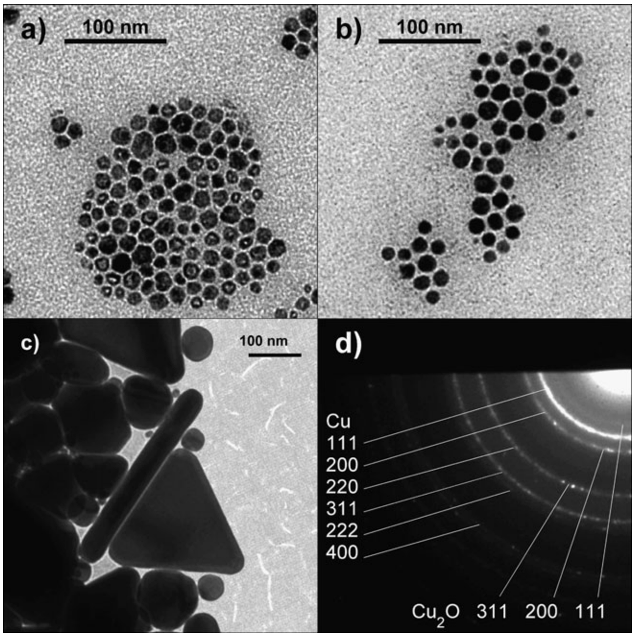
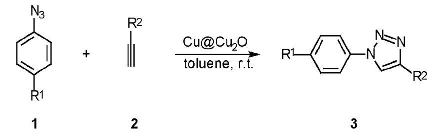


Fig. 1 (a, b, c) TEM images of Cu/Cu-oxide nanoparticles; (a) air-exposed sample; (b) air-protected sample; (c) residue insoluble in toluene. (d) Electron diffraction pattern of air-protected sample.

Table 1 Copper oxidation state in Cu/Cu-oxide nanoparticles (atomic percentage). Surface composition from XPS; total composition from XRD

	NPs protected from air		NPs exposed to air	
	Total	Surface	Total	Surface
Cu^0	68	35	7	—
Cu^I	32	40	48	77
Cu^{II}	—	25	45	23



Entry	a	b	c	d	e	f	g	h	i	j	k
R^1	H	H	H	H	H	H	H	OMe	OMe	NO_2	NO_2
R^2	COOMe	Ph	CH_2OH	CH_2Br	$(CH_2)_4OH$	CH(Ph)OH	CH_2NH_2	COOMe	CH_2OH	COOMe	CH_2OH

Scheme 1 Dipolar cycloadditions between aryl azides **1** and alkynyl dipolarophiles **2**.

reactions between aryl azides **1** and alkynyl dipolarophiles **2** in the presence of mixed Cu/Cu-oxide NPs (Scheme 1). The standard procedure was very simple, requiring the stirring of an equimolecular mixture of the reactants at room temperature in toluene in the presence of catalytic amounts (13–20% in weight with respect to **1**) of air-protected Cu/Cu-oxide NPs. Filtration of the undissolved material, namely the NP catalyst, occurred over a celite pad. Subsequent evaporation of the solvent gave 1-aryl-4-substituted 1,2,3-triazoles **3** as the only regioisomers. Reaction times and product yields are given in Table 2. The structures of products **3** were determined through analytical and spectroscopic methods. In particular, the ^1H NMR spectra show resonances of the proton in the 5-position of the 1,2,3-triazole ring that perfectly agree with literature data.[14]

A number of alkynyl dipolarophiles have been used in reactions with aryl azides bearing substituents with very different electronic demands (Scheme 1). Reaction outcomes are very similar irrespective of R^1 and R^2, as required for a genuine "click" reaction. As can be seen in Table 2, the above cycloadditions are fully regioselective and the reaction times are shorter than uncatalysed reactions[4c] and a recent copper-cluster catalysed example.[8] As expected, internal dipolarophiles 3-hexyn-1-ol and 3-phenyl-2-propyn-1-ol (isomeric to terminal dipolarophiles 6-hexyn-1-ol and 1-phenyl-2-propyn-1-ol, respectively), and dimethyl acetylenedicarboxylate (DMAD) gave no reaction. The reactive behaviour is in agreement with a mechanism involving the formation of Cu^I acetylide species, probably on the NP surface.[5] The presence of coordinated oleylamine on the NP surface might have a beneficial effect on the rate and regioselectivity of the cycloadditions, as already observed for bulky amines.[3b]

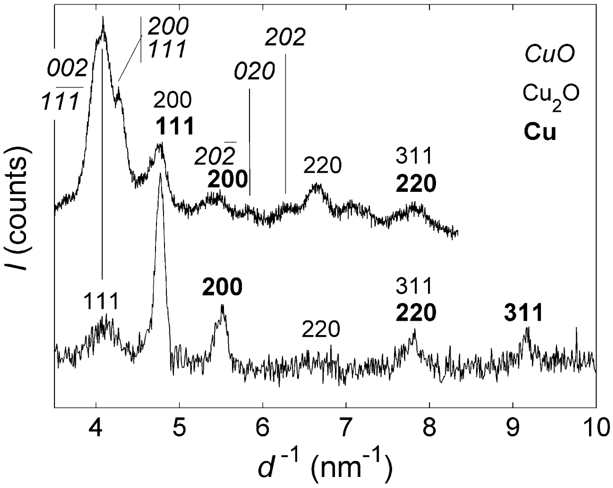


Fig. 2 XRD pattern of Cu/Cu-oxide nanoparticles. Top: air-exposed sample, radiation: CuK_α; bottom: air-protected sample, radiation: MoK_α.

Table 2 Cu/Cu-oxide NP catalysed aryl azide–alkyne cycloadditions

Entry	Product	Time/h	Yield (%)
1	**3a**	3	95
2	**3b**	2.5	>95
3	**3c**	2	>95
4	**3d**	2.5	87
5	**3e**	4	90
6	**3f**	4	>95
7	**3g**	3	89
8	**3h**	2.5	90
9	**3i**	2.5	>95
10	**3j**	4	95
11	**3k**	4	90

In conclusion, we have determined the morphology and the surface and total composition of mixed Cu/Cu-oxide NPs and their dependence on the exposure to air. The NP surface is mostly composed of both Cu^I and Cu^{II} oxide. These NPs efficiently catalyse the azide–alkyne cycloaddition, thus providing a copper oxide nanoparticle-based example which enhances the favourable features of "click" chemistry.[3]

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10 We attempted several variations of the above procedure using oleylamine or oleic acid solutions in benzyl ether as a reaction medium with a lower surfactant : metal molar ratio (down to 10) and extending the time interval at 230 °C up to five days. In all cases, the reaction crude appeared as a clear, light brown solution from which no precipitate could be collected after addition of several volumes of ethanol.

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