

# Cu-Based Nanoalloys in the Base-Free Ullmann Heterocycle-Aryl Ether Synthesis

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## Abstract:

We report the first liquid–liquid Ullmann etherification process mediated not only by oxidatively stable Cu but also by CuZn and CuSn nanoparticle catalysts in conjunction with microwave heating that also avoids the use of solid and expensive bases. Conditions have led to improved turnovers and excellent yields in heteroaromatic Ullmann-type coupling reactions. Further enhancement is achieved upon the addition of 18-crown-6 as a kinetic promoter.

## Introduction

Despite being introduced more than 100 years ago,<sup>1–3</sup> Ullmann-type aryl ether syntheses remain an essential tool for industrial-scale fine chemical synthesis<sup>4–6</sup> and have recently been the subject of review.<sup>7,8</sup> Commensurate with their importance, research efforts have been directed towards tailoring homogeneous catalysts of copper<sup>9–11</sup> and palladium,<sup>12–15</sup> and in this context a better understanding of the ligand effects

influencing catalyst performance has been achieved. Solvents typically employed in these reactions possess strong polar moments. As a result of the work of Strauss,<sup>16</sup> the industrially important solvent DMA has attracted particular attention by virtue of its ability to enhance yields through improved catalyst solubility and decreased energy consumption through selective heating effects when deployed in tandem with microwave heating.<sup>17–19</sup> Hence, the single-mode microwave-assisted synthesis of phenoxy pyridines using chloroheterocycles in conjunction with activated phenols has resulted in higher product yields than were achievable with conventional heating. However, in common with other applications of single-mode microwave-assisted reactions, this setup suffered from the drawback that reactions could only be conducted on a small scale.<sup>20</sup> More recently, efforts have been made to circumvent these limitations of scale in batch-type reactions and also to avoid difficulties associated with the reliable monitoring of reaction temperatures under single-mode microwave irradiation, by deploying multimode microwave apparatus in the synthesis of 4-phenoxy pyridine.<sup>21</sup>

Whilst the deployment of copper-based molecular catalysts in organic synthesis is not new, the employment of nanopar-

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ticulate copper represents a much more recent research trend. Exploitable methods exist for the fabrication of Cu(0),<sup>22–25</sup> CuO and Cu<sub>2</sub>O nanomaterials,<sup>26,27</sup> and applications have been reported in “click” chemistry (in both stirred batch reactor and supported modes)<sup>28</sup> and Suzuki<sup>29</sup> and Sonogashira<sup>30</sup> coupling reactions. Other applications exist in fine chemical synthesis, for example, in the fields of arene–sulfur bond formation in the synthesis of thiophenols (by Cu(0)), and aryl dithiocarbamates, and also in the asymmetric hydrosilylation of ketones (by CuO).<sup>10,31</sup> Further tests have demonstrated the potential of Cu nanoparticles in the reduction of carbonyl compounds and imines, where they achieved yields comparable to those noted using more toxic nickel catalysts.<sup>32</sup> Increases in Fermi potential resulting from particle sizes being in the nanoregime have been invoked to explain the promotion of reactions proceeding, for instance, via radical pathways (e.g., coupling aryl halides and thiophenols).<sup>31</sup>

The potential for synergic effects between metals has led to investigation of the activity of bimetallic nanoparticles in catalysis.<sup>33–36</sup> Hence, ZnO-supported copper has already established itself as a catalyst system in such industrial methanol syntheses as the Haldor–Topsøe process, and considerable effort has been directed towards the elucidation of cooperative

effects between the metals,<sup>37,38</sup> with the presumed formation of reactive CuZn proceeding by highly dynamic behavior of the corresponding alloy phases.<sup>39</sup> In spite of the potential of these systems, bottom-up approaches for the synthesis of CuZn(O) nanocatalysts remain little explored,<sup>40</sup> with a wet-chemical process for colloidal CuZn nanoparticles having been reported in 2003.<sup>39</sup> This development notwithstanding, the thermodynamic instability of organozinc reagents has presented obstacles to the precise control of stoichiometry in CuZn systems.<sup>37,38</sup> In a similar vein, few reports exist detailing preparations, via chemical reduction, of CuSn nanoparticles.<sup>41–43</sup> While Calò et al. have demonstrated the efficiency of bronze alloys as catalysts in the Heck reaction of aryl iodides and activated aryl bromides,<sup>44</sup> Saito and Koizumi reported the use of CuSn in the Ullmann-type synthesis of aromatic nitro compounds.<sup>45</sup> In this latter case, yields of up to 91% were achieved in 3 h. However, as with CuZn, CuSn alloy phases have previously exhibited instability, and this has been seen as being responsible for the leaching of Cu during catalytic tests.<sup>44</sup>

Cu nanocatalysts have previously been deployed in etherification, although this required the use of both expensive and chemically unstable aryl iodide substrates.<sup>46</sup> More recently, practical limitations associated with the oxidative instability of Cu nanoparticles<sup>47</sup> have been overcome by utilizing the stabilizing properties of anti-agglomerants used during the reduction-by-solvent of Cu(OAc)<sub>2</sub> to Cu(0). The resulting nano-Cu exhibited long-term oxidative stability and was employed in the microwave-assisted Ullmann-type ether synthesis of 4-phenoxypyridine from stable chloropyridine salts and unactivated phenol.<sup>21</sup> For this type of Ullmann reaction, oxidatively stable nano-Cu was shown to be more efficient than homogeneous Cu(I) and Cu(II) catalysts, giving superior yields in significantly less time than was previously

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required for comparable systems.<sup>48</sup> We now report the extension of these initial studies to the bimetallic nanocopper systems CuZn and CuSn, demonstrating the potential of bimetallic nanocatalysts for further and significant increases in turnover frequency. Moreover, with the aim of fabricating a continuously operating reactor, it is necessary to avoid the in situ use or generation of solid substrates or byproducts that could otherwise limit process intensification due to process operation failure (e.g., by clogging pipework). Continuous processing is a convenient method for up-scaling, albeit thus far mainly applied in bulk chemical synthesis and far less in fine chemical production. Nevertheless upon up-scaling, continuously operated systems are economically favorable if byproduct formation and reaction times are minimized through chemistry optimization. We have, therefore, sought to enhance the mass transfer properties of the system by obviating the use of a cesium carbonate base for phenol activation<sup>49,50</sup> and by kinetically promoting etherification. We now report liquid–liquid-type Ullmann etherification using copper-based bimetallic nanoparticle catalysts.

## Experimental Section

**Nanoparticle Synthesis and Characterization.** Monometallic Cu(0) nanoparticles were prepared by a literature route.<sup>21</sup> For bimetallic colloids, copper(II) sulfate pentahydrate (0.250 g, 1 mmol) and 0.8 g of poly(*N*-vinylpyrrolidone) (PVP,  $M(\text{average}) = 24000$ ) were added to 120 mL of anhydrous ethylene glycol in a two-necked round-bottom flask. The resulting mixture was heated to 80 °C and stirred for 2 h. The resulting blue solution was cooled to 0 °C. Solutions of zinc(II) chloride (0.136 g, 1 mmol) or tin(II) chloride (0.261 g, 1 mmol) in 2 mL of water (LC–MS grade, resistivity 18.2 MΩ·cm at 25 °C; purified by a Millipore purification system with a combined Jetpore ion-exchange resin, activated carbon and UV irradiation at 185 and 254 nm), and a solution of sodium hypophosphite monohydrate (0.213 g, 2 mmol) in 5 mL of water (LC–MS grade) were added promptly. After adjusting the pH value to 9–11 by adding 5 mL of 1 M NaOH (aq, LC–MS grade), the reaction was stirred for 1 h at 120 °C to yield a yellowish-red colloidal suspension. Aliquots were purified by extracting 50 mL suspensions using excess acetone (~250 mL). After sedimentation of the particles overnight, ~90% of the supernatant was decanted and the remaining suspension centrifuged for 5 min. Upon removal of the acetone layer, the colloidal precipitate was resuspended in 50 mL of DMA. Samples for electron microscopy were prepared by droplet coating of DMA suspensions on carbon holey film-

coated Ni grids and were examined using a JEOL JEM-3011 high-resolution transmission electron microscope at nominal magnifications in the range 300,000–800,000. The exact magnification was previously characterized using images of lattice fringes in large (>10 nm) colloidal gold particles. Electron optical parameters  $C_s = 0.6$  mm,  $C_c = 1.2$  mm, electron energy spread = 1.5 eV, beam divergence semiangle = 1 mrad were used. Mean particle sizes were calculated by counting the diameters of 100 randomly chosen particles in lower magnification images. Data processing and calculation of standard deviation used Origin Pro. 8.0. Elemental composition was elucidated by energy dispersive X-ray emission spectroscopy (nominal beam width = 4 nm) using a Princeton Gamma-Tech prism Si/Li detector and an Avalon 2000 analytical system.

**Synthesis and Characterization of 4-Phenoxy-pyridine.** A baffled glass reactor was loaded with DMA (15 mL) and 4-chloropyridine (6 mmol, equating to 0.4 mol dm<sup>-3</sup>), phenol(ate) (9 mmol, equating to 0.6 mol dm<sup>-3</sup>), and 18-crown-6 (~0.01 equiv with respect to phenolate) as appropriate, were added. The mixture was stirred at 45 °C until complete dissolution occurred. The solution was treated with an appropriate amount of catalyst (1.5 mol % with respect to 4-chloropyridine). The resulting slurry was heated in a microwave device (Milestones Multimode Microwave, type ETHOS 2450 MHz, 2.5 kW) (130–140 °C for 120 min.). Bulk temperatures during the reaction were measured using a fibre-optic probe and an infrared sensor. All reactions were carried out under argon. The yield of 4-phenoxy-pyridine was determined by measuring the <sup>1</sup>H NMR spectra of reaction aliquots against unreacted material. The <sup>1</sup>H NMR spectroscopic data were compared with the literature, as were additional qualitative GC–MS measurements (Shimadzu QP 5000, zebron column ZB35).

## Results and Discussion

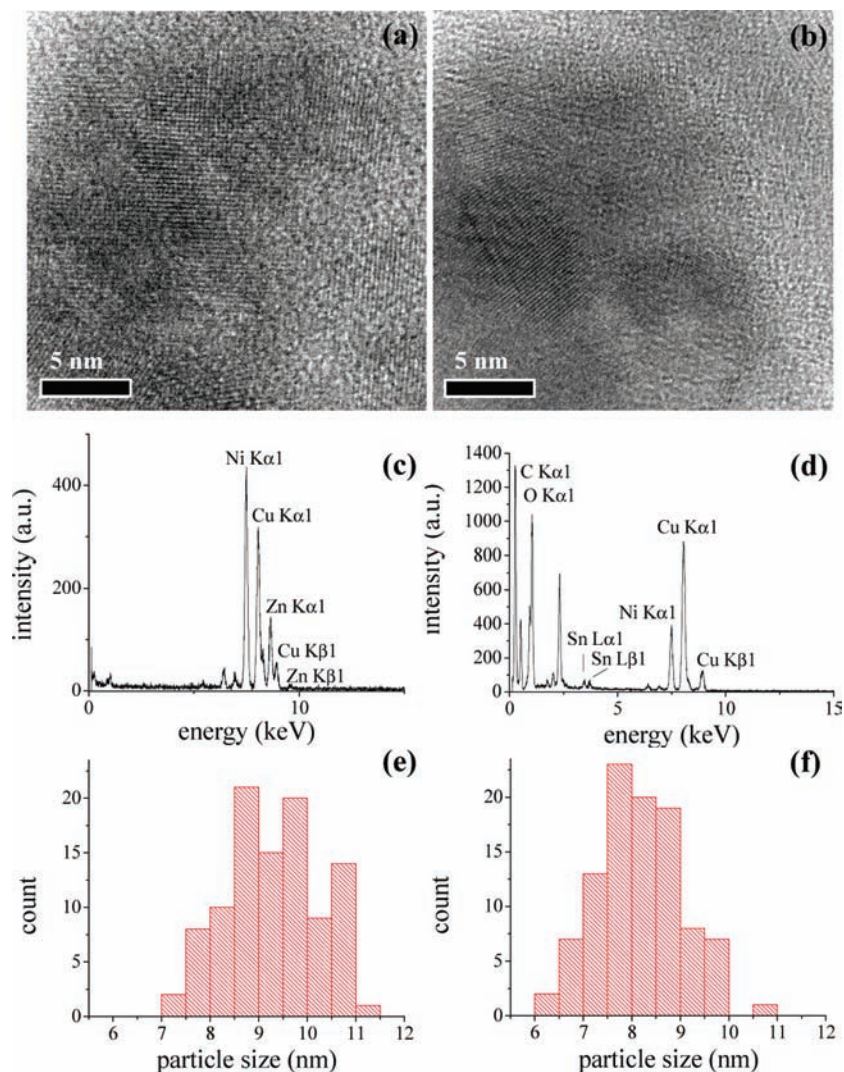
The preparation of oxidatively stable poly(*N*-vinylpyrrolidone) (PVP)-capped Cu nanoparticles from Cu(OAc)<sub>2</sub> has been noted recently,<sup>21</sup> and the adaptability of the reported method is shown by the simplicity with which heterometallic CuM colloids can be targeted. Accordingly, a mixture of copper(II) sulfate pentahydrate and PVP in ethylene glycol was treated with either zinc(II) chloride or tin(II) chloride and thereafter with sodium hypophosphite monohydrate at 0 °C and the pH adjusted to 9–11. A colloidal suspension resulted after 1 h at 120 °C (Figure 1). Using nanostructured Cu(0) and CuM (M = Zn, Sn) in the absence or presence of a crown ether (vide infra) the etherification temperature can be lowered from 140 to 130 °C (Scheme 1) whilst recording yields of up to 90% after 2 h. At temperatures below 115 °C yields decreased considerably, leading to 130 °C being taken as the optimum operational temperature for these nanoalloys. Data are given in Table 1.

Entries 1 and 2 reveal that, in spite of the higher reaction temperature, the use of nano-Cu in conjunction with phenol/Cs<sub>2</sub>CO<sub>3</sub> gives an inferior turnover in comparison to that obtained when potassium phenolate is used instead. Taken together with the need to avoid the

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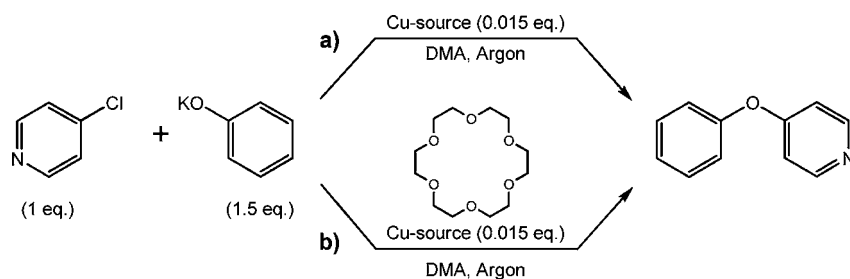
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**Figure 1.** CuZn and CuSn nanoparticles (left and right columns, respectively). Representative HRTEM images (a, b;  $\times 800k$ , respectively), EDS data (c, d; 4 nm beam, C, O, and Ni lines from carrier grid), particle size distributions (e, f; mean sizes  $9.30 \pm 0.94$  nm and  $8.15 \pm 0.88$  nm, respectively).

**Scheme 1.** Ullmann ether synthesis of 4-phenoxyppyridine with and without addition of 18-crown-6<sup>a</sup>



<sup>a</sup> Conditions: microwave heating, 130 °C, batch stirred at 1500 rpm.

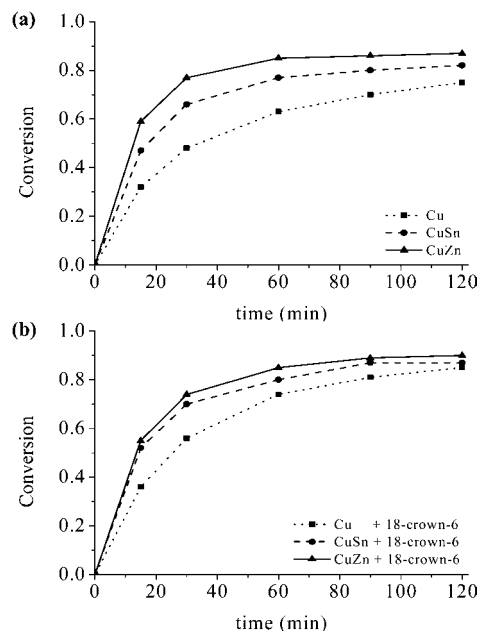
generation of solid deposits (controlling solubility, mass transfer, and ion-exchange mechanisms), this observation led us to focus on base-free conditions. Since the role of  $\text{Cs}_2\text{CO}_3$  is to deprotonate the phenol, affording a naked ion as a nucleophilic substituent in the subsequent  $\text{S}_{\text{N}}\text{Ar}$  reaction, it follows that omission of the base requires the deployment of an activated phenol. In this context, the use of potassium phenolate led to an improvement in yield from 63% (reached after 2 h, entry 1) to 75% (entry 2,

Figure 2a) at reduced temperature. Under the same conditions, heterobimetallic nanocatalysts showed higher conversions. Hence, 4-phenoxyppyridine was formed in 82% yield using nano-CuSn and in 87% yield using nano-CuZn (entries 4 and 6). Noting that equilibrium was reached after 2 h (Figure 2a), we hypothesized that  $\text{K}^+$  deactivated the catalyst over time. This could occur through complexation by the capping agent altering the conformation of the polymer and rendering the catalyst

**Table 1.** Cu(M)-catalyzed formation of 4-phenoxyppyridine

entry	Cu-source <sup>a</sup>	particle size (nm)	additive	T (°C)	time (min)	yield (%) <sup>c</sup>	TOF (s <sup>-1</sup> )
1 <sup>b</sup>	Nano-Cu	9.6	Cs <sub>2</sub> CO <sub>3</sub>	140	120	63	0.02
2 <sup>d</sup>	Nano-Cu	9.6	—	130	120	75	0.04
3 <sup>d</sup>	Nano-Cu	9.6	18-crown-6	130	120	85	0.05
4 <sup>d</sup>	Nano-CuSn	8.2	—	130	120	82	0.11
5 <sup>d</sup>	Nano-CuSn	8.2	18-crown-6	130	120	87	0.12
6 <sup>d</sup>	Nano-CuZn	9.3	—	130	120	87	0.10
7 <sup>d</sup>	Nano-CuZn	9.3	18-crown-6	130	120	90	0.06

<sup>a</sup> 0.015 equiv with respect to 4-chloropyridine. <sup>b</sup> See ref 21. <sup>c</sup> By <sup>1</sup>H NMR spectroscopy. <sup>d</sup> Potassium phenolate used as nucleophile.

**Figure 2.** Conversion vs time in the absence (a) and presence (b) of 18-crown-6.

surface inaccessible to substrate. Alternatively, it is possible that KCl formed during the reaction could not be retained in the solvent phase. To exclude these effects, crown ether was added as a solubilizing agent for both potassium phenolate and KCl. When nano-Cu was tested in the presence of 18-crown-6 (0.01–0.014 equiv relative to phenolate) as a kinetic promoter, the yield of 4-phenoxyppyridine improved from 75% to 85% (entry 3 and Figure 2b). Similar enhancements were noted for the use of nano-CuSn (yield increased to 87%, entry 5) and nano-CuZn (yield increased to 90%, entry 7). We attribute the performance maximum noted for CuZn to a combination of particle ligand-shell effects and intermetallic effects stemming from interaction of the alloying metals. Hence, the coordinative strength of the capping agent (which is dependent on ligand characteristics and particle surface structure) is known to influence substrate access through variations in polymer density (e.g., for Pd colloids<sup>51</sup>). However, whilst intermetallic effects may be important, it should be noted that the alloy phase fluxionality discussed in the Introduction is known to result in segregation of the metals during the reaction, ultimately causing catalyst deactivation.<sup>44</sup>

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This is consistent with our preliminary observations for both bimetallic systems, which in contrast to monometallic copper, rapidly lost their activity. It seems likely that in either case the alloying metal undergoes sacrificial oxidation, with segregation leading to the formation of a zinc/tin oxide shell, as has been noted elsewhere for nanobrass.<sup>52</sup> Detailed further studies that seek to compare pre- and postreaction catalyst surface structures by X-ray photoelectron spectroscopy (XPS) are currently underway.

In conclusion, we have extended recent advances in the field of microwave-assisted etherification with nanoscopic Cu(0)<sup>21</sup> to encompass the copper-based nanoalloys CuSn and CuZn. This has allowed reductions in both reaction time and temperature with respect to the use of slurry-type Ullmann-type etherification reactions employing either commercial Cu(0) or stable Cu nanoparticles.<sup>21</sup> Similarly, excellent selectivity was maintained while improving on previously reported yields for the multimode microwave-assisted synthesis of 4-phenoxyppyridine. Targeting the fabrication of continuous-flow operation as a means of overcoming limits of scale traditionally associated with microwave-assisted transformations, we have successfully eliminated Cs<sub>2</sub>CO<sub>3</sub> without depleting efficiency. This step, whilst it introduces the need for using metal phenolate reagents, avoids the use of an additive that otherwise represents an additional cost and source of processing difficulties. Notably, we have demonstrated kinetic enhancement of the reaction through the application of 18-crown-6 as an alkali metal scavenger. In addition, only 1.5 mol % of nanostructured copper catalyst was needed to obtain yields of up to 90%, whereas previous experiments required the use of as much as 10 mol % of commercial copper or copper-wires. We next aim to marry this research with previous reports of the fabrication of nanocatalyst-supporting fused silica capillary microreactors<sup>53</sup> and so develop the reusability of nano-CuM systems in continuous-flow microreactors. To achieve this, we are supporting CuM colloids on glass beads packed into fused silica capillaries, with the beads providing both the extra surface area required for efficient operation and promising further amplification of the benefits of microwave heating

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through hotspot formation at the catalyst-decorated surface.<sup>54–57</sup> These studies are ongoing and will be reported in due course.

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### Supporting Information Available

Details of catalytic tests, spectroscopic data, nano-CuM synthesis, and characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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