

# Stabilized Naked Sub-nanometric Cu Clusters within a Polymeric Film Catalyze C–N, C–C, C–O, C–S, and C–P Bond-Forming Reactions

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## Supporting Information

**ABSTRACT:** Sub-nanometric Cu clusters formed by endogenous reduction of Cu salts and Cu nanoparticles are active and selective catalysts for C–N, C–C, C–O, C–S, and C–P bond-forming reactions. Sub-nanometric Cu clusters have also been generated within a polymeric film and stored with full stability for months. In this way, they are ready to be used on demand and maintain high activity (TONs up to 10<sup>4</sup>) and selectivity for the above reactions. A potential mechanism for the formation of the sub-nanometric clusters and their electronic nature is presented.



## 1. INTRODUCTION

Catalysis by supported metallic nanoparticles has been performed for many years in academia and industry, and a large number of commercial catalysts base their activity on metal nanoparticles of less than 5 nm.<sup>1</sup> However, the advances made in materials science allow us today to prepare well-defined metal nanoparticles of nanometer or even sub-nanometer size, opening new opportunities in heterogeneous catalysis on metals and oxides.<sup>2,3</sup> It is interesting to notice that catalysis by homogeneous metal catalysts either as transition metal complexes or as metal salts in solution, and heterogeneous catalysis by supported or unsupported metal nanoparticles, have been advancing separately, with little interaction and cross-fertilization. However, we believe that they are just two different sides of the same coin, and new unifying concepts need to be developed to bridging the gap between homogeneous and heterogeneous catalysis.<sup>4</sup>

It has been shown<sup>5–9</sup> for a number of reactions catalyzed by gold and palladium organic complexes and salts that neither the metal complex nor the salt was the active catalytic species, but they decompose to form sub-nanometric clusters with 3–10 atoms which catalyze the reactions with very high turnover frequencies (TOFs) and turnover numbers (TONs). For those same reactions, an induction period is also observed when nanometer-size gold or palladium nanoparticles are used as catalysts, and the reaction starts when the sub-nanometric metal

clusters are formed in the reaction media.<sup>10–12</sup> It appears then that metal clusters formed by a small number of atoms, that expose the specific frontier orbitals of the metal for reactivity, may fill the gap between the single metal atom with organic ligands and the metal nanoparticles. If this is the case, it could be expected that small clusters of non-noble metals, such as Cu, could also present enhanced catalytic properties.

Copper shows unique catalytic activity<sup>13–21</sup> for some cross-coupling reactions, provided that suitable ligands, such as diamines, are added to the reaction medium. These novel Cu-catalyzed cross-coupling reactions have rapidly found implementation in organic synthesis,<sup>22–24</sup> though it would be desirable to decrease the amount of Cu (1–5 mol%) and diamine (5–20 mol%) typically employed for these reactions.<sup>25</sup> Cu cluster complexes have proved to be competent reaction intermediates for these reactions,<sup>16,26</sup> and, despite the fact that different ligand-stabilized Cu clusters and naked Cu clusters have been synthesized,<sup>27–30</sup> the use of well-defined Cu clusters in catalysis is very rare.<sup>31</sup>

In the present work, we will show that Cu clusters with up to 7 Cu atoms, formed in situ by endogeneous reduction, are active and selective catalysts for C–N, C–C, C–O, C–S, and C–P bond-forming reactions. Alternatively, Cu clusters will be

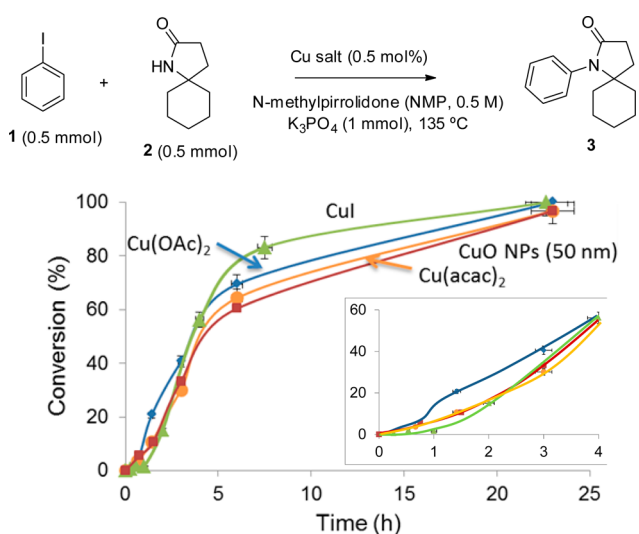
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formed within a polymeric film to be stored for months, keeping high activity and selectivity for the above-named reactions, with TONs up to  $10^4$ . The possible mechanism of formation of the Cu clusters and their chemical nature will be also discussed.

## 2. RESULTS AND DISCUSSION

**C–N, C–C, C–O, C–S, and C–P Cross-Coupling Reactions with in Situ-Formed Sub-nanometric Cu Clusters.** Figure 1 shows the kinetic results for the cross-



**Figure 1.** Kinetic results for the cross-coupling reaction between iodobenzene **1** and amide **2** catalyzed by commercially available Cu compounds at 0.5 mol%: Cu(OAc)<sub>2</sub> (blue diamonds), CuO nanoparticles of 50 nm average size (red squares), Cu(acac)<sub>2</sub> (orange circles), and CuI (green triangles). The inset shows a magnification of the initial points of the curves, where an ~1 h induction time can be observed for all the Cu catalysts tested. The reaction was followed by gas chromatography using dodecane as an external standard after dilution in acetonitrile. Each point is an average of three runs. Error bars are also given.

coupling reaction between iodobenzene **1** and amide **2** (Goldberg reaction) in the presence of Cu(OAc)<sub>2</sub>, Cu(acac)<sub>2</sub>, CuI, or CuO nanoparticles (~50 nm) at 0.5 mol%, under basic conditions in *N*-methylpyrrolidone (NMP) as a solvent. A ~1 h reaction induction time can be observed in all four cases, and, after that, the formation of product **3** starts with a similar reaction rate for all the Cu catalysts employed. The final yield and selectivity to the coupled product was typically >90%, and other bases (K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>) and amide solvents (*N*-dimethylformamide, DMF) proved suitable for the reaction under the present experimental conditions.

Other Cu salts (CuCl, CuBr, CuCN, CuSO<sub>4</sub>, CuBr<sub>2</sub>) gave similar sigmoidal kinetic curves with high yields of product **3** after 24 h. It was possible to achieve high final yields of product **3** with just 0.1 mol% of CuI (see Supporting Information (SI) Figure S1), though the induction period gets longer as the amount of Cu salt decreases. Following the reaction by absorption and emission ultraviolet–visible spectroscopy (UV–vis) with the non-chromophoric 1-iodooctene as a reaction substrate (see SI Figure S2) unveiled that the transition bands corresponding to the Cu salts disappear during the induction time, and new bands corresponding to Cu clusters of 2–7 atoms appear just after the induction time, when the Goldberg

coupling starts and proceeds. Electrospray ionization mass spectrometry (ESI-MS) confirmed the presence of Cu clusters of 2–7 atoms in solution only when the coupling starts, but not during the induction time. These results suggest that Cu clusters of low atomicity are formed during a period that corresponds to the induction time for the Goldberg reaction between iodobenzene **1** and amide **2**.

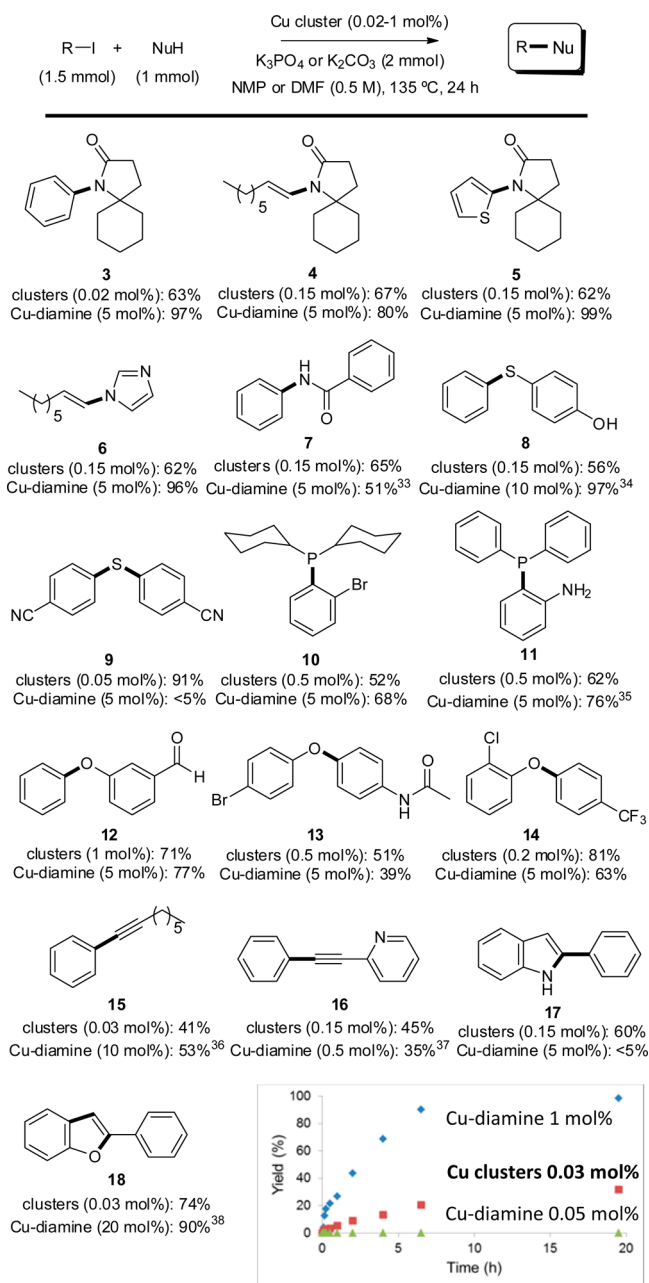
The amount of Cu clusters in solution could be evaluated by the method of Ohno et al.<sup>32</sup> using a sample of well-defined Cu clusters with an average size of 5 atoms (Cu<sub>5</sub>) as a reference (SI Figure S3).<sup>30</sup> The analytical measurements revealed that the efficiency of formation of Cu<sub>5</sub> from CuI is ~3% for any concentration of starting CuI. This means that the amount of Cu clusters in solution for the Goldberg reaction in Figure 1 is 0.003 mol%, the TON being >10<sup>4</sup>.

At this point, the possible scope of the Cu clusters was tested for other C–N, C–C, C–O, C–S, and C–P cross-coupling reactions. The results given in Figure 2 show that a wide array of nucleophiles can be coupled with different aryl iodides under heating conditions in amide solvents, with 0.02–1 mol% Cu clusters in solution. The reactivity of nucleophiles follows the order thiols > phenols > amides ≈ alkynes > imidazoles > phosphines ≫ amines, allowing selective functionalizations. Blank experiments without any Cu gave up to 30% of products in particular cases, but kinetic experiments showed that the Cu-catalyzed reactions ran with at least 2 orders of magnitude higher rates than the thermal reaction and with higher selectivity. Notice that the Cu cluster system can couple thiourea twice (product **9**) and also give directly the one-pot coupling–cyclization reaction to form indoles and benzofurans (products **17** and **18**).

The results obtained for each reaction under typical conditions with diamine ligands, either reported in the literature or obtained here by us, are presented as a reference in Figure 2, and kinetic studies for the Goldberg coupling between **1** and **2** are also included. From the results, it is possible to say that, though the Cu cluster gives a higher TON per atom of active Cu and higher selectivity toward different nucleophiles than the Cu–diamine catalyst, the latter gives higher yields than the cluster and is able to couple the more difficult to react bromo and chloro derivatives. In situ UV–vis measurements during the Cu–diamine-catalyzed reactions did not show any evidence of the presence of Cu clusters, and, as it can be seen in the kinetic curve in Figure 2, no induction time was found. If diamines are added to the Cu cluster-catalyzed reaction before or after the induction period, when the Cu clusters are formed, the outcome of the reaction is not affected.

With all the above data in hand, we can say that the Cu clusters and the Cu–diamine complexes present intrinsic catalytic differences. While the Cu clusters are more active for aryl iodides and have a better reactivity with different nucleophiles under optimized conditions, the Cu–diamine catalyst operates under relatively milder conditions, has a wider functional group tolerance, and is successful for more-demanding reactions. A Hammett plot for different aryl iodides during the Goldberg reaction catalyzed by the Cu cluster (SI Figure S4) shows  $\rho = +0.84$ , which indicates that the activation of the carbon–halide bond by Cu plays a significant role during the coupling as it occurs for the Cu–diamine catalyst.<sup>13,14,16</sup>

**Mechanism of Formation of the Cu Clusters.** *Endogenous Reduction of Cu Salts in Amide Solvents.* The cross-coupling reactions observed when using the amide as a solvent do not occur with solvents such as toluene or dioxane,



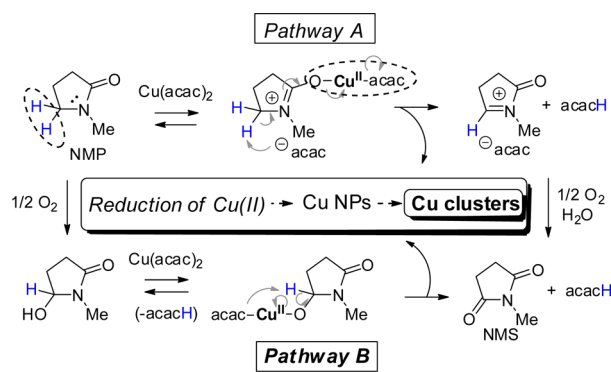
**Figure 2.** Scope of the Cu cluster-catalyzed cross-coupling reactions. Isolated yields are reported, and the new bonds are shown in bold. The Cu clusters are generated in situ from CuI or added within the EVOH polymer (see ahead). For comparison, the values with Cu–diamine catalysts are also given, reaction conditions: substrates (1 mmol), CuI (5–20 mol%), *N,N*-dimethylethylenediamine (10–40 mol%),  $\text{K}_3\text{PO}_4$  (2 mmol), anhydrous toluene or dioxane (0.25 M), nitrogen atmosphere, 110  $^\circ\text{C}$ , 24 h. The inset shows the kinetics for the Goldberg coupling between **1** and **2** under typical reaction conditions for diamine-assisted coupling and the conditions reported here.

even at 135  $^\circ\text{C}$ , unless diamine is added. Furthermore, formation of Cu clusters was not detected in toluene or dioxane by UV–vis spectroscopy. These results indicate that the amide solvent plays an active role in the formation of the clusters, and we have attempted to reveal that role. Thus, when NMP was used as a solvent, *N*-methylsuccinimide (NMS) was found as a product after heating different Cu salts at 135  $^\circ\text{C}$ , and the formation of NMS increased linearly with the amount

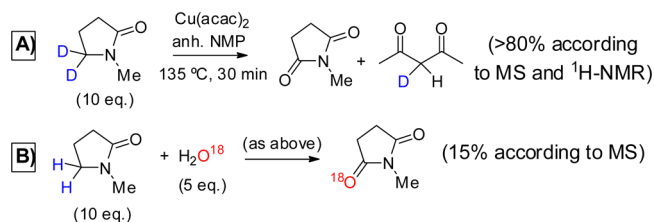
of starting Cu salt. In the case of DMF, gaseous  $\text{CO}_2$  and dimethylamine were found as decomposition products after heating the Cu salts.<sup>39</sup>

Examination of the DMF solution by UV–vis showed the expected Cu clusters, and high-resolution transmission electron microscopy (HR-TEM, see SI Figure S5) also showed Cu nanoparticles of  $\sim 5$  nm in solution. This result indicates that, apparently, both Cu clusters and Cu nanoparticles are formed in the amide solvent when Cu salts are heated. The above observations suggest that the amide solvent can act as a stoichiometric reducing agent for Cu through the hydrogen atoms in the  $\alpha$ -carbon to the nitrogen. In accordance, no Goldberg coupling reaction at all occurs when NMS is used as a solvent.

Figure 3 shows two possible mechanisms for the reduction of  $\text{Cu}(\text{acac})_2$  in NMP under heating. In pathway A, the reduction



#### Isotopic experiments:



**Figure 3.** Proposed mechanism for the endogenous reduction of  $\text{Cu}(\text{acac})_2$  in NMP, and isotopic experiments.

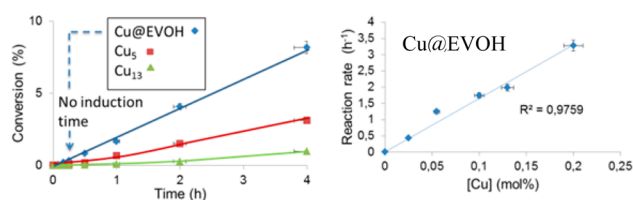
of  $\text{Cu}(\text{acac})_2$  in NMP occurs after coordination of the Lewis acid Cu(II) to the amide oxygen and subsequent H-atom abstraction by the anion.<sup>40</sup> Reductive elimination gives Cu(0) atoms that agglomerate into nanoparticles. In pathway B, the reduction of Cu(II) occurs after spontaneous aerobic oxidation of NMP<sup>23</sup> to the  $\alpha$ -amidoalcohol that then coordinates to Cu(II) and triggers a reductive elimination to form Cu(0) atoms and NMS.<sup>41,42</sup> To check that the H-atom transfer from the amide readily occurs, *S*- $d_2$ -NMP was synthesized<sup>43,44</sup> and heated in the presence of Cu(II) acetylacetonate. Gas chromatography–mass spectrometry (GC-MS) measurements showed the formation of 3-*d*-pentane-2,4-dione, which was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy. Since that product is common to both reaction pathways, a new isotopic experiment was performed with an excess of  $\text{H}_2^{18}\text{O}$  in the reaction medium in order to differentiate between the two pathways in Figure 3. Indeed, the presence or absence of the  $^{18}\text{O}$  atom from labeled water in the final oxidation product NMS can differentiate pathway A from B. GC-MS measurements showed that only 15% of the NMS formed contains  $^{18}\text{O}$ .



Thus, the absence of significant amounts of  $^{18}\text{O}$  isotopic NMS discards, in principle, the hydrolysis of the postulated iminium carbon in pathway A, and it suggests pathway B as the main route for the endogenous reduction of Cu salts to Cu clusters and nanoparticles by the amide solvent under the present heating conditions. Nevertheless, the question remains whether the Cu clusters and nanoparticles form at the expense of each other or they form concomitantly.

**Dissolution of Cu Nanoparticles to Cu Clusters.** When freshly prepared Cu nanoparticles of 5 nm diameter in DMF, free of clusters, were used as catalysts for the Goldberg reaction, a short induction period ( $\sim 15$  min) was still observed, after which small Cu clusters were detected (see Figure S6). This result confirms that the Cu clusters and not the nanoparticles are the true active catalysts for the cross-coupling reaction. Taking into account that any Cu salt gives an induction period of  $\sim 1$  h, which is much longer than the induction period observed when starting the reaction with the nanoparticles, and while it was enough time to form Cu nanoparticles from the different salts, it seems plausible than the Cu clusters are formed at expenses of the nanoparticles. Small Cu nanoparticles may very well melt at  $135\text{ }^\circ\text{C}$  (reaction conditions) to release clusters in an auto-accelerated process, since as the nanoparticle becomes smaller its melting point decreases, providing a thermodynamically plausible explanation for the formation of the clusters.<sup>45–48</sup> In order to assess that the Cu nanoparticles, and no other possible species in solution, are the catalytic precursors of Cu clusters, monodisperse Cu nanoparticles free of Cu salts and clusters were independently prepared by reduction of Cu(I) iodide with  $\text{NaBH}_4$  and stabilized on polyvinylpyrrolidone (PVP) with different particle average sizes (1.5, 3.5, and 5.5 nm, see SI Figure S7 for characterization). When the freshly prepared PVP-stabilized 1.5 nm Cu nanoparticles were used as catalysts for the coupling reaction between iodooctene and either amide 2 or imidazole (see SI Figures S8 and S9), a very short induction time ( $\sim 15$  min) was found, after which the coupling reaction started with initial rates and final yields comparable to those found for the Cu clusters of 2–7 atoms. The induction time was very similar for the larger nanoparticles (15 and 20 min for 3.5 and 5.5 nm average particle size, respectively), with an overall catalytic activity slightly lower than that of the smaller nanoparticles. In situ UV–vis spectroscopy showed that the nanoparticles are partially dissolved in  $<5$  min under the heating conditions to form Cu clusters that catalyze the Goldberg reaction after an additional 15 min induction time. Thus, we can say that Cu clusters are rapidly formed at the expense of the different Cu nanoparticles but that these Cu clusters are not yet the true catalysts of the reaction, since an additional  $\sim 10$  min induction time is still found.

**Nature of the Catalytically Active Copper Clusters.** Well-defined Cu clusters with an average size of 5 atoms ( $\text{Cu}_5$ ) were prepared according to a reported electrochemical method.<sup>30</sup> We expected that these naked  $\text{Cu}_5$  clusters should catalyze the Goldberg reaction, since the UV–vis and ESI-MS characterization of these  $\text{Cu}_5$  clusters correlates well with the clusters formed during reaction (Figure S10). Disappointingly, Figure 4 shows that the electrochemically formed  $\text{Cu}_5$  clusters gave a short but clear induction time of 30 min when used as a catalyst for the Goldberg reaction at 0.05 mol%, which indicates that the electrochemically prepared  $\text{Cu}_5$  clusters are not the true catalysts of the reaction (for the whole kinetics, see SI Figure S11). For the sake of comparison, Cu clusters with an average



**Figure 4.** Left: Initial points of the kinetic curves for the cross-coupling reaction between iodobenzene 1 and amide 2 in the presence of diverse Cu clusters at 0.05 mol%. Right: Linear correlation between the initial reaction rate for the Goldberg reaction and the amount of Cu clusters containing EVOH polymer ( $\text{Cu@EVOH}$ ) used as a catalyst, no induction time was found in any case. The reactions were followed by gas chromatography using dodecane as an external standard after dilution with diethyl ether. Each point is an average of three runs. Error bars are also given.

size of 13 atoms ( $\text{Cu}_{13}$ ) were also prepared electrochemically (see SI Figure S12), and the kinetic results show an induction time of 1 h. Notice that the induction time found with Cu salts at this catalytic amount (0.05 mol%) is  $\sim 4$  h, much longer than for the  $\text{Cu}_5$  and  $\text{Cu}_{13}$  clusters prepared by the electrochemical method. The results indicate that these clusters are similar but not exactly the true catalytic species of the Goldberg reaction, although the atomicity of  $\text{Cu}_5$  fits very well with those clusters formed during the reaction and which were associated with the catalytically active species.

UV–vis measurements showed that the electrochemically prepared  $\text{Cu}_5$  and  $\text{Cu}_{13}$  clusters rearrange during the coupling reaction conditions to give new absorption and emission bands after the induction time, corresponding exclusively to 2–7 atom Cu clusters as it occurs with Cu salts, and then the coupling reaction starts (see SI Figure S13).

Further characterization of  $\text{Cu}_5$  and  $\text{Cu}_{13}$  clusters formed electrochemically was performed in order to gain more insight into the nature of these clusters and their evolution during reaction. Cyclic voltammetry of the  $\text{Cu}_5$  and  $\text{Cu}_{13}$  clusters showed some oxidation and reduction peaks corresponding to Cu(I); zeta-potential measurements of the  $\text{Cu}_5$  and  $\text{Cu}_{13}$  solutions indicate positively charged species (see SI Figure S14A,B); ESI-MS measurements of freshly prepared  $\text{Cu}_5$  and  $\text{Cu}_{13}$  clusters showed the presence of oxygen atoms in the cluster; and X-ray photoelectron spectroscopy (XPS) showed Cu(0) species in the clusters (see SI Figure S14C,D).<sup>49,50</sup> These results indicate that the electrochemically prepared Cu clusters in solution are not only the Cu(0) observed by XPS but also some oxidized form of Cu(I) that, in any case, are not the active catalyst for the coupling since they must rearrange during the induction period.

Concerning Cu nanoparticles, XPS measurements showed that the Cu nanoparticles on PVP contain 30% of Cu(I) oxide already present in the freshly prepared samples. Remarkably, the induction time (15 min) and  $\text{TOF}_0$  ( $45\text{ h}^{-1}$  at 0.2 mol%) found for electrochemically prepared oxidized Cu clusters correlate well with those of dissolved Cu nanoparticles (15–20 min induction time,  $\text{TOF}_0 = 65\text{ h}^{-1}$ ).<sup>51</sup> The dissolution of Cu(I) oxide from Cu nanoparticles was observed some time ago for the Ullmann coupling between iodobenzenes and diarylamines; in fact, it was already proposed by Paine that some common form of Cu(I) ions was formed and could catalyze the reaction, regardless of the starting Cu source for this reaction.<sup>52</sup> Although a direct correlation with the work of

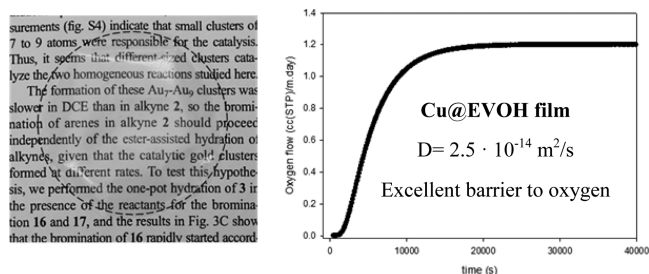
Paine is difficult, the similarities between his conclusions and our results here are striking.

After storage at room temperature without atmospheric protection, the PVP-stabilized Cu nanoparticles showed further oxidation to Cu(I) and then to Cu(II), according to XPS measurements, and the smaller the nanoparticle, the easier the oxidation. While the 5.5 nm (average size) Cu nanoparticles still keep significant amounts of Cu(0) and Cu(I) after 1 day, the 1.5 nm (average size) Cu nanoparticles are nearly fully oxidized. Kinetic results showed a significantly lower catalytic activity for the further oxidized nanoparticles containing Cu(II) (see SI Figures S7–S9), and, in contrast with freshly prepared samples, the catalytic activity of the 1.5 nm PVP-stabilized Cu nanoparticles after 1 day was lower than that of the bigger (3.5 and 5.5 nm) Cu particles. In other words, the higher the amount of Cu(I), the higher the catalytic activity.

With these data in hand, we propose that the catalytically active clusters are not Cu(0) or Cu(II) but some form of deoxygenated Cu(I).

**Synthesis of Deoxygenated Cu(I) Clusters by One-Pot Reduction–Stabilization within an Oxygen-Protective Polymer: The Catalytic Species.** If we consider deoxygenated Cu(I) as the plausible species to catalyze the cross-coupling, an explanation for the induction time found in Figure 4 could be the need to remove the oxygen atoms from the Cu(I) cluster. To check this, we attempted the synthesis of non-oxidized naked Cu clusters of low atomicity outside of the reaction. Deoxygenation of the electrochemically prepared oxide Cu cluster by reducing agents such as citric acid, hydrogen, and NaBH<sub>4</sub> failed, and the direct synthesis of deoxygenated Cu clusters from Cu salts with hydride agents also failed. Thus, we turned our attention to prepare Cu clusters within an oxygen- and water-free environment, in such a way that the Cu(I) clusters could be liberated into the reaction without interacting with oxygen. The strategy involves the following steps: (1) incorporation of a Cu(II) salt within an oxygen-refractive solid material, (2) in situ reduction of the embedded Cu, (3) isolation of the Cu cluster-containing material, and (4) rapid liberation of the Cu clusters into the reaction medium by dissolution of the Cu-containing material to perform the coupling reaction. For that purpose and after much experimentation, we found that ethylene–vinyl alcohol copolymer (EVOH), a well-known polymer that protects against atmospheric oxygen and humidity,<sup>53</sup> was able to carry out the one-pot reduction–polymerization of Cu(NO<sub>3</sub>)<sub>2</sub> using carvacrol as an in situ mild reduction agent. A detailed preparation of the Cu clusters–EVOH film (Cu@EVOH) can be found in the SI (with characterization in Figures S15–S19), and Figure 5 shows a photograph of the obtained film.

The transparent film of Cu@EVOH incorporates Cu quantitatively, and experiments of adsorption of molecular oxygen (see Figure 5) confirm that the new Cu-containing material does not allow oxygen to diffuse easily. The crystallinity of the polymer was not affected by Cu introduction according to infrared measurements, and scanning electron microscopy gives an estimated film thickness of 0.013 mm, in concordance with the results obtained with a digital micrometer. The water adsorption of the material is very low according to the water gain and the water diffusion coefficient value of the EVOH polymer. The film does not change after several months stored in plastic foil. Cyclic voltammetry measurements showed that the inner layers of the polymer contain Cu(I) species, while the external layers contain Cu(II)



**Figure 5.** Left: Photograph of the transparent Cu@EVOH film. The circle marks the area in which the film is present. Right: Evolution of oxygen flow through the developed film under isostatic conditions at 23 °C. From this curve, an oxygen permeability value of  $(4.1 \pm 0.2) \times 10^{-21} \text{ m}^3 \cdot \text{m} / (\text{m}^2 \cdot \text{s} \cdot \text{Pa})$  was estimated. By applying the solution to Fick's law with the boundary conditions of a permeation test, the diffusion coefficient was calculated to be  $2.5 \times 10^{-14} \text{ m}^2/\text{s}$ . This value is in agreement with that reported for an excellent barrier to oxygen.

species.<sup>54</sup> Diffuse reflectance UV–vis spectroscopy of Cu@EVOH showed well-defined bands that correspond to Cu clusters of ~3–5 atoms (absorption at 275–300 nm, emission at 300 nm) and ~10–13 Cu atoms (absorption at 380 nm, emission at 400 nm). No plasmonic Cu bands were found, and, in agreement with this, HR-TEM measurements of the film did not show any visible Cu nanoparticle  $\geq 1 \text{ nm}$ . Quantification by the spectrophotometric method<sup>52</sup> gives 4% of Cu<sub>5</sub> clusters out of the total Cu of the polymer. These results indicate that (1) Cu(II) is reduced within the EVOH polymer to Cu(I) to some extent, (2) Cu(I) clusters are formed and remain stable for months, and (3) much of the starting Cu(II) still remains in the outer part of the polymer. The last point can be due to an incomplete reduction of the starting Cu(II) salt or to a progressive re-oxidation of Cu(I) to Cu(II) in the outer layers of the film that are more exposed to air.

The Cu@EVOH was introduced in DMF at the reaction temperature, and the amount of Cu in solution was followed by ICP-AES over time, while the size of the species in solution was addressed by absorption and emission UV–vis and ESI-MS (see SI Figure S20). We found that the velocity of diffusion of Cu from the polymer to hot DMF is 2 orders of magnitude higher than the reaction coupling, and that the Cu species found in solution kept the same size as within the polymer, i.e., 3–10 atoms. These results confirm that Cu@EVOH rapidly leaches into solution the embedded Cu(I) clusters under reaction conditions. One may then expect that these suitably sized Cu(I) clusters could catalyze the Goldberg reaction without a detectable induction time if they are the catalytically active species. Indeed, Figure 4 shows that the induction time for the coupling reaction between **1** and **2** completely disappears with Cu@EVOH at 0.05 mol% and that a linear correlation between the amount of Cu@EVOH and the initial reaction rate exists. Additionally, a Hammett plot for different iodides with the Cu@EVOH catalyst gives the same value as for the Cu clusters generated in situ from Cu salts (see SI Figure S4). Thus, we can conclude that de-oxygenated Cu(I) clusters of 2–7 atoms are the catalytically active species during the ligand-free Cu-catalyzed Goldberg reaction shown in Figure 1.

### 3. CONCLUSIONS

De-oxygenated Cu(I) clusters of 2–7 atoms catalyze the cross-coupling of iodoaromatics and iodoalkenes with nitrogen, carbon, oxygen, sulfur, and phosphorus nucleophiles with high

efficiency under ligand-free conditions. The clusters are generated either by endogenous reduction of Cu salts in amide solvents to form Cu nanoparticles that then dissolve into Cu clusters, or by dislodging the clusters from PVP-stabilized Cu nanoparticles, or by in situ reduction of Cu salts within an oxygen-protective polymer.

#### 4. EXPERIMENTAL SECTION

**Typical Reaction Procedure.** Tripotassium phosphate (424 mg, 2 mmol) was placed in a 1.5 mL vial equipped with a magnetic stir bar, and anhydrous *N*-methylpyrrolidone or *N*-dimethylformamide (NMP or DMF, 1 mL) was added. The desired amount of the copper iodide, the corresponding halide (1.5 mmol), and the coupling counterpart (1 mmol) were then added. The vial was sealed, and the resulting mixture was placed in a pre-heated oil bath at 135 °C and magnetically stirred. After 24 h, slow addition of dimethyl ether or dichloromethane (5 mL) and water (6 mL), separation of the organic layer, and two extractions of the aqueous layer with dimethyl ether or dichloromethane were carried out before the combined organic layers were dried over MgSO<sub>4</sub> and then filtered. The solvent was removed under vacuum at room temperature, and the residue was purified by flash column chromatography on silica gel to afford the corresponding product. For kinetics, aliquots of 0.05 mL were periodically taken and diluted in acetonitrile or diethyl ether (1 mL) for GC analysis, using dodecane as an external standard. The same aliquots without dodecane were used for UV-vis measurements. Further details can be found in the SI.

**Preparation of Cu@EVOH.** Pellets of EVOH polymer (with ~4% w/w carvacrol) were dissolved in a 1:1 (v:v) mixture of 1-propanol and distilled water at 75 °C. Once dissolved, the mixture was left to cool to room temperature, and Cu(II) nitrate was added in order to obtain a metal loading of 0.031 mmol Cu/g dry polymer. Further details can be found in the SI.

#### ■ ASSOCIATED CONTENT

##### ● Supporting Information

Additional Figures S1–S20, experimental procedures, and compound characterization, including NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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##### Notes

The authors declare no competing financial interest.

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