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Making Copper(0) Nanoparticles in Glycerol: a Straightforward Synthesis for a Multipurpose Catalyst

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Dedicated to the Laboratoire Hétérochimie Fondamentale et Appliquée on the occasion of its 50th anniversary.

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Abstract. Small zero-valent copper nanoparticles (CuNPs) have been straightforward prepared from Cu(I) and Cu(II) precursors in glycerol and in the presence of polyvinylpyrrolidone as stabilizer. Thanks to the negligible vapor pressure of the solvent, these original nano-systems could be directly characterized in glycerol besides solid state, exhibiting relevantly homogeneous colloidal dispersions, also even after catalysis. CuNPs coming from the well-defined coordination complex di-μ-hydroxo-bis[(*N*,*N*,*N'*,*N'*-tetramethylethylenediamine)copper(II)] chloride ([Cu(κ^2-*N*,*N*-TMEDA)(μ-OH)]$_2$Cl$_2$) have been highly efficient in C-C and C-heteroatom bond formation processes. This new catalytic system has proved its performance in C-N couplings and in the synthesis of differently substituted propargylamines through cross-dehydrogenative couplings, multi-component reactions such as A^3 (aldehyde-alkyne-amine) and KA^2 (ketone-alkyne-amine) couplings, as well in the formation of heterocycles such as benzofurans, indolizines, and quinolines under smooth conditions. No significant copper amount was detected in the extracted organic compounds from the catalytic phase by Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES) analyses, proving a highly efficient immobilization of copper nanoparticles in glycerol. From a mechanistic point of view, spectroscopy data (infrared and ultraviolet-visible spectra) agree with a surface-like catalytic reactivity.

Keywords: Copper; Nanoparticles; Glycerol; Multicomponent reactions; C-heteroatom bond formation; Catalyst recycling

Introduction

The use of metal nanoparticles (MNPs) dispersed in a liquid phase for catalytic applications represents an attractive field, because MNPs can be easily tuned on their surface state and in consequence on their reactivity, leading to more versatile catalytic systems. The immobilization of MNPs in a "liquid" support also results in high efficiencies in terms of activity, selectivity, and recyclability, combining the main advantages of classical homogeneous and heterogeneous catalysts.[1,2] In the last years, nano-catalysts prepared from earth-abundant, inexpensive, and often less toxic metals, have incited a great interest in the context of developing more sustainable processes.[3] In this frame, copper turns into an interesting metal from a catalytic point of view, basically because it generates different types of structures (from complexes, chains and coordination polymers to nanoclusters), exhibiting different oxidation states, and accordingly enabling a large panel of reactivity.[4]

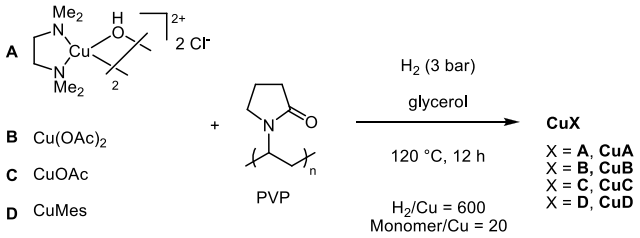
Making C-C and C-heteroatom bonds involving catalyzed multi-component methodologies is an interesting approach, in particular for the synthesis of heterocycles, structures present in a wide variety of compounds showing different biological properties; accordingly, these synthetic approaches become specially valuable in medicinal chemistry.[5] In contrast to palladium, copper generally exhibits a minor versatility and mainly a lesser ability to be efficiently recycled, probably due to its inherent higher reactivity giving inactive species during the catalytic transformations (out-of-the-loop intermediates). With the aim of both stabilizing copper species and immobilizing them in a liquid support, we decided to prepare Cu(0)NPs in glycerol, based on our previous study concerning Cu$_2$ONPs.[6] From a mechanistic point of view, the use of zero-valent copper catalytic precursors permits the generation of oxidized metal species in a controlled way, leading to a more efficient reactivity.

In this work, we have focused on the direct synthesis of Cu(0)NPs in glycerol under dihydrogen

atmosphere in order to avoid the solvent oxidation, using PVP as stabilizing agent. This represents an advantageous methodology for the preparation of Cu(0)NPs because PVP prevents both nanoparticles agglomeration and a strong coordination at the metal surface, thus favoring the catalytic reactivity without poisoning the metal surface. This new nanocatalyst system has been successfully applied in the synthesis of amines including anilines through C-N cross-coupling reactions,[7] the synthesis of propargylamines by direct C-H bond activation *via* cross-dehydrogenative couplings,[8] multi-component A^3 and KA^2 reactions, and tandem A^3-cycloisomerization processes for the synthesis of heterocycles such as benzofurans, indolizines, and quinolines.[9]

Results and Discussion

Synthesis and characterization of Cu(0) nanoparticles. Copper(0) nanoparticles (CuNPs) were prepared following a bottom-up methodology,[6a],[10] by decomposition of Cu(II), $[Cu(\kappa^2\text{-}N,N,N',N'\text{-TMEDA})(\mu\text{-OH})]_2Cl_2$ and $Cu(OAc)_2$ (TMEDA = tetramethylethylenediamine), and Cu(I), Cu(Mes) and Cu(OAc) (Mes = mesityl) metal-based precursors under hydrogen gas atmosphere, in glycerol and in the presence of polyvinylpyrrolidone (PVP) as stabilizer (Scheme 1). In any case, red-purple colloidal solutions were obtained.



Scheme 1. Synthesis of Cu(0) nanoparticles **CuX** (X denotes the metallic copper precursor) in glycerol using PVP as stabilizer.

Except for $Cu(OAc)_2$ (**CuB**), the as-prepared colloidal solutions were constituted by well-dispersed spherical nanoparticles as proven by TEM analyses, recorded from the colloidal solutions, given the negligible vapor pressure of glycerol (Figure 1). The mean diameter of CuNPs was in the range 1.7 - 2.4 nm.

In the absence of PVP, no colloidal systems could be obtained, observing the formation of a red precipitate. Different reaction parameters were optimized, such as temperature (T lower than 120 °C did not permit a full reduction of starting precursors; see Fig. S1 in the Supporting Information), Cu/polymer ratio (no significant differences were observed at different monomer/Cu ratios; see Fig. S2 in the Supporting Information), and H_2/total copper ratio (no significant effect in CuNPs morphology was observed, but an impact in catalysis could be evidenced, see catalysis discussion in the next section). Under these optimized conditions, glycerol did not exhibit hydrogenolysis.[11]

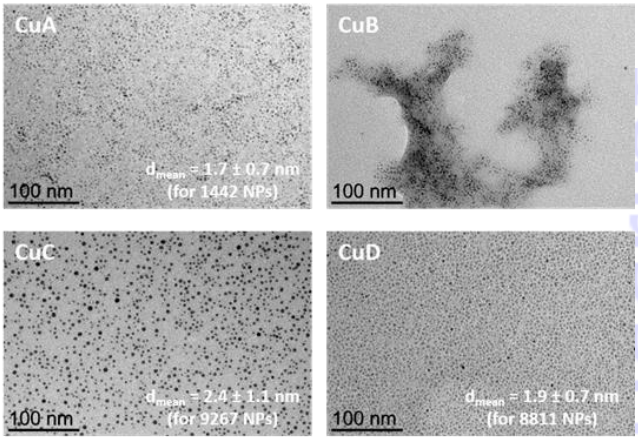


Figure 1. TEM analyses recorded in liquid phase of copper zero-valent nanoparticles dispersed in glycerol, starting from Cu(II) metallic precursors (**CuA**, **CuB**) and from Cu(I) ones (**CuC**, **CuD**).

These colloidal CuNPs in glycerol exhibited a surface plasmon band (SPR) between 578-600 nm in agreement with the formation of small spherical nanoparticles (Figure 2a).[12] **CuA** and **CuD** exhibited absorption bands at lower wavelength due to their relative smaller size. The larger bands observed for **CuA** and **CuC** could be associated to the presence of acetates at the metal surface acting as capping agents and inducing a broader bandwidth.[12a] **CuA** showed lower wavelength adsorption (the smallest NPs) and sharper band, fact that points to a less modified surface, in agreement with a higher catalytic reactivity (see next section). The synthesis of **CuA** was monitored by UV-vis spectroscopy (Figure 2b). The band centered at *ca.* 580 nm appeared after 40 min of reaction, getting the maximum intensity after 1 h of reaction. Then, the band broadened (monitored up to 12 h of reaction), probably due to the capping effect of the solvent. CuNPs in glycerol were stable for several months as proven by TEM and UV-vis analyses (see Fig. S3 for UV-Vis spectrum and TEM in the Supporting Information), only observing a slight increase in the CuNPs size (1.7 nm for freshly prepared **CuA**; 2.0 nm after 60 days of being prepared).

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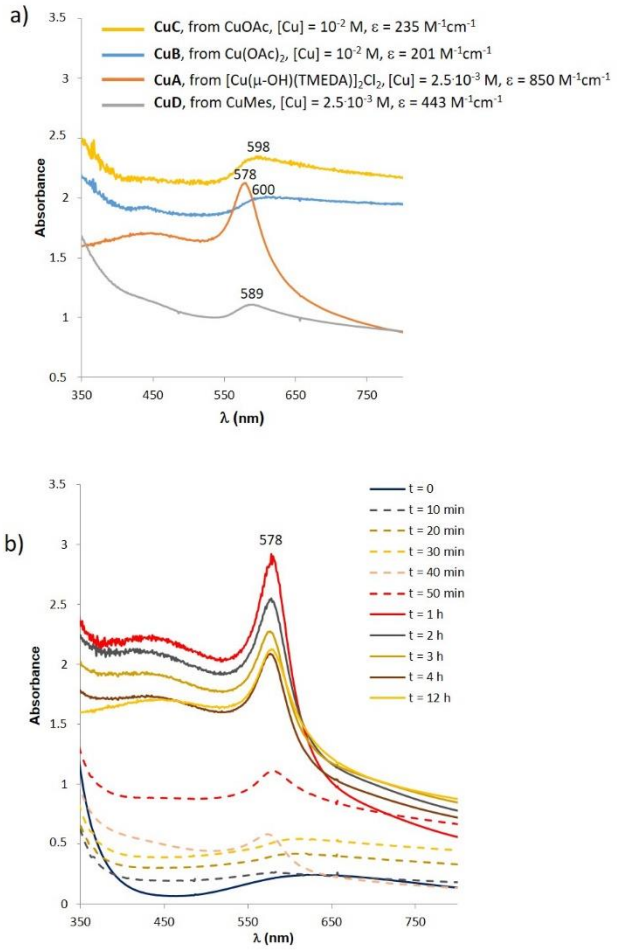


Figure 2. UV-vis analyses for CuNPs in glycerol: a) spectra for as-prepared **CuA**-**CuD** in glycerol; b) spectra corresponding to the monitoring of the synthesis of **CuA** (up to 12 h).

Given the better efficiency in catalysis of the CuNPs synthesized from [Cu(κ²-*N,N,N'N'*-TMEDA)(μ-OH)]$_2$Cl$_2$ (see next section), these CuNPs were selected for a thorough characterization. CuNPs at solid state were isolated by centrifugation from the corresponding glycerol solution (**CuA(s)**). EDX analysis, IR spectrum and elemental analyses of the obtained solid pointed to a stabilizer-free material. Actually, only Cu was detected by EDX and elemental analysis, without observing any significant absorption band in the corresponding IR spectrum (4000 – 400 cm^{-1} region), features that rule out the presence of PVP, TMEDA and copper oxides, Cu_2O and CuO (see Fig. S4 in the Supplementary Information). Powder XRD (see Fig. S5 in the Supporting Information) and HR-TEM (Figure 3a) analyses of **CuA(s)** clearly showed the formation of crystalline zero-valent nanoparticles, exhibiting the expected face-centered cubic structure for bulk copper. XPS data also evidenced the presence of Cu(0) at the metal surface (Figure 3b); comparing with the Cu(II) starting material, we could observe the disappearance of Cu 2p satellites, characteristic feature of Cu(0) materials.[13]

Red powder of **CuA(s)** after being re-dispersed both in acetone and in glycerol exhibited homogeneous spherical nanoparticle dispersions, showing similar mean diameters to that observed directly from the as-prepared **CuA** in glycerol (*i.e.* before centrifugation) (see Fig. S6 in the Supplementary Information). Comparing the SPR band of **CuA(s)** re-dispersed in glycerol with that corresponding to colloidal **CuA** in glycerol freshly synthesized (*i.e.* in the presence of PVP), the wavelength is the same (578 nm) in agreement with the similar nanoparticle mean size in both cases. However, this band was larger for the material in the absence of PVP, probably due to the capping effect of glycerol (coordination to the metal surface) when no other stabilizer is present in the solution (see Fig. S7 in the Supporting Information). In addition, PVP-free **CuA(s)** nanoparticles in glycerol were less stable than those in the presence of polymer, as proven by the copper precipitation observed after two days in solution, in contrast to the high stability observed (over several months) for **CuA** in glycerol stabilized by PVP.

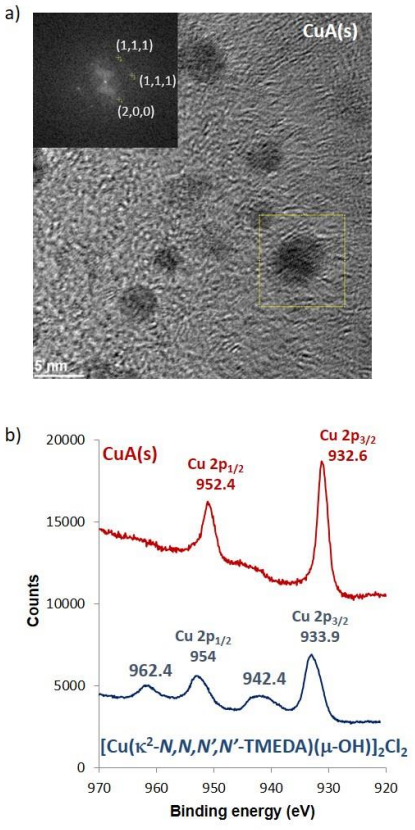


Figure 3. a) HR-TEM micrograph for **CuA(s)**; the crystallographic planes spots observed by Fast Fourier Transform carried out on one selected nanoparticle are inserted; b) High-resolution XPS spectra corresponding to the Cu 2p binding energy region for **CuA(s)** (red trace) and [Cu(κ²-*N,N,N',N'*-TMEDA)(μ-OH)]$_2$Cl$_2$ (blue trace).

Electrochemical studies of **CuA(s)** re-dispersed in glycerol and deposited on a platinum electrode also corroborated the Cu(0) nature of the prepared NPs (Figure 4a and Fig. S8a in the Supplementary Information for the cyclic voltammogram traces of starting materials). Actually, **CuA** exhibited two reversible oxidation waves at +0.14 V and +0.54 V, which can be attributed to the oxidation of Cu(0) to Cu(I) and then Cu(I) to Cu(II) respectively; no reduction processes were observed applying negative potentials (Fig. S8b in the Supplementary Information).[14] At higher scanning rate (1000 $mV.s^{-1}$), only one wave was observed at +0.34 V, attributed to a two electron process (Cu(0) to Cu(II)) (Figure 4b). No accumulation of Cu(0) on the Pt electrode during the analysis was observed.

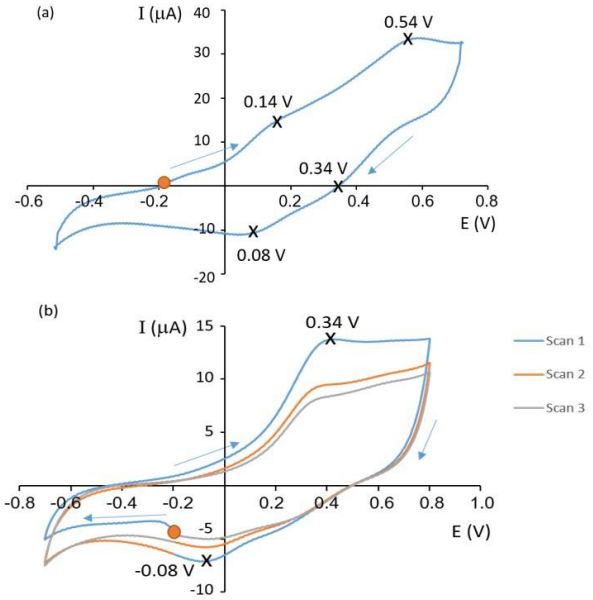
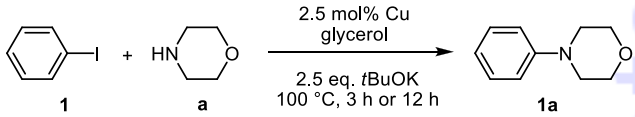


Figure 4. Cyclic voltammetry corresponding to **CuA** in glycerol (platinum electrode, 70 °C, KNO_3 10^{-2} M as reference electrolyte): (a) at scanning rate: 100 $mV.s^{-1}$; (b) at scanning rate: 1000 $mV.s^{-1}$. The orange dots indicate the starting point of the experiment.

CuNPs applied in single step C-N bond formation processes. Transformations involving carbon-nitrogen bond formation represent an important field in catalysis due to the relevance in the synthesis of drugs and natural products.[15] *N*-arylation was firstly described in 1903 by Ullmann involving the coupling between an aryl halide and an aniline derivative catalyzed by an organocuprate complex, under harsh conditions (high temperature and stoichiometric amounts of copper).[16] Since then, many researches have been developed providing new insights in this reaction, in particular by the use of efficient metal-based nano-catalysts exhibiting controlled morphologies.[5a],[7b],[17]

In the present study, we considered the Cu-catalyzed C-N bond formation between iodobenzene and morpholine as the benchmark transformation, with the aim of optimizing the reaction conditions: nature of base, ratio of iodobenzene/base and iodobenzene/morpholine, load of catalyst, temperature and time (see Table S1 in the Supporting Information). We also evaluated the effect of the H_2/total copper ratio in the synthesis of CuNPs (H_2/Cu in the range: 600 – 60), observing irrelevant differences in their morphology (see Fig. S9 in the Supporting Information) and also small effects in catalysis, being the most active system that prepared using the higher H_2/Cu ratio (see Table S2 in the Supporting Information). The best results were obtained using *t*BuOK as a base at 100 °C for 12 h of reaction and 2.5 mol% of **CuA** as catalytic precursor (entry 1, Table 1). It is important to underline that the catalytic system was also active using 1 mol% of total copper (conversion of 60%; entry 9, Table S1). Under these optimized conditions, we analyzed the effect of the other nanocatalysts on this reaction (Table 1). **CuB** was the least active catalytic system (entry 2, Table 1), and **CuC** and **CuD** both provided moderate results at shorter (3 h) and longer (12 h) reaction times (entries 3 and 4 respectively, Table 1). In the absence of copper, no reaction was observed. We also evaluated the activity of the metallic precursors used for the syntheses of CuNPs, showing in general lower activity than the corresponding preformed nanoparticles for short times (see Table S3 in the Supporting Information), and what is more important, these systems could not be recycled.

Table 1. C-N bond formation between iodobenzene and morpholine catalyzed by CuNPs in glycerol.[a)]



Entry	Catalyst	Conversion (%)[b)c)]	Isolated yield (%)[b)]
1	**CuA**	95 (73)	90 (66)
2	**CuB**	47 (<10)	39 (n.d.)
3	**CuC**	81 (67)	77 (59)
4	**CuD**	81 (64)	73 (58)
5	-	n.r.	n.r.

[a)] Results from duplicate experiments. Reaction conditions: 0.4 mmol of iodobenzene, 2.0 mmol of morpholine and 1 mmol of *t*BuOK in glycerol (1 mL, 2.5 mol% total Cu) at 100 °C for 3 h or 12 h. [b)] In brackets, results after 3 h of reaction; n.d. = not determined; n.r. = no reaction. [c)] Determined by GC and GC-MS using *n*-decane as internal standard.

We applied the most efficient catalyst, **CuA**, in the synthesis of different amines and anilines, starting from iodobenzene together with secondary (**a-d**) and

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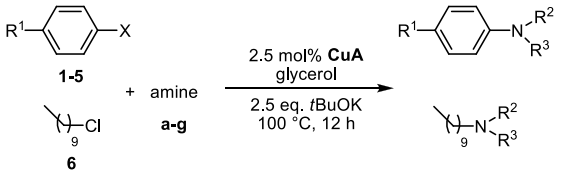
primary (**e, f**) amines, and also ammonia in aqueous solution (**g**), obtaining high isolated yields (entries 1-7, Table 2). Iodo-aryl derivatives (**2-4**) also gave effective couplings (entries 8-12, Table 2), with aryls bearing both electro-donating (**2**; entries 8 and 11, Table 2) and electron-withdrawing (**3, 4**; entries 9-10 and 12, Table 2) substituents. It is noteworthy to mention that **CuA** permitted the chemoselective synthesis of **1g**, **2g** and **3g** (entries 7, 11-12 and 15, Table 2), overriding potentially competing processes between these formed aniline products and iodo-aryl substrates towards *N*-substituted anilines (no reaction was observed using aniline as reagent).[18] Bromo-aryl substrates bearing an electron withdrawing group could be also activated, but using higher copper load (5 mol%) and longer reaction time (24 h) (entries 13-15, Table 2). Unfortunately, bromobenzene and 4-bromoanisole were inactive.

Interestingly, 1-chlorodecane (**6**) was easily activated to give the corresponding *N*-substituted morpholine **6a** in high yield (80%, entry 16, Table 2), which increased with 1-bromodecane as reagent (93% isolated yield); in the absence of catalyst, no reaction took place. Even more important, substrate **6** reacted with NH_3 (aq) to mainly produce the corresponding secondary amine didecylamine (**6g-I**, entry 17, Table 2). Furthermore, using 5 mol% of catalyst, tridecylamine (**6g-II**) was mainly formed (70% of **6g-II** and 25% of **6g-I**; entry 18, Table 2), showing a sustainable way to produce tertiary alkyl-amines in contrast to those reported in the literature involving harsh conditions and hazardous reagents.[19]

The catalytic phase was recycled 5 times without loss of activity for the synthesis of aniline using iodobenzene and NH_3 (aq) as reagents (Figure 5a). The reactions were based on 1 mmol of iodobenzene under the conditions described in Table 2. Copper ICP-AES analyses of the aniline extracted from the catalytic phase indicated a very low metal content (0.03 ppm, after the 1st run; 0.02 ppm, after the 2nd and 5th runs). The activity loss after the 5th run can be associated to the CuNPs size increase (Figure 5b). Comparing the same reactivity with the reported works using CuNPs,[20] **CuA** exhibited a manifest longer lifetime (see Table S4 in the Supporting Information). Using the molecular complex $[Cu(\kappa^2\text{-}N,N,N',N'\text{-TMEDA})(\mu\text{-OH})]_2Cl_2$ as catalytic precursor, the activity dropped after the first run (see Fig. S10 in the Supporting Information).

With the aim of introducing two different *N*-based groups on the same substrate, 1-bromo-4-iodobenzene was successively treated with NH_3 (aq) and morpholine respectively, taking into account that ammonia reacted slower than morpholine towards the activation of C-Br bond. Actually, after 24 h and using 5 mol% of **CuA**, only 30% of benzene-1,4-diamine was formed in contrast to 57% of 4-(4-morpholin-4-yl-phenyl)morpholine obtained under the same conditions (Scheme 2a). The sequential process led to 4-morpholinylaniline in 50% isolated yield (Scheme 2b).

Table 2. Synthesis of amines and anilines catalyzed by **CuA** in glycerol. [a]



Entry	Substrate (R^1, X)	Amine	Product	Conv. (Isolated yield) (%) [b]
1	**1** (H, I)	**a**	**1a**	95 (90)
2	**1** (H, I)	**b**	**1b**	90 (84)
3	**1** (H, I)	**c**	**1c**	78 (69)
4	**1** (H, I)	**d**	**1d**	>99 (94)[c]
5	**1** (H, I)	**e**	**1e**	96 (90)
6	**1** (H, I)	**f**	**1f**	95 (87)
7	**1** (H, I)	NH_3(aq) **g**	**1g**	99 (96)
8	**2** (OMe, I)	**a**	**2a**	98 (96)
9	**3** (NO_2, I)	**a**	**3a**	98 (95)
10	**4** (CN, I)	**a**	**4a**	>99 (92)
11	**2** (OMe, I)	NH_3(aq) **g**	**2g**	>99 (90)
12	**3** (NO_2, I)	NH_3(aq) **g**	**3g**	95 (89)
13	**5** (NO_2, Br)	**a**	**5a**	>99 (92)
14	**5** (NO_2, Br)	**c**	**5c**	91 (86)
15	**5** (NO_2, Br)	NH_3(aq) **g**	**5g**	94 (85)
16	**6** (Cl)	**a**	**6a**	88 (80) >99 (93)[e]
17	**6** (Cl)	NH_3(aq) **g**	$(C_{10}H_{21})_2NH$ **6g-I**	>99 (84)[f]
18	**6** (Cl)	NH_3(aq) **g**	$(C_{10}H_{21})_3N$ **6g-II** $(C_{10}H_{21})_2NH$ **6g-I**	>99 (70/25)[g]

[a] Results from duplicate experiments. Reaction conditions: 0.4 mmol of substrate, *t*BuOK/amine/substrate = 2.5/5/1; in 1 mL of the catalytic glycerol solution of **CuA** (2.5 mol% total Cu) at 100 ºC for 12 h. [b] Conversions determined by GC and GC-MS using *n*-decane as internal standard. [c] Results at 24 h of reaction; after 12 h, 87% conversion. [d] 5 mol% **CuA** and 24 h of reaction. [e] Data using 1-bromodecane as substrate. [f] Less than 10% of tridecylamine was detected. [g] Yields determined by GC: 70% for **6g-II**; 25% for **6g-I.**

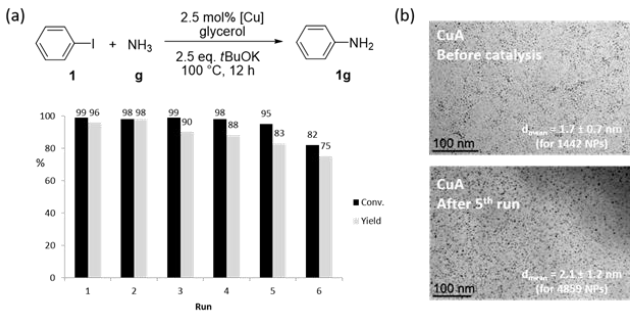
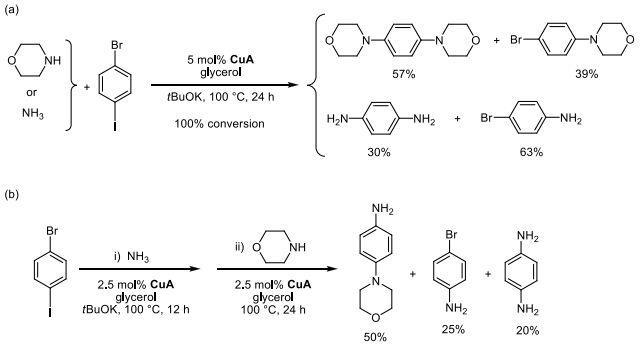


Figure 5. (a) **CuA**-catalyzed the synthesis of aniline by reaction of iodobenzene and ammonia (aqueous solution). Diagram showing the recycling of the catalytic phase; (b) TEM analyses recorded in glycerol of **CuA** before catalysis (top) and after the 5th run (bottom).



Scheme 2. (a) **CuA**-catalyzed C-N bond formation of 1-bromo-4-iodobenzene using independently morpholine and NH_3(aq); (b) **CuA**-catalyzed sequential C-N bond formation using NH_3(aq) and morpholine as *N*-based reagents. Figures indicate isolated yields.

CuNPs applied in the synthesis of propargylamines. Copper has fruitfully proven its ability to form C-C and C-N bonds, in particular for the synthesis of biologically active compounds.[21] Propargylamines stand for crucial intermediates in pharmaceutical and medicinal fields.[22] We applied **CuA** in the synthesis of di- (*via* cross-dehydrogenative coupling of anilines and terminal alkynes), tri- (*via* A^3 coupling), tetra-substituted propargylamines (*via* KA^2 coupling) based on the substitution of carbon atom at α position of the nitrogen moiety (Figure 6), and also in the synthesis of heterocycles through propargylamine intermediates, in particular indolizines, benzofurans, and quinolines.[9a]

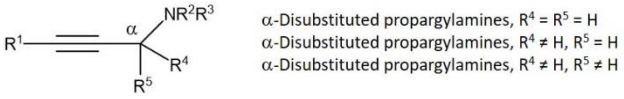


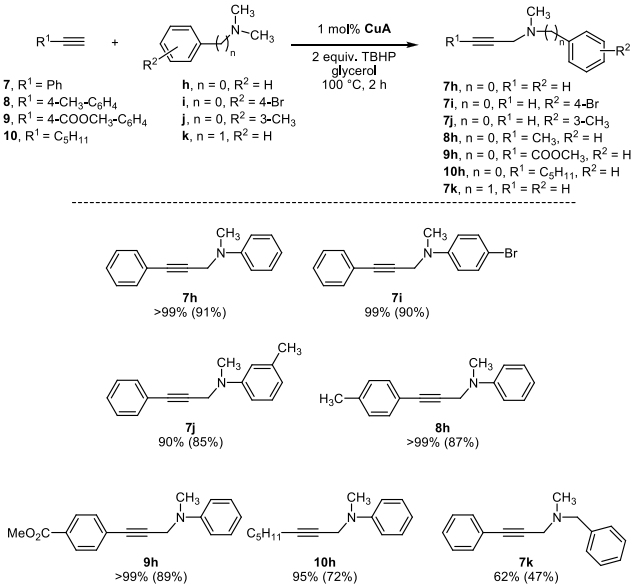
Figure 6. General structure of propargylamines according to the substitution on the carbon atom at α position of the amino group.

CuA catalyzed cross-dehydrogenative coupling. Since the first alkynylation reaction of C_{sp3}-H bonds linked to a nitrogen fragment catalyzed by Cu(I) salts described by Li and co-workers,[23] many other works have been reported requiring relative high metal load and harsh conditions,[8] but only few recent reports involve copper-based nanoparticles,[24] leading to higher catalytic activity in comparison with Cu(I) salts. However, no well-defined Cu(0) nanoparticles have been previously applied in this type of transformation.

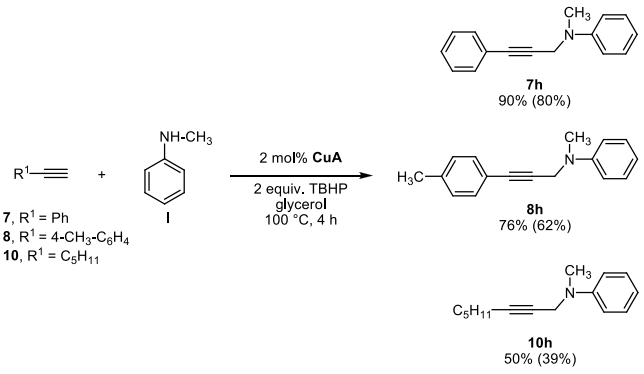
Firstly, we chose the process between phenylacetylene and *N*,*N*-dimethylaniline (**h**) using *tert*-butyl hydroperoxide (TBHP) as oxidant, as benchmark reaction in order to optimize the reaction conditions: temperature, ratio of reagents, nature and load of catalyst, and time (see Table S5 in the Supporting Information). The best results were obtained using 1 mol% of **CuA** as catalytic precursor and 2 equivalents of each TBHP and *N*,*N*-dimethylaniline at 100 °C for 2 h (Scheme 3). Substitution on the aryl fragments on both alkynes (**7-9**) and anilines (**h-j**) did not affect significantly the formation of the corresponding propargylamine (isolated yields > 85% for **7h-7j**, **8h**, and **9h**, Scheme 3). The alkyl-substituted alkyne hept-1-yne was also active, giving 72% of the expected product (**10h**, Scheme 3). Moreover, *N*,*N*-dimethylbenzylamine (**k**) reacted with phenylacetylene, leading exclusively to the propargylamine **7k** without activation of the methylene group. Actually, it is important to highlight that this catalytic system represents the first work reported in the literature using a Cu(0)-based catalyst, giving high conversions under lower catalyst load and/or shorter reaction times than those previously published based on Cu(I) and Cu(II) materials (see Table S6 in the Supporting Information).[23],[24a],[25]

When the mono-substituted *N*-methylaniline **l** was used, higher catalytic load (2 mol%) and longer time (4 h) were required (Scheme 4). **CuA** catalyzed sequential methylation and C-H activation, where TBHP acts as both oxidant and methylating agent, through a plausible single electron transfer mechanism, giving the corresponding *N*-aryl-*N*-

methyl propargylamines **7h**, **8h** and **10h** (Scheme 4). In fact, when catechol (1 equiv.) was added as radical scavenger in the synthesis of **7h**, the reaction did not take place. These results are in agreement with the behavior observed by Phan, Truong *et al*. using copper ferrite nanoparticles, but in our case the reaction proceeded under smoother conditions.[26] However, conversions and yields were significantly lower than those obtained from *N*,*N*-dimethylaniline (**7h**, **8h** and **10h**; see Scheme 3).



Scheme 3. Cross-dehydrogenative coupling reactions catalysed by **CuA** in glycerol. Reaction conditions: 0.5 mmol of alkyne, alkyne/amine/TBHP = 1/2/2; in 0.5 mL of the catalytic glycerol solution of **CuA** (1 mol% total Cu) at 100 °C for 2 h; figures indicate conversions (determined by GC and GC-MS using *n*-dodecane as internal standard); in brackets, isolated yields.



Scheme 4. CuA-catalyzed cross-dehydrogenative coupling reactions, where the oxidant TBHP acts as a methylating agent. Figures indicated conversions (determined by GC and GC-MS using *n*-dodecane as internal standard); in brackets, isolated yields.

CuNPs applied in one-pot multi-component processes A^3 and KA^2. The well-established A^3 coupling reaction of aldehydes, terminal alkynes, and amines offers a direct approach to the synthesis of propargylic amines.[27] However, the related process involving ketones is still a significant challenge and only a few copper-based catalysts are efficient mainly based on Cu(I) catalysts.[28],[29]

We applied **CuA** as catalytic system for the synthesis of propargylamines (Scheme 5 and Table S7 in the Supporting Information). Benzaldehyde (**12**) reacted with morpholine (**a**) and different terminal alkynes, including aromatic (**7**-**9**, **11**) and alkyl (**10**) derivatives, giving high conversions (>84%) towards the exclusive formation of the corresponding A^3 coupling product (A^3**-1** – A^3**-5**, Scheme 5). Other alkyl secondary amines, such as piperidine (**b**) or diethylamine (**m**) along with *N*-benzylmethylamine (**n**), also gave the expected product (A^3**-6** – A^3**-8**, Scheme 5). Furthermore, aromatic aldehydes bearing both electron-donor and electron-withdrawing groups (**13-15**) as well as cyclohexanecarboxaldehyde (**16**), were efficiently coupled (A^3**-9** – A^3**-12**, Scheme 5). The catalytic phase could be recycled up to seven times (each run based on 0.5 mmol of benzaldehyde), without observing significant leaching of copper (< 0.04 ppm determined by ICP-AES) (see Fig. S11 in the Supporting Information).

However, aniline and cyclohexylamine did not lead to the formation of propargylamines, only observing the formation of the corresponding imines (see entries 13-14 in Table S7 in the Supporting Information).

Pursuing our interest in applying one-pot multi-component processes for the synthesis of privileged scaffolds present in natural products and biologically active compounds,[30] we decided to use *ortho*-functionalized benzaldehydes in order to prepare indolizines, benzofurans and quinolines (see Tables S8-S10 in the Supporting Information),[31] by an intramolecular cycloisomerization *via* the formation of a propargylamine intermediate (Figure 7).

We could isolate these types of heterocycles in high yields (>80%): A^3**-13** – A^3**-16** indolizines; A^3**-17** – A^3**-22** benzofurans; and quinolines A^3**-23** – A^3**-24**; for the latter compounds, the reaction was slower and higher copper loading (5 mol%) was required to obtain the desired quinoline derivatives, using morpholine as co catalyst (see Scheme S1 in the Supporting Information).[32]

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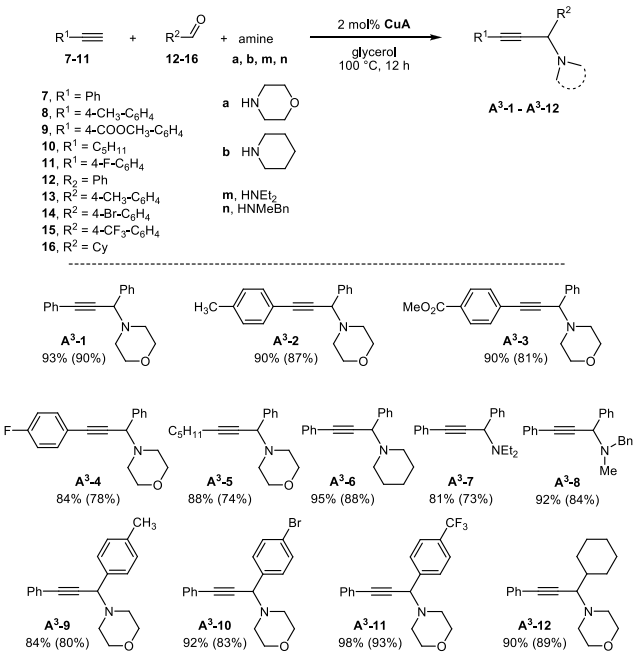


Scheme 5. CuA-catalyzed A^3 coupling in glycerol. Reaction conditions: 0.5 mmol of aldehyde, aldehyde/amine/alkyne = 1/1.2/1.2; in 1 mL of the catalytic glycerol solution of **CuA** (2.5 mol% total Cu) at 100 °C for 12 h; figures indicate conversions (determined by GC and GC-MS using *n*-dodecane as internal standard); in brackets, isolated yields.

In the case of 2,3-disubstituted benzofurans, the addition of *N*,*N*-dimethylaminopyridine (DMAP) was key for the formation of the heterocycle; in its absence, the cyclization did not take place and only the corresponding propargylamine could be obtained, proving that DMAP acts as a Brønsted base to deprotonate the OH group and then favoring the 5-exo-dig cyclization process, without formation of the 6-endo-dig ring closure towards pyran derivatives (see Table S9 in the Supporting Information). When hept-1-yne was used as alkyne, the 2-pentylidene-2,3-dihydrobenzofuran (Z)-**A^3-22** was exclusively obtained in a high yield (see Fig. S12 in the Supporting Information), in contrast to the equimolar mixture of benzofuran and 2-alkylidene-2,3-dihydro-benzofuran formed using CuCN as catalytic precursor.[33]

We also tested the analogous but more challenging process involving ketones, the known multi-component ketone-aldehyde-amine KA^2 process for the synthesis of propargylamines. In contrast to the A^3 processes (Scheme 5), KA^2 reactions required 10 mol% of catalyst and the presence of titanium tetraisopropoxide (TTIP, 10 mol%) in order to promote the formation of the imine intermediate (Scheme 6).[34] Under these conditions, the corresponding cyclohexyl compounds **KA^2-1** – **KA^2-3** from cyclohexanone (**17**) were successfully obtained. Furthermore, **CuA** allowed the formation of the tetrasubstituted propargylamine **KA^2-4** from the acyclic ketone pentan-3-one (**18**), in contrast to the reported systems using Cu(I)- and Cu(II)-NPs.[29c],[35] However, acetophenone could not be activated, even using 1 equivalent of TTIP.

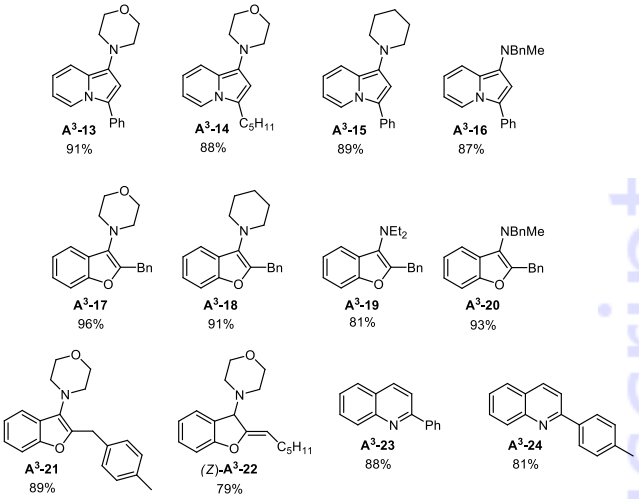
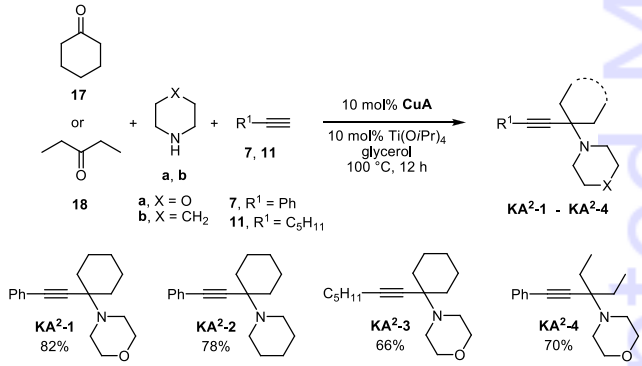


Figure 7. CuA-catalyzed A^3-cycloisomerization tandem processes for the synthesis of indolizines (**A^3-13** – **A^3-16**), benzofurans (**A^3-17** – **A^3-22**), and quinolines (**A^3-23** – **A^3-24**). Figures indicate isolated yields. For reaction conditions, see Tables S8-S10 in the Supporting Information.



Scheme 6. CuA-catalysed KA^2 multi-component processes for the synthesis of propargylamines **KA^2-1** – **KA^2-4**. Figures indicate isolated yields. For reaction conditions, see experimental part.

The most common catalysts reported in the literature involved in A^3 and KA^2 processes, are based on Cu(I) and Cu(II) salts or their corresponding oxides in usual organic solvents; [29a],[35c],[36],[37] only few cases are described under solvent-free conditions (see Tables S11 and S12 in the Supporting Information).[29a],[36e],[37b] To the best of our knowledge, this is the first work using Cu(0)NPs for this type of multi-component reactions, showing the convenience of using glycerol as environmental friendly and efficient solvent.

With the aim of evidencing the plausible formation of molecular copper species, we carried out IR and UV-vis studies starting with both copper(0) nanoparticles and phenylethynylcopper(I) (Figure 8).[38] In the IR region corresponding to the C≡C bond stretching (*ca.* 2100-1900 cm^{-1}), the mixture of **CuA** with phenylacetylene in glycerol showed the formation of a shoulder at *ca.* 2070 cm^{-1}, together with a narrow absorption at 2108 cm^{-1} corresponding to free phenylacetylene in glycerol. After heating the mixture at 100 °C for 2 h, the broad signal increased in intensity together with the apparition of a large band at 1960 cm^{-1}. The relative small shift to lower wavenumbers in relation to the free phenylacetylene ($\Delta\nu$ ~ 30 cm^{-1}, 2108 (free phenylacetylene) *vs* 2070 cm^{-1} (capping phenylacetylene)) points a weak σ–π bonding interaction between C≡C bond and the metal, in agreement with that observed for ruthenium nanoparticles;[39] note that phenylethynylcopper(I) in glycerol shows a narrow band at 1927 cm^{-1} exhibiting a notable shift to lower frequencies ($\Delta\nu$ ~ 180 cm^{-1}), proving the existence of a strong σ–π bonding interaction between Cu(I) and C≡C bond, accordingly to its polymeric structure.[40] Thus, the formation of this type of Cu(I)-based structures did not seem to be formed when CuNPs are involved. UV-vis spectra also evidenced the differences between both types of copper structures (Figure 8b). No change in the position of the SPR band was observed for **CuA** in the presence of phenylacetylene at room temperature; however, this band was larger probably due to the capping effect triggered by the alkyne.[12a] Upon heating (at 100 °C for 2 h), a shoulder appears at *ca.* 460 nm which can be attributed to a charge transfer transition.[40b] The intensity of this absorption notably increased in the presence of morpholine, acting as a base, in relation to the SPR band, preserving the solution a red-orange color, in clear contrast with the behavior of phenylethynylcopper(I) in the presence of morpholine. Actually, the Cu(I) compound in acetone showed two bands at 460 and 400 cm^{-1}, attributed to a charge transfer and intra-ligand π–π* transitions,[41] respectively. However, in the presence of morpholine, both bands disappeared giving quickly a blue solution corresponding to Cu(II) species, as proven by the large band centered on *ca.* 640 cm^{-1} (d-d transition), and a strong absorption band at 350 nm corresponding to phenylacetylene.

With these spectroscopic data, the formation of Cu(I)-based molecular species during the A^3 process catalyzed by **CuA** seems unlikely, in agreement with the insignificant copper leaching observed in the extracted organic compounds (from ICP analyses) and the slight differences in size observed for the CuNPs after catalysis (from TEM analyses). Moreover, for the A^3 coupling among benzaldehyde, morpholine and phenylacetylene, a low Cu leaching was detected at short times (for 48% conversion, 0.04 ppm Cu; for 61% conversion, 0.03 ppm Cu; for 94% conversion, 0.04 ppm Cu). This behavior seems to rule out a homogeneous regime (see Scheme S1 in the Supporting Information). In addition, the stoichiometric reaction among phenylethynylcopper(I), benzaldehyde, and morpholine only gave 55% yield of the corresponding propargylamine (see Scheme S2 in the Supporting Information), in contrast to 90% using **CuA** as catalyst (compound **A^3-1** in Scheme 5), proving the higher ability of phenylethynylcopper(I) to coordinate amines than Cu(0)NPs,[41] and in consequence disfavoring the formation of the iminium species, intermediate leading to the formation of the corresponding propargylamine.

Conclusions

For the first time, small zero-valent copper nanoparticles (d_{mean} = 1.7-2.4 nm) were directly formed in glycerol from reduction of Cu(II) and Cu(I) precursors in the presence of PVP, under low hydrogen gas pressure in order to avoid the glycerol oxidation. CuNPs coming from the reduction of the coordination complex $[Cu(\kappa^2\text{-}N,N,N',N'\text{-TMEDA})(\mu\text{-OH})]_2Cl_2$ were the most active in catalysis and thus chosen for a deep structural study, including TEM and XPS analyses for CuNPs dispersed in glycerol. **CuA** nanoparticles were stable in glycerol for months without showing any sign of agglomeration. It is also important to highlight that CuNPs isolated at the solid state, meaning PVP-free nanoparticles, could be well re-dispersed in glycerol. **CuA** proved to be a robust and versatile catalyst being applied to several kind of reactions (C-N couplings, cross-dehydrogenative couplings, and multi-component aldehyde(ketone)-alkyne-amine processes). Actually, **CuA** was successfully applied in the synthesis of anilines and amines by C-N cross-couplings. It is important to underline the selective synthesis of di- and tri-alkylamines using 1-chlorodecane and aqueous ammonia as reagents, as well as the synthesis of dissymmetrically di-substituted benzenes by two sequential C-N bond formation processes starting from 1-bromo-4-iodobenzene. In addition, A^3 couplings led to the formation of both trisubstituted propargylamines and different types of heterocycles such as indolizines, benzofurans and quinolines, by tandem A^3-cycloisomerization processes using *ortho*-functionalized benzaldehydes as substrates. More challenging KA^2 couplings could also be performed, activating cyclic and also acyclic ketones. The catalytic phase was recycled more than five times preserving the activity, without detecting a significant amount of copper in the extracted organic products. In relation to the catalytic regime, spectroscopy data manifestly point to a surface catalytic reactivity, without formation of molecular Cu(I) species, such as phenylethynylcopper(I) which is poisoned by the presence of amines.

Zero-valent copper nanoparticles in glycerol are currently applied in Cu-catalyzed processes leading

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to targeted compounds interesting for the fine chemistry sector.

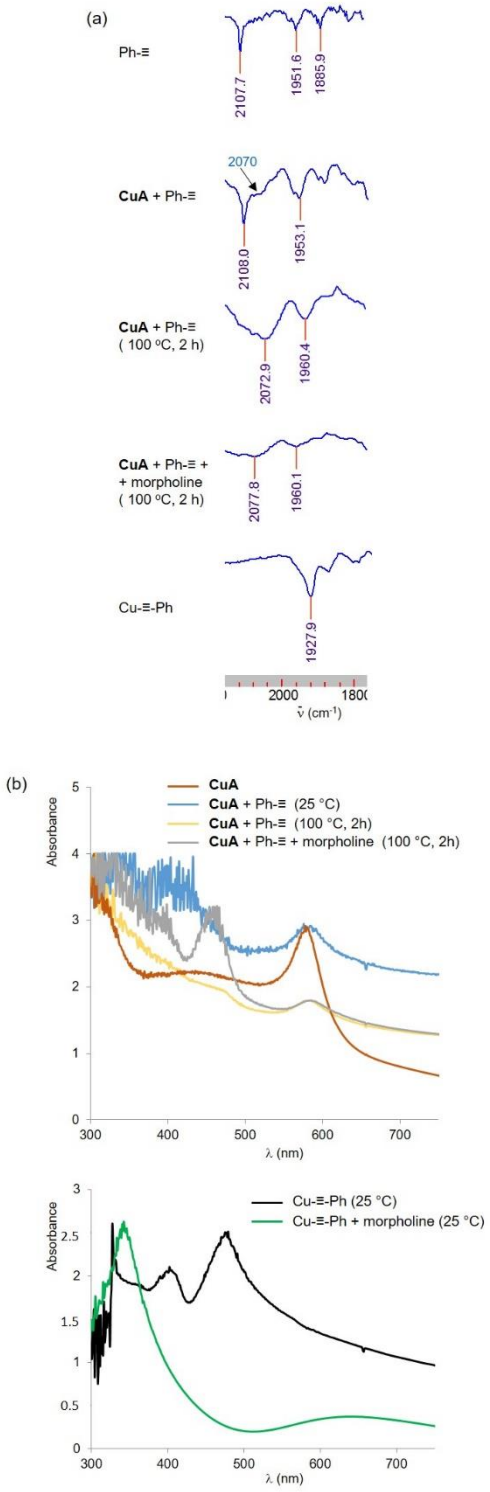

Figure 8. IR (a) and UV-vis spectra (b) corresponding to the analyses of **CuA** and phenylacetylene in glycerol; IR spectra were recorded using KBr plates (deposition of a film of the corresponding mixture between two KBr plates); UV-vis spectra were recorded in glycerol for **CuA** and in acetone for phenylethynylcopper(I).

Experimental Section

Synthesis of CuNPs in glycerol, CuA-CuD. 0.05 mmol of copper precursor (11.6 mg for [Cu(κ^2-*N,N,N',N'*-TMEDA)(μ-OH)]$_2$Cl$_2$; 9.1 mg for Cu(OAc)$_2$; 6.1 mg for CuOAc; 9.1 mg for mesitylcopper(I);) and PVP (Mn = 10,000; 111.1 mg; Cu/monomer = 1/20) were dissolved in degassed glycerol (5 mL) and stirred under argon atmosphere at room temperature in a Fischer-Porter bottle until complete dissolution. The system was then pressurized under 3 bar of H_2 and stirred at 120 °C overnight, resulted in a red-wine colloidal suspension. Copper nanoparticles in the solid state (red powder) were isolated from glycerol solutions by centrifugation at 5000 rpm for 30 min and then decantation.

General procedure for CuNPs-catalyzed C-N bond formation in glycerol. The appropriate aryl halide or alkyl halide (0.4 mmol) and the corresponding primary amine, secondary amine, ammonia aqueous solution (32 wt% in water; 2.0 mmol) and *t*BuOK (1.0 mmol) were added to 1 mL of preformed nanoparticles in glycerol (0.01 mmol of total copper) under argon. The resulting mixture was heated up to 100 °C, stirred for 12 h and then cooled down to room temperature. Organic products were extracted from glycerol using dichloromethane or ethyl acetate (5 x 3 mL) and the solvent was evaporated under vacuum. The product was then purified by short-column chromatography on silica gel. All the products were identified by GC-MS analysis, ^{1}H and ^{13}C NMR spectroscopy.

General procedure for CuNPs-catalyzed sequence process involving two C-N bond steps. 1-bromo-4-iodobenzene (0.4 mmol), ammonia aqueous solution (32 wt% in water; 2.0 mmol) and *t*BuOK (1.0 mmol) were added to 1 mL of preformed nanoparticles in glycerol (0.01 mmol of total copper) under argon. The resulting mixture was heated up to 100 °C, stirred for 12 h and then cooled down to room temperature. The reaction mixture was then maintained under vacuum at 40 °C for 5 min to remove residual ammonia. Morpholine (2.0 mmol) and 1 mL of preformed nanoparticles in glycerol (0.01 mmol of total copper) were then added to the catalytic phase under argon. The resulting mixture was continuously stirred at 100 °C for 24 h and then cooled down to room temperature. Organic products were extracted from glycerol using dichloromethane (5 x 5 mL) and the solvent was evaporated under vacuum. The product was then purified by short-column chromatography on silica gel. All the products were identified by GC-MS analysis, ^{1}H and ^{13}C NMR spectroscopy.

General procedure for CuNPs-catalyzed cross-dehydrogenative coupling reactions in glycerol. Terminal alkyne (0.5 mmol) and the appropriate secondary or tertiary amine (1.0 mmol) and *t*BuOOH aqueous (70 wt.% in water; 1.0 mmol) were added to a pressure-cap tube containing 0.5 mL of preformed nanoparticles in

glycerol (0.005 mmol of total copper). The reaction mixture was stirred at 100 °C for 2 h and then cooled down to room temperature. Organic products were extracted from glycerol using dichloromethane (5 x 3 mL) and the solvent was evaporated under vacuum. The product was then purified by short-column chromatography on silica gel. All the products were identified by GC-MS analysis, ^{1}H and ^{13}C NMR spectroscopy.

General procedure for CuNPs-catalyzed A^3 three-component coupling reactions in glycerol. Aldehyde (0.5 mmol), secondary amine (0.6 mmol) and terminal alkyne (0.6 mmol) were added to 1 mL of preformed nanoparticles in glycerol (0.01 mmol of total copper) under argon. The resulting mixture was refluxed at 100 °C for 12 h and then cooled down to room temperature. Organic products were extracted from glycerol using dichloromethane (5 x 3 mL) and the solvent was evaporated under vacuum. The product was then purified by short-column chromatography on silica gel. All the products were identified by GC-MS analysis, ^{1}H and ^{13}C NMR spectroscopy.

General procedure for CuNPs-catalyzed KA^2 three-component coupling reactions in glycerol. Ketones (0.5 mmol), secondary amine (0.6 mmol), terminal alkyne (0.6 mmol) and titanium isopropoxide (0.05 mmol) were added to 5 mL of preformed nanoparticles in glycerol (0.05 mmol of total copper) under argon. The resulting mixture was refluxed at 100 °C for 12 h and then cooled down to room temperature. Organic products were extracted from glycerol using dichloromethane (10 x 5 mL) and the solvent was evaporated under vacuum. The product was then purified by short-column chromatography on silica gel. All the products were identified by GC-MS analysis, ^{1}H and ^{13}C NMR spectroscopy.

General procedure for recycling of the catalytic phase. After extraction of the organic products, the catalytic phase remaining copper nanoparticles was maintained under vacuum at 80 °C for 1 h and then the corresponding reagents were added to the catalytic phase under argon. The reaction mixture was heated and stirred at the desired temperature for a stipulated time period and then cooled down to room temperature. The products were also extracted, purified, and identified as stated for the previous run.

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FULL PAPER

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