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Cross-Dehydrogenative Coupling of Tertiary Amines and Terminal Alkynes Catalyzed by Copper Nanoparticles on Zeolite

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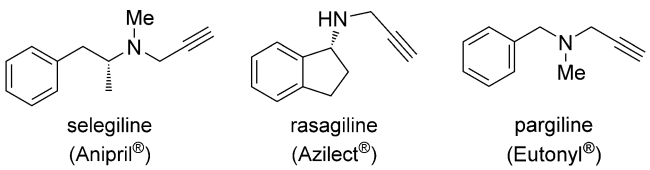
Abstract: A wide range of catalysts based on supported copper nanoparticles have been prepared and tested in the cross-dehydrogenative coupling of tertiary amines and terminal alkynes. Copper nanoparticles on zeolite Y were found to be the most effective catalyst in the presence of *tert*-butyl hydroperoxide as the oxidant. Contrary to the previously reported methodologies involving copper catalysts, reactions have been accomplished without the need of an inert atmosphere and in the absence of solvent, using 1.5 mol% catalyst. A variety of tertiary amines, including aromatic, benzylic and aliphatic ones, have been coupled with both aromatic and aliphatic alkynes to furnish the corresponding propargylamines in moderate-to-excellent yields. The procedure has been successfully scaled-up to 12 mmol with a high conversion (93%). Moreover, the catalyst has been reused in seven cycles maintaining a good performance. Its catalytic activity has been compared with that of an array of commercial copper catalysts, being superior as regards the conversion and minimizing the alkyne homocoupling as a side reaction. The negative filtration test points to a heterogeneous nature of the process. Based on compelling experimental evidence, a novel reaction mechanism has been delineated which outlines the essential role of free radicals and the couple copper(I)/copper(II).

Keywords: alkynes; amines; copper; cross-dehydrogenative coupling; heterogeneous catalysis; nanoparticles; supported catalysts; zeolites

Introduction

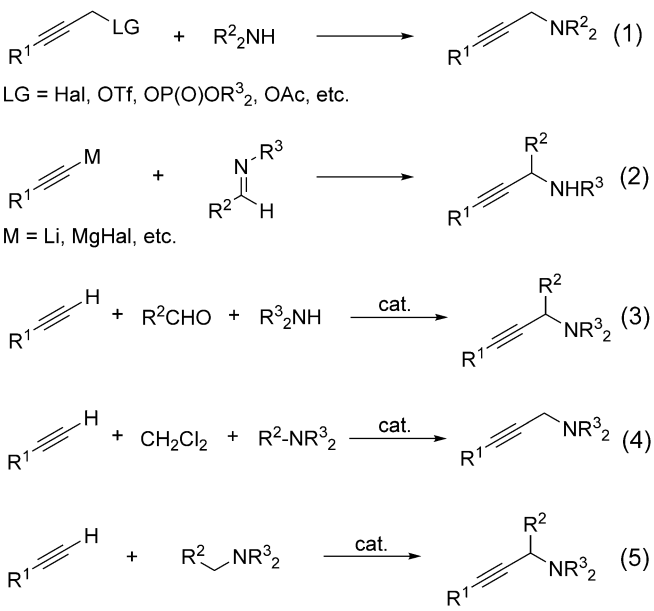
Propargylamines are a versatile class of compounds extensively applied as precursors in the synthesis of heterocyclic compounds such as quinolines,[1a] phenanthrolines,[1b] pyrroles,[1c] pyrrolidines,[1d] indolizines,[1e] or oxazolidinones,[1f] among others.[2] They have also been utilized as intermediates in the total syntheses of some natural and pharmaceutical products.[3] The propargylamine moiety can be found in a variety of bioactive compounds,[4] some of which have been confirmed to be potent anti-apoptotic agents that protect neurons against cell death in cellular and animal models of neurodegenerative disorders. Indeed, they have been shown to delay the necessity for symptomatic therapy in untreated Parkinson's disease patients, results consistent with a neuroprotection role for compounds of this type.[5] For instance, selegiline (Anipril®) and rasagiline (Azilect®) are current propargylamine-containing drugs for monotherapy in patients with early Parkinson's disease and for adjunctive therapy in patients with moderate to advanced disease.[5c] Pargyline (Eutonyl®) is an irreversible inhibitor of monoamine oxidase (MAO) with antihypertensive properties (Figure 1).[5d]

Conventional methods for the formation of the propargylamine moiety include the direct amination



selegiline (Anipril®) rasagiline (Azilect®) pargiline (Eutonyl®)

Figure 1. Some examples of bioactive propargylamines.



Scheme 1. Some general methods for the synthesis of propargylamines.

of propargyl halides,[6a] triflates,[6b] phosphates, or acetates,[6c] or the more widely practiced addition of alkynylmetal reagents to imines [Scheme 1, Eq. (1) and Eq. (2)].[7] The latter approach, normally involving stoichiometric amounts of lithium or magnesium acetylides, requires strict control of the reaction conditions and its application is precluded in the presence of reactive functional groups. More interesting is the metal-catalyzed multicomponent coupling of aldehydes, amines, and alkynes (A^3 coupling)[8] or the nucleophilic substitution of *in-situ* generated chloromethylamines catalyzed by copper or silver [Scheme 1, Eq. (3) and Eq, (4), respectively].[9]

In recent years, the catalytic cross-dehydrogenative coupling (CDC) has emerged as a powerful tool in organic synthesis which enables the construction of carbon-carbon bonds in an atom-economic and efficient manner [Scheme 1, Eq. (5)].[10] In particular, the effective synthesis of propargylamines by CDC of terminal alkynes and tertiary amines, pioneered by Li et al.,[11] has been accomplished under copper,[11,12] iron[13] or zinc[14] catalysis in the presence of an oxidant. Photoredox catalysis with ruthenium complexes is an alternative CDC path when the synthesis of propargylamines derived from tetrahydroisoquinolines is pursued.[15] However, all the aforementioned methodologies are based on homogeneous catalysis, making the recovery and reutilization of the catalyst troublesome. During the development of the present work,[16] reusable copper ferrite and metal-organic framework catalysts have been published for the CDC of terminal alkynes and tertiary amines.[17] Another common feature for the reported methods is the limited substrate scope covered, as well as the presence of an inert atmosphere, generally a requirement under copper catalysis.[11,12]

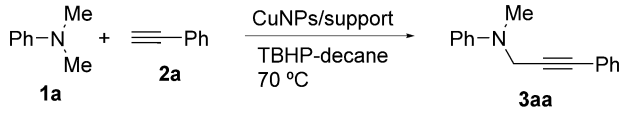
In the last decade, nano-catalysis has been established as a sustainable and competitive alternative to conventional catalysis since the metal nanoparticles possess a high surface-to-volume ratio, which enhances their activity and selectivity, while at the same time maintaining the intrinsic features of a heterogeneous catalyst.[18] Owing to our increasing interest in metal colloids,[19] we have developed some supported copper catalysts with diverse applications in organic synthesis.[20] We wish to present herein a full study on the CDC access to propargylamines, by means of reusable supported copper nanoparticles, without the requisite of an inert atmosphere and under solvent-free conditions; our efforts to clarify the reaction mechanism are also included.

Results and Discussion

Initially, a variety of supported copper catalysts was prepared by addition of the support to a suspension of the freshly prepared copper nanoparticles (CuNPs), with the latter being readily generated from copper(II) chloride, lithium metal and a catalytic amount of DTBB (10 mol%) in THF at room temperature.[21] The as-prepared catalysts were tested in the CDC of *N,N*-dimethylaniline (**1a**) and phenylacetylene (**2a**) as model substrates, using *t*-BuOOH-decane as oxidizing agent[22] (Table 1). A control experiment in the absence of catalyst led to the unchanged starting materials (entry 1). Solvent optimization with activated carbon as support[20c,d] (entries 2–10) allowed us to conclude that the absence of solvent and the presence of an inert atmosphere had a beneficial effect on the conversion (entry 10). Other inorganic supports such as TiO_2, montmorillonite K-10 and zeolite Y exhibited better performance in comparison with activated carbon or MgO, either in the presence or absence of an inert atmosphere (entries 11–18). The conversion attained with these three catalysts could be notably improved by using a slight excess of the alkyne and *t*-BuOOH-H_2O as the oxidant under an argon atmosphere (entries 19–21). However, only Cu on zeolite Y could be effectively reused (entries 19–21, footnotes [f] and [g]). A control experiment with zeolite Y (without Cu) demonstrated the inertness of this support towards the title reaction (entry 22).

Parallel to the above experiments with zeolite Y (ZY) and TBHP-decane, we studied any possible effect of the method of preparation of the catalyst on the outcome of the CDC reaction (Table 2). Three methods were implemented: impregnation (A), reduction-supporting (B, the general method in Table 1) and impregnation-reduction (C), with or without

Table 1. Optimization of the type of support.[a]



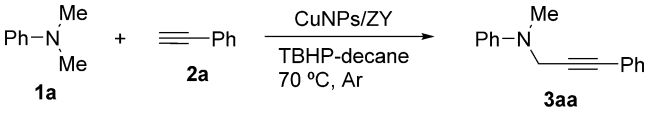
Entry	Support [wt% Cu]	Solvent/ atmosphere	Conv. [%][b]
1	no catalyst	none	0
2	act. carbon[c] [1.4]	MeCN	23
3	act. carbon [1.4]	CH_2Cl_2	0
4	act. carbon [1.4]	MeOH	0
5	act. carbon [1.4]	H_2O	0
6	act. carbon [1.4]	*i*-PrOH	16
7	act. carbon [1.4]	PhMe	0
8	act. carbon [1.4]	THF	0
9	act. carbon [1.4]	none	24
10	act. carbon [1.4]	none/Ar	33
11	TiO_2 [3.0]	none	63
12	TiO_2 [3.0]	none/Ar	53
13	mont K-10[d] [1.8]	none	62
14	mont K-10 [1.8]	none/Ar	67
15	MgO [1.5]	none	43
16	MgO [1.5]	none/Ar	9
17	zeolite Y [3.0]	none	62
18	zeolite Y [3.0]	none/Ar	67
19	TiO_2 [3.0][e]	none/Ar	88 (0)[f]
20	mont K-10 [1.8][e]	none/Ar	92 (63)[f] (0)[g]
21	**zeolite Y [3.0][e]**	**none/Ar**	**89 (91)[f] (93)[g]**
22	zeolite Y [0]	none/Ar	0

[a] **1a** (0.5 mmol), **2a** (0.5 mmol), CuNPs/support (20 mg), *t*-BuOOH-decane (1.0 equiv.), solvent (1 mL), 70 °C, 24 h.
[b] Conversion determined by GLC.
[c] Activated carbon.
[d] Montmorillonite K-10.
[e] **1a** (1.0 mmol), **2a** (1.2 mmol), CuNPs/support (50 mg), *t*-BuOOH-H_2O (1.2 equiv.), 70 °C, 24 h.
[f] Second cycle.
[g] Third cycle.

prior thermal treatment. In general, the presence of water, either in the original zeolite or in the impregnation step, favored the incorporation of copper (Table 2, compare entries 1 and 2 with 3, and 6 with 7). In spite of the fact that method A provided higher conversions, only catalysts prepared by method B could be reused.

Finally, the possibility of performing the CDC without the need of an inert atmosphere was explored by varying the amount of catalyst, and type and amount of TBHP (Table 3). The reactions in TBHP-decane (1.2 equiv.) under Ar showed an interesting trend: the conversion increased when decreasing the amount of catalyst (Table 3, entries 1–4), whereas a larger amount of the oxidant did not exert any significant improvement, either under Ar or air (Table 3, entries 5–7). Careful analysis of the data in Table 3 allows us to conclude that there is a minimum influence in the conversion of both the TBHP solvent and the atmosphere (compare entries 2, 3, and 11 with 9, 8 and 13, respectively). High-to-quantitative conversions were reached when using 2 equiv. of the oxidant (Table 3, entries, 11 and 13–15), even at a lower catalyst loading (entry 15, 0.38 mol%). Therefore, the

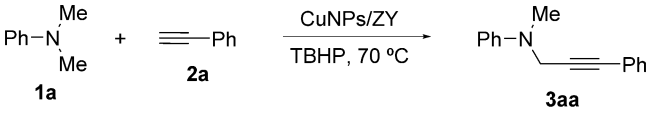
Table 2. Optimization of the method for catalyst preparation.[a]



Entry	Method[b]	[wt% Cu]	Conv. [%][c]
1	**A**-THF/Ar	1.0	86
2	**A**-THF/Ar[d]	2.1	77
3	**A**-H_2O/air	4.4	65
4	**B**-THF/Ar	3.8	69
5	**B**-THF/Ar[d]	3.7	56
6	**C**-THF/Ar[d]	1.7	53
7	**C**-H_2O/air	3.6	48

[a] **1a** (1.0 mmol), **2a** (1.2 mmol), CuNPs/ZY (1.5 mol%), *t*-BuOOH-decane (1.2 equiv.), 70 °C, 20 h, Ar.
[b] Method of preparation of the catalyst: **A**, impregnation; **B**, reduction–supporting; **C**, impregnation–reduction.
[c] Conversion determined by GLC.
[d] ZY was previously dried at 100 °C for 0.5 h.

Table 3. Optimization of the conditions.[a]



Entry	Atmosphere	Catalyst [mg][b]	TBHP (equiv.)[c]	Conv. [%][d]
1	Ar	100	decane (1.2)	38
2	Ar	50	decane (1.2)	69
3	Ar	25	decane (1.2)	80
4	Ar	12.5	decane (1.2)	83
5	Ar	50	decane (2.0)	76
6	air	50	decane (1.2)	67
7	air	50	decane (2.0)	77
8	Ar	25	H_2O (1.2)	76
9	Ar	50	H_2O (1.2)	73
10	Ar	50	H_2O (1.5)	82
11	**Ar**	**50**	**H_2O (2.0)**	**>99**
12	air	50	H_2O (1.2)	84
13	**air**	**50**	**H_2O (2.0)**	**>99**
14	air	25	H_2O (2.0)	91
15	air	12.5	H_2O (2.0)	90

[a] **1a** (1.0 mmol), **2a** (1.2 mmol), CuNPs/ZY, *t*-BuOOH, 70 °C, 20 h.
[b] Prepared by the method **B** (Table 2, entry 4).
[c] 6 M in decane or 80% in H_2O.
[d] Conversion determined by GLC.

conditions in entry 13 were considered as the optimum for the substrate scope study (see below).

The copper-on-zeolite Y catalyst prepared by the method B was characterized by different means. The copper content in the catalysts, *ca.* 3.0–3.8 wt%, was determined by inductively coupled plasma optical emission spectroscopy (ICP-OES). Analysis by TEM revealed the presence of spherical monodisperse nanoparticles ($\sigma = 0.347$) unevenly distributed on the zeolite surface with diameters of *ca.* 1.7 ± 0.7 nm (Figure 2). Energy-dispersive X-ray (EDX) analysis on various regions confirmed the presence of copper,[20a] with energy bands of 8.04, 8.90 keV (K lines) and 0.92 keV (L line) (Figure 3). X-ray diffraction (XRD) and selected area electron diffraction (SAED) analyses mainly showed signals corresponding to zeolite Y (see the Supporting Information).[23a] XPS analysis showed four Cu ($2p_{3/2}$) peaks at 932.6, 934.6, 941.5 and 944.1 eV. These peaks could be assigned to Cu_2O (932.6 eV) and CuO (934.6 eV), with the peaks at 941.5 and 944.1 eV being the satellite shake-up features characteristic of Cu^{2+} species (Figure 4).[23b,c]

With the optimized catalyst and conditions in hand, we next studied the substrate scope (Table 4). First,

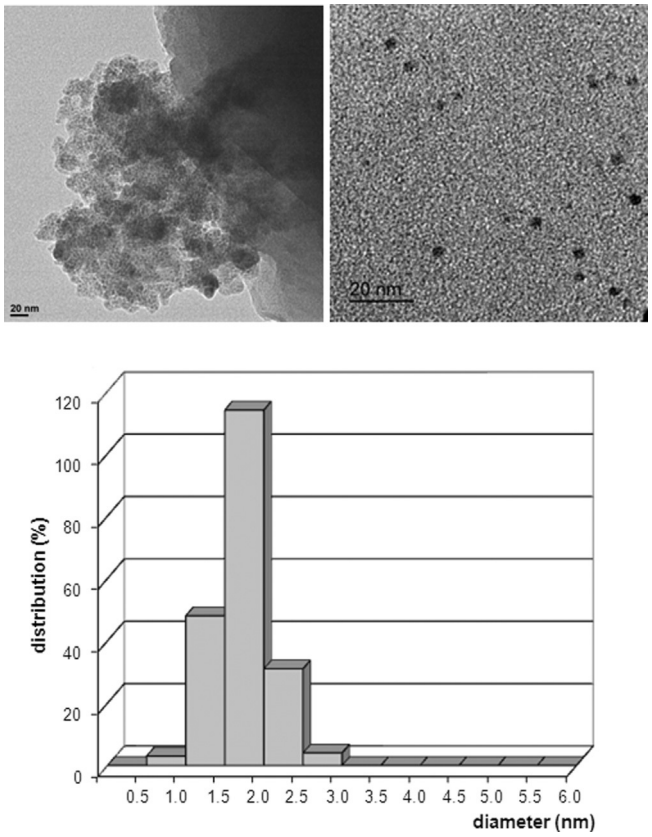


Figure 2. TEM micrograph (*top*) and particle size distribution (*bottom*) of CuNPs/ZY. The sizes were determined for 200 nanoparticles selected at random.

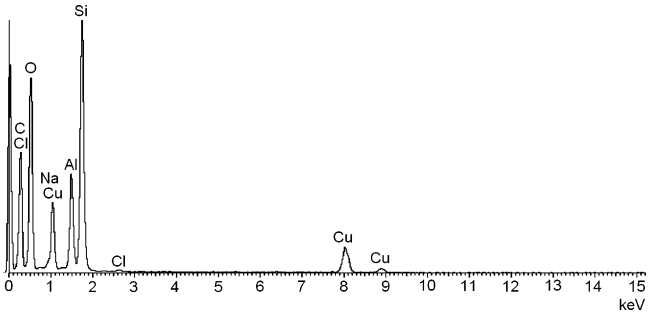


Figure 3. EDX spectrum of CuNPs/ZY.

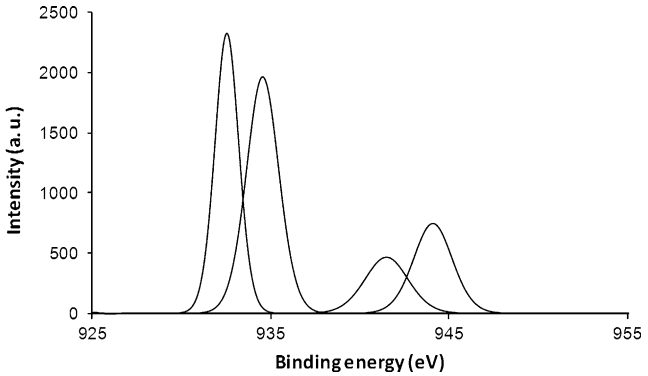


Figure 4. XPS spectrum of CuNPs/ZY at the Cu $2p_{3/2}$ level.

N,N-dimethylaniline was combined with aromatic alkynes bearing either electron-donating or electron-withdrawing groups to give the corresponding products **3aa**–**3ad** in good-to-excellent yields (Table 4, entries 1–4). The method was equally effective for aliphatic alkynes, including alkyl-chain, cyclic and functionalized alkynes (Table 4, entries 5–9). It is noteworthy that the reaction conditions were compatible with the presence of chloro, ester and alcohol functionalities (Table 4, entries 7–9). Then, the electronic character of the starting aniline was changed; electron-donating groups at the *para* position favored the CDC to furnish the propargylamines **3ba** and **3ca** in high yields (Table 4, entries 10 and 11). In contrast, *N,N*-dimethylanilines with electron-withdrawing groups at the *para* position reacted sluggishly, even at 100 °C, affording the expected products **3da** and **3ea** in modest yields (Table 4, entries 12 and 13). This result is not so unexpected if we consider that electron-withdrawing groups at the *para* position can destabilize the intermediate iminium species.

Concerning benzylamines, the coupling of the *N,N*-dimethyl derivatives was highly regioselective, taking place at the methyl group instead of at the benzylic position, in good yields (Table 4, entries 14 and 15). 2-Phenyl-1,2,3,4-tetrahydroisoquinoline gave the expected product **3ha** in moderate yield (Table 4, entry 16). Finally, we must point out that the same

Table 4. CDC of tertiary amines and terminal alkynes catalyzed by CuNPs/ZY.[a]

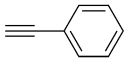
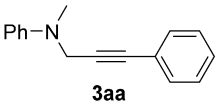
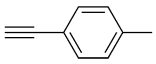
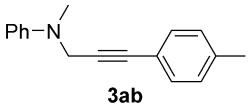
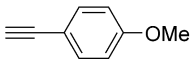
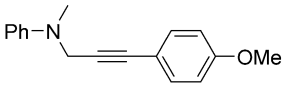
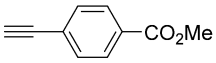
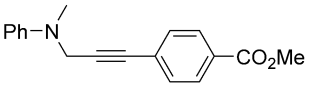
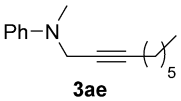
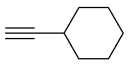
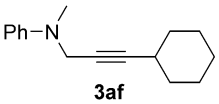
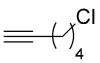
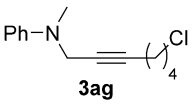
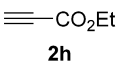
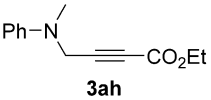
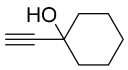
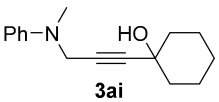
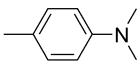
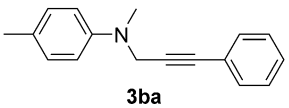
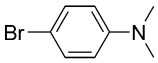
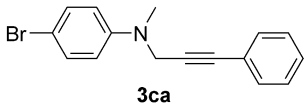
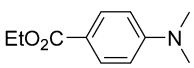
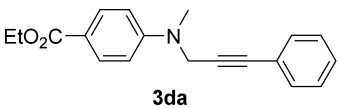
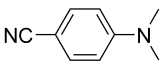
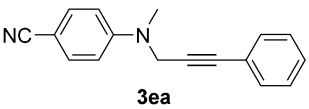
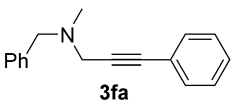
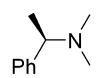
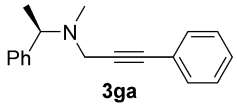
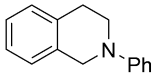
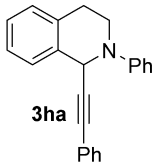
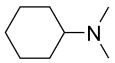
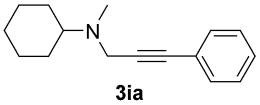
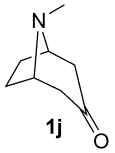
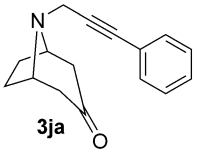
Entry	Amine	Alkyne	Product	Yield [%][b]
1	 **1a**	 **2a**	 **3aa**	98
2	**1a**	 **2b**	 **3ab**	87
3	**1a**	 **2c**	 **3ac**	90
4	**1a**	 **2d**	 **3ad**	73
5	**1a**	 **2e**	 **3ae**	80
6	**1a**	 **2f**	 **3af**	95
7	**1a**	 **2g**	 **3ag**	93
8	**1a**	 **2h**	 **3ah**	86
9	**1a**	 **2i**	 **3ai**	75
10	 **1b**	**2a**	 **3ba**	87[c]
11	 **1c**	**2a**	 **3ca**	90
12	 **1d**	**2a**	 **3da**	43[d]
13	 **1e**	**2a**	 **3ea**	50[d][e]
14	 **1f**	**2a**	 **3fa**	73

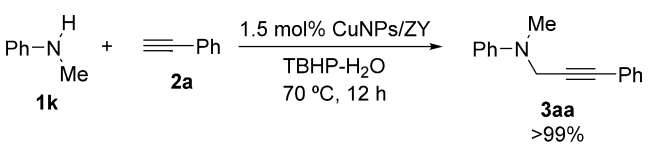
Table 4. (Continued)

Entry	Amine	Alkyne	Product	Yield [%][b]
15	 **1g**	**2a**	 **3ga**	70
16	 **1h**	**2a**	 **3ha**	62
17	 **1i**	**2a**	 **3ia**	95
18	 **1j**	**2a**	 **3ja**	50

[a] **1** (1.0 mmol), **2** (1.2 mmol), CuNPs/ZY (1.5 mol%), *t*-BuOOH-H_2O (2.0 equiv.), 70 °C, 15–20 h.
[b] Isolated yield.
[c] Yield after distillation.
[d] Reaction at 100 °C.
[e] NMR yield.

catalytic system was successfully applied to the CDC of aliphatic amines and alkynes; aliphatic amines are very rarely studied substrates[14] and, in general, copper catalysis in the presence of an oxidant leads to poor yields of the CDC products.[12a] We were delighted to check that the CDC of both *N,N*-dimethylcyclohexylamine (**1i**) and tropinone (**1j**) with phenylacetylene (**2a**) provided the propargylamines **3ia** and **3ja** in excellent and modest yields, by exclusive reaction at the methyl group (Table 4, entries 17 and 18).

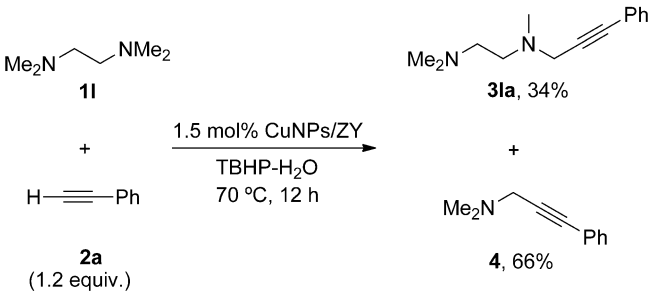
Interestingly, the CDC of the secondary amine *N*-methylaniline (**1k**) with phenylacetylene (**2a**) produced quantitatively the same propargylamine **3aa** as that derived from **1a** (Scheme 2). This methylation–alkynylation process has been recently described by Phan and Truong et al. using copper ferrite (5% $CuFe_2O_4$, DMA, 140 °C)[24a] and a copper MOF (5% catalyst, DMA, 120 °C)[24b] in the presence of TBHP (3 equiv.) as the oxidant under argon.



Scheme 2. CDC of **1k** and **2a** catalyzed by CuNPs/ZY.

Under the same conditions as above but using TMEDA (**1l**) as the tertiary amine, a mixture of monoalkynylated **1l** (**3la**) and aminomethylated **2a** (**4**) was obtained. This result is in agreement with the observations of Li et al.,[25] namely: TBHP favored the formation of **4** *versus* **3la**, contrary to what is observed with molecular oxygen (Scheme 3).

It is worthwhile mentioning that all the CDC reactions were carried out without air exclusion. In addition, the catalyst could be easily recovered by centrifugation and reutilized, leading to propargylamine **3aa** in high yield over seven consecutive cycles (Figure 5). Furthermore, the standard procedure was successfully scaled-up to 12 mmol, giving rise to the



Scheme 3. CDC of **1l** and **2a** catalyzed by CuNPs/ZY.

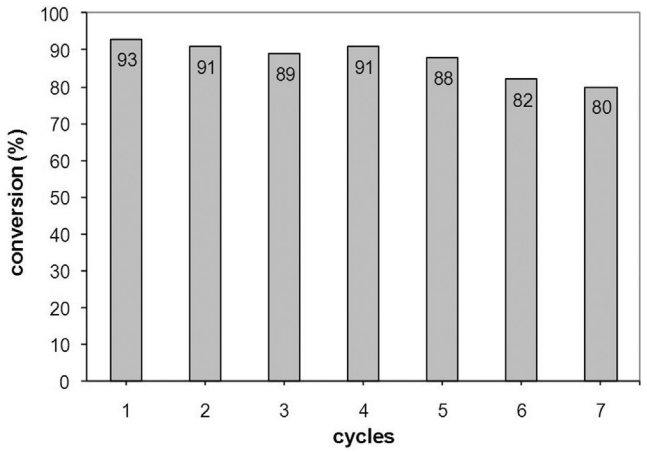


Figure 5. Recycling of CuNPs/ZY in the synthesis of **3aa**.

product in 93% conversion at 1.5 mol% catalyst loading and 67% at 0.38 mol%. The kinetic profile for the CDC of **1a** and **2a** at 12 mmol scale shows an induction period of *ca.* 1 h (Figure 6).

In order to unveil the nature of the catalysis, the standard reaction of **1a** and **2a** was run up to a 5% conversion. Then, the catalyst was filtered and the resulting filtrate was subjected to additional heating at 70 °C for 12 h; the original conversion remained constant (5%). The negligible amount of copper (0.78 ppb) detected by ICP-MS analysis of a filtrate sample, confirmed the absence of leaching and points to a heterogeneous nature of the process. The likelihood of the catalyst acting as a reservoir for metal species that leach into solution and readsorb cannot be fully rejected.[26] However, recently, Scaiano et al. combined standard bench-scale techniques with single-molecule spectroscopy to monitor the CuNP-catalyzed azide-alkyne cycloaddition (which also involves copper acetylides) and proved that catalysis occurs at the surface of the CuNPs.[27]

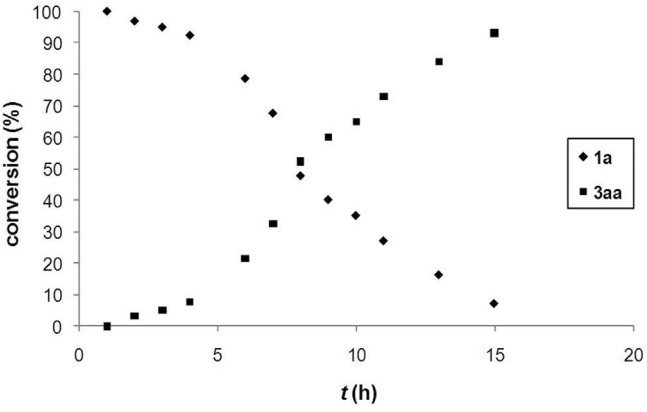
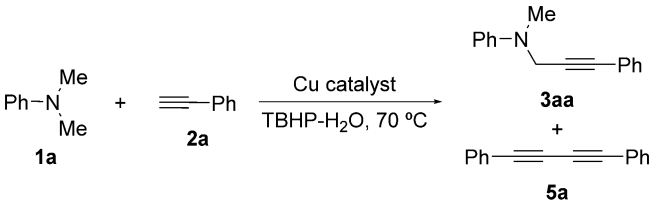


Figure 6. Plot showing the evolution of the CDC of **1a** and **2a** at 12 mmol scale (standard conditions, 1.5 mol% CuNPs/ZY).

We next compared the CuNPs/ZY catalyst with some commercially available copper catalysts in the standard reaction of *N,N*-dimethylaniline (**1a**) and phenylacetylene (**2a**) at 1–10 mol% catalyst loading (Table 5 and Figure 7). CuCl (10 mol%), CuBr (10 mol%) and CuBr·SMe_2 (2 mol%) gave the highest conversions into **3aa** (Table 5, entries 4, 6 and 14). All the other commercial catalysts led to substantial amounts of the by-product 1,4-diphenylbuta-1,3-diyne (**5a**), resulting from the alkyne homocoupling.[28] The CuNPs/ZY catalyst was found to be distinctly superior, reaching the highest conversion without producing the undesired diyne (Table 5, entry 16). Therefore, the nanosized character of the catalyst seems to be fundamental.

There has been much debate around the mechanism of the CDC, particularly concerning the radical or ionic generation of the intermediate iminium ion.[11d,29] A series of control experiments were conducted, including the use of radical scavengers, in order to gain an insight into the reaction mechanism (Table 6). Among the different radical traps tested, 2,6-di-*tert*-butylphenol and, more markedly, TEMPO inhibited considerably the CDC, with the concomitant formation of 2,6-di-*tert*-butylanisole (*ca.* 40%) and 1-methoxy-2,2,6,6-tetramethylpiperidine (*ca.* 75%), re-

Table 5. CDC of **1a** and **2a** catalyzed by commercial Cu catalysts.[a]



Entry	Catalyst	mol [%]	**1a**/**3aa**/**5a** [%][b]
1	Cu(0)	10	37/50/13
2	Cu_2O	10	22/53/25
3	CuO	10	93/5/2
4	CuCl	10	11/74/15
5	$CuCl_2$	10	11/39/50
6	CuBr	10	14/79/7
7	CuI	10	12/68/20
8	$Cu(OAc)_2$	10	26/61/13
9	CuBr·SMe_2	10	27/67/6
10	$Cu(OTf)_2$	10	44/40/16
11	CuBr	1	50/42/8
12	CuI	1	24/62/14
13	$Cu(OAc)_2$	2	17/59/24
14	CuBr·SMe_2	2	20/75/5
15	$Cu(OTf)_2$	2	24/56/20
16	**CuNPs/ZY**	**1.5**	**0/>99/0**

[a] **1a** (1.0 mmol), **2a** (1.2 mmol), Cu catalyst, *t*-BuOOH-H_2O (2.0 equiv.), 70 °C, 24 h, in air.
[b] The ratio was determined by GLC.

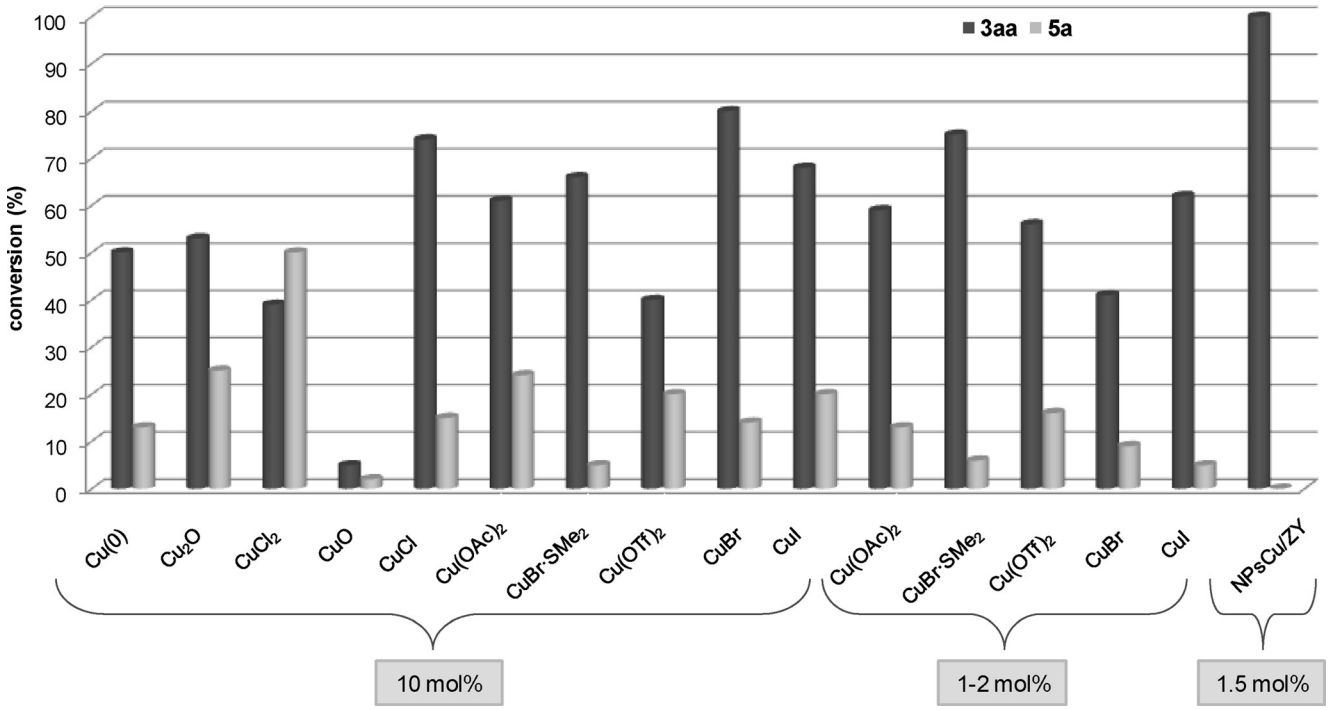
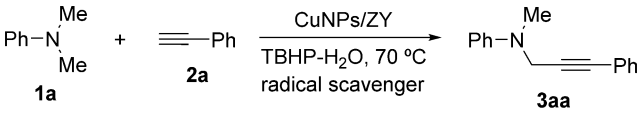


Figure 7. Graphic showing the CDC product (**3aa**)/alkyne homocoupling (**5a**) ratio in the reaction of **1a** and **2a** catalyzed by commercial Cu catalysts and CuNPs/ZY (see the conditions in Table 5).

Table 6. CDC of **1a** and **2a** in the presence of radical scavengers.[a]

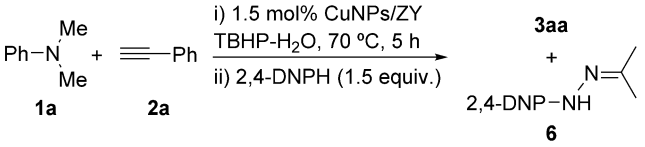


Entry	Radical scavenger	Conv. [%][b]
1	norbornene	92
2	cumene	80
3	2,6-di-*tert*-butylphenol	65[c]
4	TEMPO[d]	10[e]

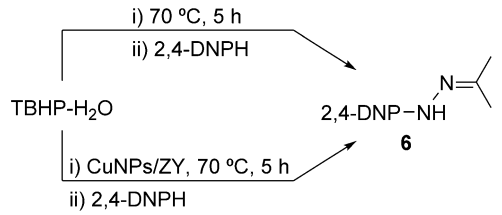
[a] **1a** (1.0 mmol), **2a** (1.2 mmol), CuNPs/ZY (1.5 mol%), *t*-BuOOH-H_2O (2.0 equiv.), radical scavenger (1.0 equiv.), 70 °C, 20 h, air.
[b] Conversion determined by GLC.
[c] 2,6-Di-*tert*-butylanisole was formed in *ca.* 40% conversion.
[d] 2,2,6,6-Tetramethylpiperidin-1-oxyl.
[e] 1-Methoxy-2,2,6,6-tetramethylpiperidine was formed in *ca.* 75% conversion.

spectively; that is, the reaction products between those traps and a methyl radical (Table 6, entries 3 and 4).

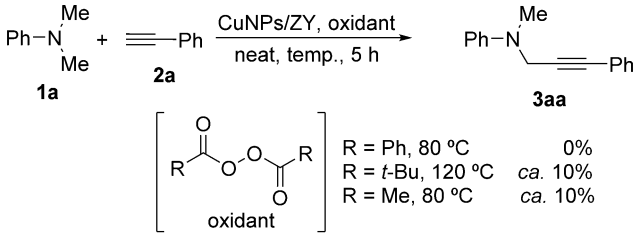
In principle, methyl radicals could be formed through a β-cleavage of TBHP, followed by a homolytic Me–CO bond cleavage, to eventually release acetone as a neutral molecule. We used 2,4-dinitrophenylhydrazine (2,4-DNPH) as an acetone scavenger to detect its presence as the corresponding hydrazone. Certainly, the addition of 2,4-DNPH to a standard reaction, that had run fo0r 5 h, led to the formation of a white precipitate which was identified as acetone 2,4-dinitrophenylhydrazone (**6**) (Scheme 4). Notwithstanding the fact that transition metals can catalyze the fragmentation of TBHP into *tert*-butoxyl radicals,[30] two control experiments proved that β-cleavage in TBHP can take place at the CDC standard temperature in the absence of the copper catalyst (Scheme 5). Additional essays performed under solvent-less conditions for 5 h with different oxidants were really very enlightening (Scheme 6): (a) benzoyl peroxide, which decomposes into $PhCO_2^{\bullet}$ and $Ph^{\bullet}$ did not give **3aa** at all; (b) di-*tert*-butyl peroxide, which is able to generate *t*-$BuO^{\bullet}$ and $Me^{\bullet}$, formed **3aa** in *ca.* 10% conversion; (c) a similar percentage was recorded with acetyl peroxide, which can split into $Me^{\bullet}$. This conversion is within the expected range for a standard reaction after 5 h (Figure 6), albeit the reaction condi-



Scheme 4. Experiment demonstrating the generation of acetone in the CDC of **1a** and **2a**.



Scheme 5. Control experiments on the transformation of TBHP into acetone.



Scheme 6. CDC of **1a** and **2a** catalyzed by CuNPs/ZY in the presence of different peroxides.

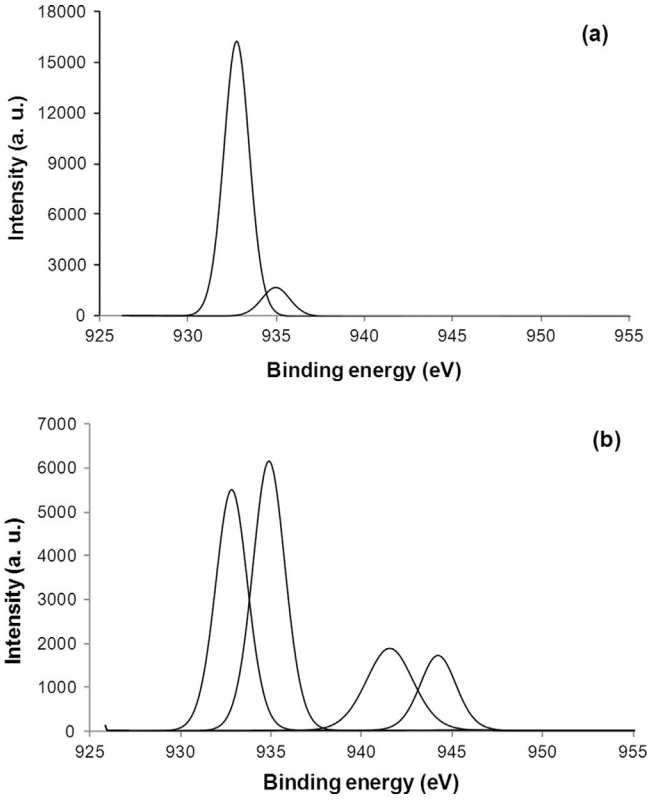
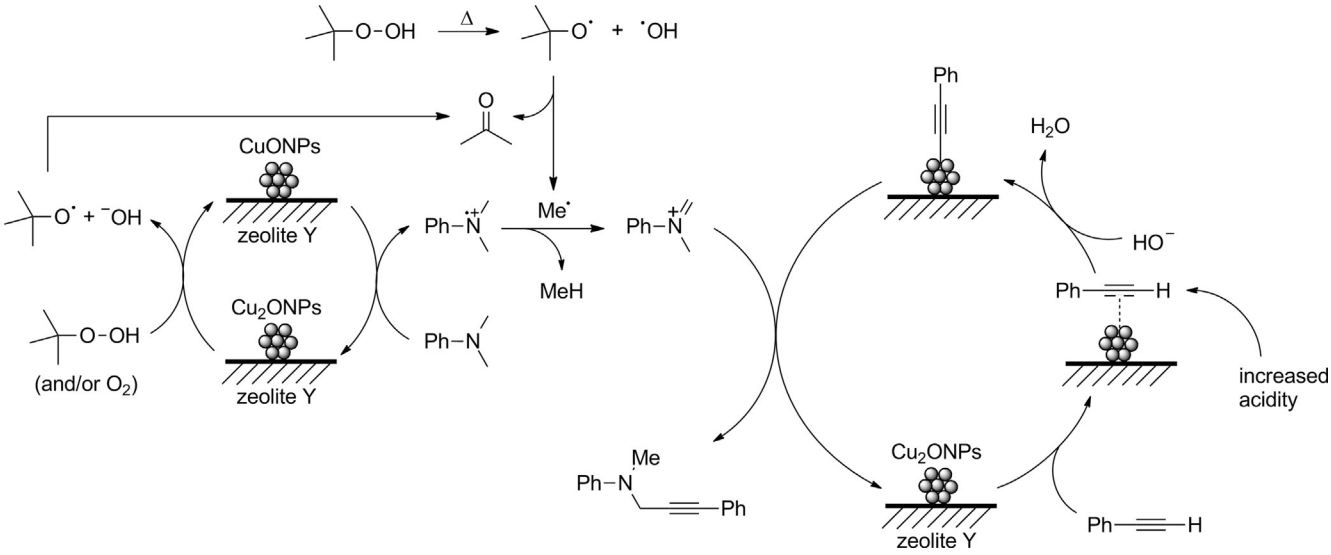


Figure 8. XPS spectrum of CuNPs/ZY at the Cu $2p_{3/2}$ level (a) at the end of the CDC and (b) after reoxidation.

tions are different: they were carried out at the decomposition temperature of the oxidant in the absence of water (Scheme 6). These results reinforce the hypothesis that highly reactive methyl radicals may play a key role in the CDC with TBHP as the oxidant.

The function of copper is also questionable, given that it can participate in the *in-situ* formation of the nucleophile but also in the oxidation of the substrate. The situation is especially intriguing when, as in our case, two oxidation states are present in the catalyst [Cu(I) and Cu(II)]. We analyzed by XPS the recovered catalyst at the end of a typical reaction and, much to our surprise, the intensity of Cu(II) was extensively depleted (Figure 8a); the copper was mostly as Cu_2O, what could be additionally corroborated by the $CuL_3M_{45}M_{45}$ Auger peak located at 571.0 eV (see the Supporting Information).[31] Treatment of the same catalyst sample with TBHP-H_2O at 70 °C for 5 h and subsequent analysis by XPS brought into view the regeneration of Cu(II) to get nearly the original Cu(I)/Cu(II) ratio (Figure 8b). This finding unmasks Cu(II) as a crucial player in the CDC, despite the general trend that Cu(I) salts perform better than the Cu(II) counterparts when an excess of oxidant is present. It is our belief that most of the success of the CDC with CuNPs resides on the conjunction of both Cu(I) and Cu(II) species and their redox activities.

Gathering and interpreting the above results, a tentative mechanism was proposed in which some of the following events could occur in parallel (Scheme 7). (a) Alkyne activation by Cu_2ONPs to form the corresponding copper acetylide; the formation of the latter was previously demonstrated by us[20b] and was found to be especially favored in aqueous medium.[32] (b) Thermal-promoted β-cleavage of TBHP to give *tert*-butoxyl and hydroxyl radicals, with further evolution of the former into methyl radicals and acetone. (c) Amine oxidation by CuONPs to give its derived radical cation and Cu_2ONPs; although some direct oxidation of the amine by TBHP cannot be ruled out, the marked decrease in intensity of Cu(II) in such an oxidative medium (Figure 8a) indicates its decisive part in this step. (d) Re-oxidation of Cu_2ONPs to CuONPs by the action of TBHP (or the combined action of TBHP and O_2) and the concomitant production of *tert*-butoxyl radical and hydroxyl anion. (e) Hydrogen-atom transfer (HAT) between the amine radical cation and the methyl radical giving rise to the iminium ion; the cooperation to some extent of other radicals in the HAT process cannot be fully discarded, although the methyl radical seems to have a prominent participation. Whether the SET comes before the HAT or *vice versa* is difficult to ascertain,[33] even though dimers of the putative radicals of **1a** in the absence of the catalyst have not been detected, which would suggest an SET-HAT sequence. (f) The eventual addition of the copper acetylide to the iminium ion would afford the propargylamine.



Scheme 7. Reaction mechanism proposed for the CDC of *N,N*-dimethylaniline and phenylacetylene catalyzed by CuNPs/ZY in the presence of TBHP.

As a final remark, we must underline that the CDC reported herein is highly regioselective; tertiary amines prone to activation in different C–H bonds underwent alkynylation exclusively at the methyl group. Such is the case of the benzylic amines **1f** and **1g**, *N,N*-dimethylcyclohexylamine (**1i**) and tropinone (**1j**). Some stereoelectronic effects have been invoked to rationalize this selectivity, namely: the necessity of periplanarity of the partially occupied orbital on the nitrogen of the intermediate amine radical cation with the α C–H bond.[29,34] Surely, this explanation can account for the selectivity attained in the case of tropinone (**1j**), but it is not so obvious in the other examples. Probably, in those cases, the HAT is merely driven by steric effects, involving the most accessible α C–H bond to the radical, to generate the terminal kinetic iminium ion rather than the internal thermodynamic one.

Conclusions

In conclusion, we have presented a new heterogeneous catalyst for the CDC of tertiary amines and terminal alkynes comprised of oxidized copper nanoparticles on sodium Y zeolite, readily prepared from commercially available chemicals under mild conditions. The catalyst (1.5 mol%), in the presence of aqueous TBHP, has been applied to the formation of an array of propargylamines in moderate-to-excellent yields. Contrary to other previously reported methodologies, it has been demonstrated that the copper-catalyzed CDC can be conducted under solvent-free conditions and without the requirement of an inert atmosphere. The reaction conditions were compatible with the presence of different functionalities such as methoxy, ester, cyano, hydroxy, halogen and ketone. Not only activated *N,N*-dimethylanilines have been covered in this study but also benzylamines and aliphatic amines. The catalyst has been successfully both reutilized in seven successive runs and adapted to a 12 mmol scale. Moreover, its catalytic activity surpasses that of various commercially available copper catalysts, depleting the formation of 1,3-diynes as by-products. We have endeavored to propose a reaction pathway which discloses the pivotal role of free radicals (methyl radical, in particular) and that of the Cu(I)/Cu(II) redox couple. The results of this study also highlight the utility of nanosized copper in catalysis when compared with bulk copper sources.

Experimental Section

General Material and Methods

Anhydrous copper(II) chloride (97%, Aldrich), lithium powder from granulated lithium (Chemetall), DTBB (4,4′-di-*tert*-butylbiphenyl, Aldrich), TBHP (5–6 M in decane or 70 wt% in water, Aldrich) and sodium Y zeolite (Aldrich) were commercially available. *N,N*-Dimethylaniline (Carlo Erba) was distilled before use. All other starting materials and reagents were commercially available and of the best grade (Aldrich, Acros, Alfa Aesar) and were used without further purification. THF was dried in a Sharlab PS-400-3MD solvent purification system using an alumina column. All reactions were carried out on a multireactor apparatus using the corresponding reactor tubes. Melting points were obtained with a Reichert Thermovar apparatus and are uncorrected. Optical rotations were measured using a Perkin–Elmer 341 polarimeter with a thermally jacketted 5 cm cell

at approximately 20 °C. Concentrations (*c*) are given in g/100 mL and [α] values are given in units of 10^{-1} deg cm^2 g^{-1}. NMR spectra were recorded on Bruker Avance 300 and 400 spectrometers (300 and 400 MHz for ^{1}H NMR; 75 and 101 MHz for ^{13}C NMR); chemical shifts are given in (δ) parts per million and coupling constants (*J*) in Hertz. Infrared analysis was performed with a Jasco 4100 LE (Pike MIRacle ATR) spectrophotometer; wavenumbers ($\tilde{\nu}$) are given in cm^{-1}. Mass spectra (EI) were obtained at 70 eV on an Agilent 5973 spectrometer; fragment ions in *m/z* with relative intensities (%) in parentheses. HR-MS analyses were also carried out in the electron impact mode (EI) at 70 eV on a Finnigan MAT95S spectrometer. Elemental analyses were performed on a Leco Micro TruSpec CHNS microanalyzer. The purity of volatile compounds and the chromatographic analyses (GLC) were determined with an Agilent 6890N instrument equipped with a flame ionization detector and an HP-5 MS 30 m capillary column (0.32 mm diameter, 0.25 μm film thickness), using nitrogen (2 mL min^{-1}) as carrier gas, $T_{injector}$ = 270 °C, T_{column} = 60 °C (3 min) and 60–270 °C (15 °C min^{-1}); retention times (t_r) are given in min. Analytical thin-layer chromatography (TLC) was carried out on ALUGRAM® Xtra SIL G UV$_{254}$ aluminium sheets. Preparative thin-layer chromatography was carried on laboratory-made TLC glass plates with silica gel 60 PF$_{254}$ (Merck). Column chromatography was performed using silica gel 60 of 40–60 microns (hexane/EtOAc as eluent). The tests for acetone determination using 2,4-dinitrophenylhydrazine were carried out following a standard published procedure.

Typical Procedure for the Preparation of CuNPs/ZY (Method A)

Anhydrous copper(II) chloride (135 mg, 1.0 mmol) was dissolved in dry THF or water (15 mL) and sodium Y zeolite (1.28 g) was added to the resulting solution. The mixture was stirred in the presence (for THF) or absence (for water) of argon overnight, followed by filtration and washing with THF or water (20 mL), and drying under vacuum (12 h).

Typical Procedure for the Preparation of CuNPs/ZY (Method B)

Anhydrous copper(II) chloride (135 mg, 1.0 mmol) was added to a suspension of lithium powder (14 mg, 2.0 mmol) and 4,4′-di-*tert*-butylbiphenyl (DTBB, 27 mg, 0.1 mmol) in dry THF (2 mL) at room temperature under an argon atmosphere. The reaction mixture, which was initially dark blue, rapidly changed to black, indicating that the suspension of copper nanoparticles was formed. This suspension was diluted with THF (18 mL) followed by the addition of sodium Y zeolite (1.28 g). The resulting mixture was stirred for 1 h at room temperature, filtered, and the solid successively washed with MeOH (5 mL) and THF (20 mL), and dried under vacuum (5 h).

Typical Procedure for the Preparation of CuNPs/ZY (Method C)

Following the impregnation method A, the resulting solid was added to a suspension of lithium powder (14 mg, 2.0 mmol) and 4,4′-di-*tert*-butylbiphenyl (DTBB, 27 mg, 0.1 mmol) in THF (2 mL) at room temperature under an argon atmosphere. The resulting mixture was stirred for 1 h at room temperature, filtered, and the solid successively washed with MeOH (5 mL), THF (20 mL) and dried under vacuum (12 h).

General Procedure for the CDC of Tertiary Amines and Terminal Alkynes Catalyzed by CuNPs/ZY

The amine (**1**, 1.0 mmol), the alkyne (**2**, 1 mmol) and *t*-BuOOH-H_2O (2.0 mmol) were added to a reactor tube containing CuNPs/ZY (50 mg, 1.5 mol%) under air. The reaction mixture was warmed to 70 °C and stirred at that temperature for 15–20 h. The resulting mixture was diluted with EtOAc (15 mL), filtered through Celite and subjected to column chromatography (silica gel, hexane-EtOAc) to give the pure propargylamines **3**. The catalyst could be recovered by diluting the reaction crude with EtOAc (15 mL), followed by centrifugation (2500 rpm, 15 min), catalyst separation and washing (EtOAc, 15 mL), and final drying under vacuum.

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