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# C–N cross-coupling reaction catalysed by efficient and reusable CuO/SiO<sub>2</sub> nanoparticles under ligand-free conditions

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Nanometric copper oxide supported on silica has been found to be a highly efficient and reusable catalyst for the C-N crosscoupling reaction of amines with aryl halides under ligand-free conditions. Various arylamines with different substituted groups can be synthesized in moderate to good yields. The catalyst can be recycled at least five times without obvious loss in catalytic activity. Copyright © 2014 John Wiley & Sons, Ltd.

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Keywords: nano-heterogeneous catalysis; reusability; C-N cross-coupling; arylamines

## Introduction

Due to the significance of *N*-arylamines and *N*-arylheterocycles in biologically important natural products, pharmaceuticals and polymers and considering their applications in materials research, their synthesis is an active area in organic synthesis.<sup>[11]</sup> Therefore, there has been great attention given to their preparation. Until now, Pd- and Cu-catalysed crosscoupling reactions have been the most efficient ones in the construction of aromatic C–N bonds both in industrial and academic settings.<sup>[2–6]</sup> Copper catalysts have proven to be not only cheaper and more readily available but also superior in terms of efficiency and functional group tolerance.<sup>[7]</sup>

Nanomaterials with high surface areas as well as reactive morphologies have been widely investigated. Recently, using nanocrystalline metal oxides as catalysts in organic synthesis has attracted much attention. Nanomaterial-catalysed reactions are generally characterized by easy product purification, efficient recycling of the catalyst and minimizing metal traces in the products.<sup>[8–13]</sup>

In almost all methods, ligands or well-defined catalysts/reagents are required. This fact contributes to an increase in the costs and, as a consequence, limits the applications. Hence, finding new recyclable catalytic systems for synthesizing such highly useful organic compounds especially under ligand-free conditions is desirable. During the past few years, there have been significant efforts in the area of heterogeneous catalysis for various organic transformations. In general, heterogeneous catalysts have higher surface area and lower coordinating sites, which contribute to their higher catalytic activity. High atom efficiency, easy product purification and reusability of the catalysts.<sup>[14,15]</sup>

Generally, aryl chlorides are less expensive and more abundant than their bromide and iodide counterparts. They are less reactive and of much greater interest for industrial applications. However, it is worth mentioning that the development of several highly effective classes of catalysts for the cross-coupling of aryl chlorides with low catalyst loadings, excellent yields and reasonable scope remains a challenge.<sup>[16,17]</sup>

## **Results and Discussion**

In continuation of our recent investigations on the synthesis and applications of various catalysts in cross-coupling reactions,<sup>[18–25]</sup> in this study, we report that CuO nanoparticles supported on silica (CuO NPs/SiO<sub>2</sub>) catalyse C–N crosscoupling of amines with various aryl halides with good yields. The reactions are effective at 120 °C in DMSO in the presence of KOH under atmospheric conditions (Scheme 1).

The CuO NPs/SiO<sub>2</sub> catalyst was prepared as follows. First, copper sulfate (1.2 g) was dissolved in the minimum amount of distilled water. Then, ammonia solution (1 ml, 25% w/w) was added to the solution in order to make the tetra ammine copper(II) complex [Cu(NH<sub>3</sub>)<sub>4</sub>]SO<sub>4</sub>. Then sodium silicate (Na<sub>2</sub>SiO<sub>3</sub>) solution (15 g, 45 wt %) was dissolved in water (10 ml) and the tetra ammine copper(II) complex was added dropwise to it. By mixing the reaction mixture,

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Scheme 1. C–N cross-coupling reaction using CuO NPs/SiO<sub>2</sub>.

a uniform and homogeneous solution was produced. Then this solution was dried in an oven at 150 °C to give a porous and spongy material. After washing the sediment, sodium sulfate was washed up and the remnant included a solid with CuO nanoparticles supported on amorphous silica. Copper oxide particles which are insoluble in water were distributed on the silica support. Then the blue solid obtained was crushed into a fine powder. Atomic adsorption spectroscopy was used to determine the amount of copper oxide supported on the silica bed. In this analysis, it was found that 0.000055 mol of copper was supported on 1 g of catalyst.

The X-ray diffraction (XRD) pattern of CuO NPs/SiO<sub>2</sub> is shown in Fig. 1. All diffraction peaks are indexed to the corresponding planes of CuO. The intense peak at 36.4° in the XRD spectrum corresponds to the (111) plane, which is the crystal plane of CuO. The diffraction of SiO<sub>2</sub> is only seen at around  $2\theta = 21.7^{\circ}$  with a broad and diffuse diffraction peak, which is related to amorphous silica of the catalyst. After reduction, the peaks of copper oxides disappear and the peaks of metallic copper appear.

In order to obtain detailed information about the microstructure and morphology of the catalyst, scanning electron microscopy (SEM; Fig. 2) and transmission electron microscopy (TEM; Fig. 3)



Figure 1. XRD pattern of CuO nanoparticles.



Figure 2. SEM image of CuO nanoparticles supported on silica.



Figure 3. TEM image of CuO nanoparticles supported on silica.

Table 1. C-N cross-coupling of N-methyl-N-benzylamine with

bromobenzene in various solvents and bases<sup>a</sup> CuO NPs/ SiO<sub>2</sub> Base, Solvent Entry Temperature Conversion Solvent Base (°C) (%)<sup>t</sup> 1 DMF KOH 120 20 2 NMP<sup>c</sup> KOH 120 10 3 DMSO KOH 120 100 4 KOH CH<sub>3</sub>CN 80 5 100 Dioxane KOH 60 6  $H_2O$ KOH 80 7 DMSO 40 NaCO<sub>3</sub> 120 8 DMSO NaHCO<sub>3</sub> 120 30 9 DMSO NaOAC 120 0 10 DMSO 70 K<sub>2</sub>CO<sub>3</sub> 120 11 DMSO NaOH 120 60 <sup>a</sup>Reaction conditions: N-methyl-N-benzylamine (1.2 mmol), bromobenzene

(1 mmol), base (2 mmol), CuO NPs/SiO<sub>2</sub> (1.1 mmol%, 0.1 g) and solvent (2 ml), 30 min.

<sup>b</sup>GC yield.

<sup>c</sup>*N*-methyl-2-pyrrolidone.

<b>Table 2.</b> C–N cross-coupling of <i>N</i> -methyl- <i>N</i> -benzylamine with bromobenzene using various amounts of catalyst <sup>a</sup>								
Entry	CuO NPs/SiO <sub>2</sub> (mmol%)	Time (min)	Conversion (%) <sup>b</sup>					
1	0.11	60	85					
2	0.22	60	100					
3	0.33	25	100					
4	0.55	10	100					
5	1.1	10	100					

<sup>a</sup>Reaction conditions: *N*-methyl-*N*-benzylamine (1.2 mmol), bromobenzene (1 mmol), KOH (2 mmol), and DMSO (2 ml), 120 °C. <sup>b</sup>GC yield.

Table 3. C-N cross-coupling reaction of various aryl halides <sup>a</sup>										
$R_{1}$ $X + HNR_{2}R_{3} \xrightarrow{CuO NPs/SiO_{2}}{KOH, DMSO} \xrightarrow{R_{2}}{N, R_{3}}$ $R_{1}$										
Entry	Х	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Time (min)	Yield (%) <sup>b</sup>				
1	I	Н	CH <sub>3</sub>	CH₂Ph	30	76				
2	I	4-OMe	CH₃	CH₂Ph	90	56				
3	I	4-NO <sub>2</sub>	CH₃	CH₂Ph	12	75				
4	I	Н	Ph	Ph	60	68				
5	I	4-OMe	Ph	Ph	180	52				
6	I	4-NO <sub>2</sub>	Ph	Ph	50	74				
7	I	Н	Мо	rpholine	42	72				
8	I	4-OMe	Ма	rpholine	70	68				
9	I	4-NO <sub>2</sub>	Мо	orpholine	30	92				
10	I	н	Ind	ole	15	89				
11	1	н	Cvclohexvl	Cvclohexvl	35	72				
12	1	н	CH3	Cyclohexyl	40	75				
13	1	н	Et	Et	55	94				
14	i.	Н	Н	Et	90	68				
15	i i	н	Pin	eridine	60	73				
16	i	н	Pvi	rrolidine	55	78				
17	Br	н	CH <sub>2</sub>	CH_Ph	10	88				
18	Br	4-0Me	CH <sub>2</sub>	CH <sub>2</sub> Ph	45	64				
10	Br	4-NO-	CH.	CH_Ph	7	79				
20	Br	4-CN	CH <sub>3</sub>	CH <sub>2</sub> Ph	12	68				
20	Br	H	Ph	Ph	30	71				
21	Br	1-0Me	Ph	Ph	120	63				
22	DI	4-01/16	Ph	Ph	20	00				
25	DI De	4-INO <sub>2</sub>	PII	PII	50	02				
24	DI De	4-CN	PII	ril	45	75				
25	Br	П	IVIC	Morpholine		76				
26	Br	4-0/vie	IVIC	Morpholine		90				
2/	Br	4-NO <sub>2</sub>	IVIC	Morpholine		95				
28	Br	н	Ind	ole	8	86				
29	Br	н	Cyclohexyl	Cyclohexyl	25	84				
30	Br	н	CH <sub>3</sub>	Cyclohexyl	25	/6				
31	Br	н	Et	Et	40	96				
32	Br	Н	Н	Et	60	73				
33	Cl	Н	CH₃	CH <sub>2</sub> Ph	12	88				
34	Cl	4-NO <sub>2</sub>	CH <sub>3</sub>	CH₂Ph	10	74				
35	Cl	Н	Ph	Ph	35	83				
36	Cl	4-NO <sub>2</sub>	Ph	Ph	35	90				
37	Cl	Н	Morpholine		30	84				
38	Cl	4-NO <sub>2</sub>	Mo	Morpholine		94				
39	Cl	Н	Ind	ole	12	87				
40	Cl	Н	Cyclohexyl	Cyclohexyl	30	81				
41	Cl	Н	CH <sub>3</sub>	Cyclohexyl	35	84				
42	Cl	Н	Et	Et	50	92				
43	Cl	Н	Н	Et	75	68				

<sup>D</sup>Isolated yield.

observations were carried out. The results show the spherical morphology of CuO nanoparticles. Careful observation of these images indicates that particle surfaces are not smooth but some small round structures are formed on the surface. The morphology of CuO NPs/SiO<sub>2</sub> shows that copper species in the catalyst have

spherical shapes and are distributed uniformly over the  $SiO_2$  support. Copper particles exhibit a narrow size distribution of 20–40 nm with an average diameter of 30 nm.

The efficiency of this catalytic system was examined in the C–N coupling reaction by optimizing the reaction conditions for the



**Scheme 2.** Proposed mechanism for the catalysed C–N cross-coupling reaction.

cross-coupling of bromobenzene with *N*-methyl-*N*-benzylamine as a model reaction.

To study the effect of the solvent on the yield of this reaction, the model reaction was carried out in various solvents using 0.1 g (0.011 mmol Cu) of CuO NPs/SiO<sub>2</sub> as the catalyst. As evident from Table 1, the highest yields and the shortest reaction times are related to the reactions in which DMSO is used as the solvent at 120 °C. We also investigated this coupling reaction using different types of bases. Among the bases we selected, KOH shows the best result.

The loading of catalyst was also optimized by employing various amounts of catalyst. The results are shown in Table 2. An amount of 0.05 g of CuO NPs/SiO<sub>2</sub> catalyst gives the best result.

The optimized reaction conditions were applied to the C-N crosscoupling reactions of various aryl halides with different secondary amines (Table 3). The substituent effects of the aryl iodides prove to be less significant than those of the aryl bromides, and the reactivity of aryl bromides with electron-withdrawing substituent is higher than that of aryl bromides with electron-donating substituent. Because of the inexpensiveness and availability of aryl chlorides, they are the best substrates for coupling reactions in comparison with their bromide or iodide counterparts. This catalytic system can be used for the C-N cross-coupling reaction of even less reactive aryl chloride derivatives with longer reaction times. Dialkylamines, secondary arylamines, N-heterocyclic compounds and primary arylamines including N-methyl-N-benzylamine, diphenylamine, morpholine, indole, dicyclohexylamine and Nmethylcyclohexanamine can be coupled with various aryl halides in excellent yields and in reasonable reaction times.

A general catalytic cycle for the C–N cross-coupling reaction using CuO NPs/SiO<sub>2</sub> as the catalyst is presented in Scheme 2. The reaction may occur via oxidative addition and then reductive elimination providing the C–N cross-coupled product followed by removal of hydrogen halide with base.<sup>[10]</sup>

As CuO NPs/SiO<sub>2</sub> is a heterogeneous catalyst, the recyclability of the catalyst in this coupling reaction was examined. The coupling of *N*-methyl-*N*-benzylamine with bromobenzene was chosen as a model reaction. After each cycle, the catalyst was

Table 4.         Recycling of CuO NPs/SiO2								
Run	1	2	3	4	5			
Time (min) Yield (%)	10 88	10 85	12 85	15 81	15 80			

recovered through simple filtration, washing with distilled water and acetone, and then drying *in vacuo*. The recovered catalyst was used directly in the next cycle. The recycling results are listed in Table 4. These results show that the catalyst is still highly efficient after at least five cycles.

# Conclusions

We report the synthesis of CuO NPs/SiO<sub>2</sub> that was used as an efficient catalyst for the C–N cross-coupling reaction of amines with aryl halides under ligand-free conditions. The scope of the reaction using this catalytic chemistry is broad: various aryl, alkyl and *N*-heterocyclic amines react with aryl halides. Of particular importance is the reaction with aryl chlorides due to their low cost. Furthermore, the CuO NPs/SiO<sub>2</sub> catalyst can be recovered and recycled through simple filtration of the reaction solution and can be reused for at least five consecutive trials without a decrease in its activity.

# Experimental

## General

<sup>1</sup>H NMR spectra were recorded at 400 MHz in CDCl<sub>3</sub> solutions at room temperature (tetramethylsilane was used as an internal standard) with a Bruker Avance 500 instrument (Rheinstetten, Germany) and Varian 400 NMR. FT-IR spectra were recorded with a

spectrophotometer (Jasco-680, Japan). Spectra of solids were obtained using KBr pellets. Vibrational transition frequencies are reported in wavenumber (cm<sup>-1</sup>). We used GC (BEIFIN 3420 gas chromatograph equipped with a Varian CP SIL 5CB column: 30 m, 0.32 mm, 0.25  $\mu$ m) for examination of reaction completion and yields. Powder XRD patterns were obtained using an X'PERT MPD, with Cu K<sub>a</sub> radiation (40 kV, 30 mA). TEM images were obtained using a Philips CM10 microscope. The Cu content in the catalyst was measured using atomic absorption spectroscopy (PerkinElmer 2380 spectrophotometer). All chemical materials were purchased from Merck and Aldrich and were used as received.

# General Procedure for the C–N Cross-Coupling Reaction of Aryl Halides

CuO NPs/SiO<sub>2</sub> (0.55 mmol%, 0.05 g), amine (1.2 mmol), aryl halides (1 mmol), KOH (2 mmol) and DMSO (2 ml) were added to a round-bottomed flask equipped with a condenser and stirred at 120 °C in an oil bath. The course of the reaction was monitored by periodically taking samples and analysing using TLC and GC. After the mixture was cooled to room temperature, the solution was first filtered and then the aqueous solution was extracted with ethyl acetate (30 ml) and distilled water (30 ml). Then, the organic phase was dried over sodium sulfate, and the solvent was removed by rotary evaporation. Column chromatography on silica gel afforded the desired product (n-hexane or n-hexane–EtOAc, 9:1). The characterization of arylamine compounds is given as Supporting Information.

#### General Procedure for the Recyclability of Catalyst

The coupling of *N*-methyl-*N*-benzylamine (1.2 mmol) with bromobenzene (1 mmol) was chosen as a model reaction for the investigation of the recyclability of the catalyst (0.5 mmol%) in DMSO (2 ml) in the presence of KOH (2 mmol) as base at 120 °C. After completion of the C–N cross-coupling, the reaction mixture was treated with water (30 ml) and ethyl acetate (30 ml). The CuO NPs/SiO<sub>2</sub> catalyst was recovered through simple filtration, washing with distilled water (20 ml) and acetone (15 ml), and then drying *in vacuo*. The catalyst was reused for the fresh C–N crosscoupling of *N*-methyl-*N*-benzylamine with bromobenzene for five runs, without a decrease in its activity.

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# **Supporting Information**

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