Synthesis of CuO on mesoporous silica and its applications for coupling reactions of thiols with aryl iodides[†]

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Novel CuO on mesoporous silica is prepared under a convenient approach, and has been shown to be an efficient catalyst for cross-coupling reactions of thiols with aryl iodides with only 1.0–5.0 mol% catalyst loading.

Aryl thioethers are important compounds in biological chemistry,^{1,2} and the transition-metal-catalyzed cross-coupling reactions of thiols with aryl halides represents the most common strategy for constructing C–S bonds.^{3–8} The combination of palladium,³ nickel,⁴ cobalt,⁵ iron^{6,7} with phosphines; indium⁸ with N,N,N',N'-tetramethylethylenediamine (TMEDA) or copper⁹ with a variety of ligands are well-known for C–S bond forming reactions. Among them, the copper-catalyzed (Ullmann-type reaction) C–S coupling is the most popular approach in this field due to its low cost when compared with most other metal catalysts.

Recent studies have revealed that copper salts could be reduced to 0.1 mol% level and still catalyze C–S coupling reactions of thiols with aryl iodides,^{9n,o} however, 20 mol% of ligand is critical for this reaction. The authors claimed that the excess ligand is needed to prevent the aggregation of the metal during the catalysis. A similar phenomenon has been reported in palladium catalysis.¹⁰ However, indium oxide¹¹ and copper oxide¹² nanoparticles have been reported to promote the C–S arylations without the assistance of additional ligand, but there remains some drawbacks in these systems. First, KOH has been shown to be the best base for these reactions and this might seriously limit the tolerance towards base-sensitive functional groups. Furthermore, poor yields were observed when electronrich iodides (for example, 4-iodoanisole) were used.

Herein we report the synthesis of a novel CuO on mesoporous silica prepared *via* a convenient sol–gel method. These well-dispersed CuO active sites appear to be highly active in this transition-metal-catalyzed cross-coupling reaction.¹³ To synthesize the CuO on mesoporous silica sample, 1.00 g of gelatin (Acros) and 0.19 g of copper nitrate pentahemihydrate (Sigma-Aldrich) was dissolved in 40.0 g of deionized water to form a clear solution at 40 °C. Then, the Cu²⁺-gelatin solution was added directly into a silicate stock solution under stirring, and a light-blue precipitate was generated in a few minutes. To

prepare the silicate stock solution, a mixture of 4.0 g of sodium silicate (SiO₂: 27 wt%, Aldrich) and a 50.0 g of water was added into a 25 mL of 1.50 M H₂SO₄ aqueous solution, and the pH of the acidified silicate solution was adjusted to 5.0 at 40 °C by using 0.1 M NaOH aqueous solution. Then the pH value of the resultant gel solution was raised to approximately 7.0 and further stirred for 2.0 h. Finally, that gel solution was poured into a polypropylene bottle and hydrothermally treated at 100 °C for 24 h without stirring. Filtration, drying and calcination at 550 °C in air for 6 h gave the CuO on mesoporous silica.

Owing to the chelating capability of the silanol (–Si–OH) and silanolate (–Si–O⁻) groups, hydrated copper ions could be incorporated on the surface of the mesoporous silica at pH = 7.0 (Scheme 1).

After calcination almost all of the CuO active sites were well dispersed and strongly bound on the high-surface-area mesoporous silica. TEM studies (Fig. 1A and B), depict a wormhole-like mesostructure where CuO nanoparticles were seldom observed. At higher magnification, the amorphous structure was observed without any CuO lattice fringes. The existence of two broad and low-intensity XRD diffraction peaks at high-angle indicates that the CuO is well dispersed onto the mesoporous silica matrix instead of forming CuO nanoparticles from self-condensation (Fig. 1C). To further investigate the dispersion and structure of the calcined CuO on mesoporous silica, TEM and SEM EDX-mapping and selected area electron diffraction were used. The similar distribution profiles of Si, O and Cu elements and diffuse ring-diffraction pattern indicate a good distribution of the CuO active sites on the mesoporous silica in accordance with the XRD result (Fig. S1 and S2, see ESI[†]). In appearance, the CuO on the mesoporous silica sample was uniformly aquamarine, rather than gray or black that was observed for CuO nanoparticle-containing mesoporous silica prepared by employing the impregnation method (Fig. S3, ESI[†]).



Scheme 1 Formation mechanism of the CuO on mesoporous silica *via* a sol-gel reaction.

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Fig. 1 (A) TEM image, (B) high-resolution TEM photograph, (C) high-angle XRD pattern and (D) N_2 adsorption–desorption isotherm of the calcined CuO on mesoporous silica templated with gelatin.

Analyzing the N₂ adsorption–desorption isotherm (Fig. 1D), the BET surface area was about 285 m² g⁻¹; and the pore size calculated by the BJH method was centered at 7.7 nm. Accordingly, the CuO that is incorporated into the mesoporous silica became highly accessible to the environment, and well dispersed active sites had been conveniently prepared and should exhibit high activity for coupling reactions with the added feature of recyclability.^{14,15}

Initially, 4-iodotoluene and 1-dodecanethiol were screend as substrates in order to determine optimal reaction conditions. The results are summarized in Table 1, the screening of bases (entries 1–7) and solvents (entries 8–11; DME = dimethoxy-ethane; dioxane = 1,4-dioxacyclohexane; DMF = N,N-dimethylformamide) revealed that satisfactory results were achieved when the reaction was performed with Cs₂CO₃ in DMSO or dioxane at 110 °C.

Table 1Optimization of CuO on mesoporous silica-catalyzedcoupling of 4-iodotoluene with 1-dodecanethiol a

		CuO on mesoporous silica 1.0 mol%	^S C ₁₂ H ₂₅
1a	2a	base, solvent 110 °C, 21 h	Ja 3a
	Base	Solvent	Yield (%)
1	КОН	DMSO	81
2	Na ₂ CO ₃	DMSO	35
3	K_2CO_3	DMSO	Trace
4	Cs_2CO_3	DMSO	85
5	KOtBu	DMSO	81
6	K_3PO_4	DMSO	55
7	Et ₃ N	DMSO	Trace
8	Cs_2CO_3	Dioxane	85
9	Cs_2CO_3	Toluene	80
10	Cs_2CO_3	DMF	62
11	Cs_2CO_3	H_2O	27

^a Reaction conditions: CuO on mesoporous silica (0.01 mmol, 1.0 mol%), 4-iodotoluene (1.0 mmol), 1-dodecanethiol (1.2 mmol), base (1.5 mmol) in 1.0 mL solvent.

Table	2	CuO	on	mesoporous	silica-catalyzed	S-arylation	of	aryl
iodide	s wi	ith thi	ols ^a					

Ar +		CuO on mesoporous silica 1.0-5.0 mol%	S
1	2	Cs ₂ CO ₃ , DMSO or dioxane 110 ℃, 21 h	3

	Product, yield (%)			Product, yield (%)	
1	S C12H25	3b , 93	13		3n , 96
2	C ₁₂ H ₂₅ OH	3c , 72	14	S	30 , 95
3	S C12H25 NH2	3d , 69	15	Meo	3p , 66
4	MeO S C12H25	3e , 86 ^{<i>b</i>,<i>c</i>}	16	S OH	3q , 80
5	E10	3f , 79	17		3r , 87
6	SC12H25	3g , 97 ^{<i>b</i>,<i>c</i>}	18	C S TN	3s , 74
7	C S C	3h , 68	19	S S N	3 t, 87
8	С ОН	3i , 95	20	Me Meo	3u , 72
9	EIO	3j , 73	21	J S S S S S S S S S S S S S S S S S S S	3 v, 77
10	O2N S	3k , 95	22	Meo	3w , 76 ^{<i>b</i>,<i>c</i>}
11	Los C	31 , 82 ^{<i>b</i>,<i>c</i>}	23	O ₂ N	3x , 93
12	Meo	3m , 82 ^{<i>b,c</i>}	24	Å s	3y , 72 ^c

^{*a*} Reaction conditions unless otherwise stated: CuO on mesoporous silica (0.01 mmol, 1.0 mol%), Cs₂CO₃ (1.5 mmol) in DMSO (1.0 mL). Entries 1–12: aryl iodide (1.0 mmol), alkyl thiol (1.2 mmol); entries 13–24: aryl iodide (1.1 mmol), aryl thiol (1.0 mmol). ^{*b*} 5 mol% of CuO on mesoporous silica. ^{*c*} Dioxane.

In order to extend the scope of this catalytic system, we examined a wide array of aryl iodides and thiols. The results are summarized in Table 2, alkyl and aryl thiols can be coupled with a series of electron-donating and -withdrawing aryl iodides. The functional groups possessing free amine (entry 3), free alcohols (entries 2, 8 and 16), nitro (entries 10 and 23) and nitrogen-containing heterocycles (entries 17–21) were coupled smoothly with a wide selection of thiols. More importantly, our system employed weak bases, tolerant of functional groups such as hydrolyzable esters (entries 4, 5, 9, 12 and 22) and enolizable ketones (6, 11, 21 and 24).

Table 3	Reuse	of	CuO	on	mesoporous	silica ^a

Run	1	2	3	4
Yield (%)	85	83	78	78

 a After 21 h, the reaction mixture was diluted with H₂O and ethyl acetate, the catalyst was recovered by centrifugation and then dried in an oven.

Furthermore, electron-rich 4-iodoanisole could be coupled in good yields (entries 15 and 20), which was in contrast to CuO-nanoparticles.^{11,12}

We next carried out the reactions using **1a** and **2a** as the model to test the recyclability of CuO on mesoporous silica. The results in Table 3 show the catalyst could be reused several runs without loss of reactivity. According to the EDS analysis, the Cu/Si atomic ratio of the sample before and after the fourth run were almost the same ($\approx 1/20$). From the TEM images of the CuO on mesoporous silica after the fourth reaction (Fig. S4, see ESI†), the mesostructures were clearly visible and the presence of CuO nanoparticles (from aggregation) were rarely found. These results indicated that the CuO active sites remained highly stabilized on the mesoporous silica during multiple catalytic trials.

In conclusion, for the first time well dispersed CuO on mesoporous silica with large surface area and robust active sites has been prepared, by using natural polymer gelatin at neutral pH. In addition, the CuO active sites were readily accessible and are shown to be highly active catalysts for coupling reactions between thiols and aryl iodides under ligand-free conditions. Based on the high chelating capability of the mesoporous silica to metal ions, we propose that mesoporous silica can be used in a variety of other catalytic applications.

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