Cross-Coupling Reactions

DOI: 10.1002/ange.200701282

Efficient CuO-Nanoparticle-Catalyzed C–S Cross-Coupling of Thiols with Iodobenzene**

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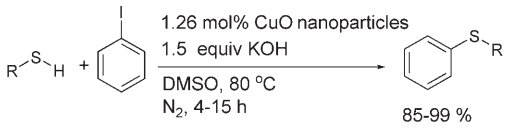
Methods for the formation of C–S bonds are indispensable tools in synthetic chemistry. Their importance stems from the prevalence of C–S bonds in compounds with biological and pharmaceutical impact, and in molecular precursors for the development of materials.[1] Traditional methods for the formation of C–S bonds often require harsh reaction conditions. For example, the coupling of copper thiolates with aryl halides takes place in polar solvents, such as HMPA, and temperatures around 200 °C. The reduction of sulfones or sulfoxides requires strong reducing agents, such as DIBAL-H or $LiAlH_4$.[2] To overcome these difficulties, considerable attention has been focused on the development of catalytic systems for the C–S cross-coupling of thiols with aryl halides.[3–7] From an industrial standpoint, these reactions are attractive because the cost and environmental impact of the process (E factor) are relatively low.[8] In 1980, Migita et al. first reported the cross-coupling of aryl halides with thiols in the presence of $[Pd(PPh_3)_4]$ as the catalyst and NaO*t*Bu as a base in polar solvents, such as ethanol at reflux or dimethyl sulfoxide (DMSO) at 90 °C.[3] Palladium-,[4] nickel-,[5] copper-,[6] and cobalt-based[7] catalytic systems have since been studied for this purpose. Although useful methods are currently available, the requirement of high temperatures, high catalyst loadings, or specially designed phosphine ligands has prompted a search for new methods. As a result of their high catalytic activity, colloidal transition-metal nanoparticles have been used widely as catalysts for organic synthesis.[9] Herein, we report that readily available CuO nanoparticles catalyze efficiently the C–S cross-coupling of aryl and alkyl thiols with iodobenzene in excellent yields (Scheme 1). The reactions are effective at 80 °C in DMSO in the presence of KOH under a nitrogen atmosphere. To the best of our knowledge, this reaction is the first example of the use of CuO nanoparticles for the catalysis of C–S cross-coupling.



Scheme 1. CuO-nanoparticle-catalyzed C–S cross-coupling of thiols with iodobenzene. R = aryl, alkyl, benzyl.

We first studied the reaction of the model substrate benzenethiol with iodobenzene (Table 1). The desired C–S cross-coupling reaction afforded diphenyl sulfide in 95% yield when the substrates were stirred with CuO nanoparticles (1.26 mol%) at 80 °C in DMSO in the presence of KOH (1.5 equiv; Table 1, entry 5). The solvents *i*PrOH, DMF, 1,4-dioxane, and toluene were less effective than DMSO. Of the bases tested, KOH gave the best results. The product was formed in lower yield with K_2CO_3. The copper(II) salts $CuSO_4 \cdot 5H_2O$, $Cu(OAc)_2 \cdot 2H_2O$, and CuO were found to be inferior to CuO nanoparticles as catalysts of the C–S coupling reaction (Table 2). Furthermore, iodobenzene was a more reactive substrate than chlorobenzene or bromobenzene (Table 3).

Table 1: CuO-nanoparticle-catalyzed coupling of benzenethiol with iodobenzene.[a]

Entry	Solvent	Base	*T* [°C]	*t* [h]	Yield[b] [%]
1	DMSO	KOH	RT	18	40
2	DMSO	K_2CO_3	RT	18	25
3	*i*PrOH	KOH	RT	18	20
4	*i*PrOH	KOH	80	10	75
5	DMSO	KOH	80	10	95
6	DMSO	K_2CO_3	80	15	45
7	DMF	KOH	80	10	5
8	1,4-dioxane	KOH	80	15	0
9	toluene	KOH	80	10	< 5
10	DMSO	NEt_3	80	10	0
11	DMSO	pyridine	80	10	0

[a] CuO nanoparticles (1.26 mol%), benzenethiol (1 mmol), iodobenzene (1.1 mmol), base (1.5 mmol), and solvent (1 mL) were stirred under a nitrogen atmosphere for the time and at the temperature indicated. [b] Yield of the isolated product. DMF = *N*,*N*-dimethylformamide.

Next, we studied the scope of the reaction with respect to the aryl thiol substrate (Table 4). 4-Methyl-, 4-methoxy-, 4-nitro-, 4-bromo-, and 2-bromobenzenethiol underwent the

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[**] This research was supported by the Council of Scientific and Industrial Research, New Delhi (01(2002)/05/EMR-II) and the Department of Science and Technology, New Delhi (SR/S1/OC-09/2002).

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Table 2: C–S cross-coupling of benzenethiol with iodobenzene in the presence of copper(II) compounds.[a]

Catalyst	*t* [h]	Yield [%]
$CuSO_4 \cdot 5H_2O$	7	35
$Cu(OAc)_2 \cdot H_2O$	7	33
CuO	7	40
CuO nanoparticles	7	85

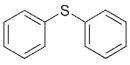
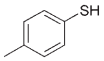
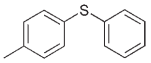
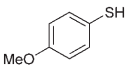
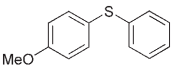
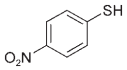
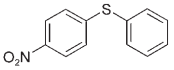
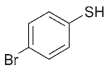
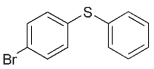
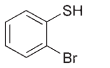
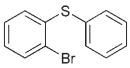
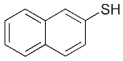
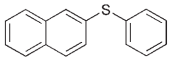
[a] Catalyst (1.26 mol%), benzenethiol (1 mmol), iodobenzene (1.1 mmol), KOH (1.5 mmol), and DMSO (1 mL) were stirred at 80°C under a nitrogen atmosphere.

Table 3: C–S cross-coupling of benzenethiol with different aryl halides.[a]

Aryl halide	*t* [h]	Yield [%]
iodobenzene	10	95
bromobenzene	10	37
chlorobenzene	10	< 5

[a] CuO nanoparticles (1.26 mol%), benzenethiol (1 mmol), aryl halide (1.1 mmol), KOH (1.5 mmol), and DMSO (1 mL) were stirred at 80°C under a nitrogen atmosphere.

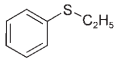
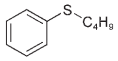
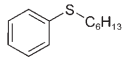
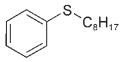
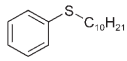
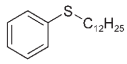
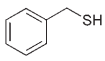
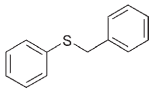
Table 4: CuO-nanoparticle-catalyzed cross-coupling of aromatic thiols with iodobenzene.[a]

Entry	Substrate	*t* [h]	Product	Yield[b] [%]
1		10		95
2		9		96
3		9.5		99
4		15		88
5		10		95
6		9		90
7		10		92

[a] CuO nanoparticles (1.26 mol%), the thiol (1 mmol), iodobenzene (1.1 mmol), KOH (1.5 mmol), and DMSO (1 mL) were stirred for the time indicated at 80°C under a nitrogen atmosphere. [b] Yield of the isolated product.

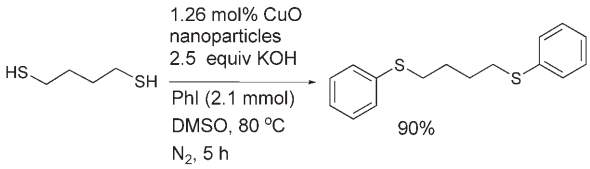
C–S cross-coupling reaction with iodobenzene to afford the corresponding products in 88–99% yield. Substrates with electron-donating groups were more reactive than those with electron-withdrawing groups. Similar reactivity was observed for 2-naphthalenethiol. These reaction conditions are also suitable for the coupling of alkyl thiols with iodobenzene (Table 5); ethane-, butane-, and hexanethiol afforded the corresponding cross-coupled products in 91–96% yield (Table 5, entries 1–3). The reactions of substrates with a longer alkyl chain (octane-, decane-, and dodecanethiol) and of benzyl thiol required slightly longer to reach completion

Table 5: CuO-nanoparticle-catalyzed reaction of alkyl thiols with iodobenzene.

Entry	Substrate	*t* [h]	Product	Yield[b] [%]
1	C_2H_5SH	4		95
2	n-C_4H_9SH	6		96
3	n-$C_6H_{13}SH$	7		91
4	n-$C_8H_{17}SH$	7.5		90
5	n-$C_{10}H_{21}SH$	8		89
6	n-$C_{12}H_{25}SH$	11		85
7		11		98

[a] CuO nanoparticles (1.26 mol%), thiol (1 mmol), iodobenzene (1.1 mmol), KOH (1.5 mmol), and DMSO (1 mL) were stirred at 80°C under a nitrogen atmosphere for the time indicated. [b] Yield of the isolated product.

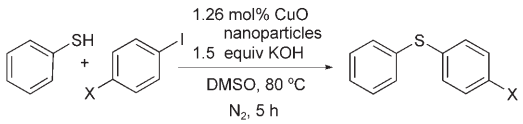
(Table 5, entries 4–7). Both SH groups of butane-1,4-dithiol underwent the cross-coupling reaction to give the corresponding bisarylated product in high yield (Scheme 2).



Scheme 2. CuO-nanoparticle-catalyzed C–S cross-coupling of butane-1,4-dithiol with iodobenzene.

Finally, the reactivity of aryl iodides with electron-withdrawing and electron-donating substituents was studied (Table 6). 1-Iodo-4-nitrobenzene underwent the cross-coupling reaction with benzenethiol to give the desired product in

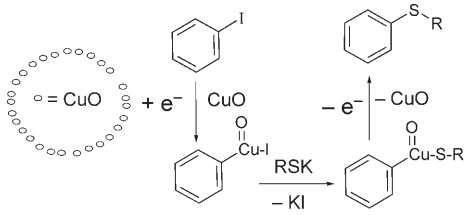
Table 6: CuO-nanoparticle-catalyzed reaction of benzenethiol with aryl iodides.[a]



Entry	X	Yield[b] [%]
1	H	71
2	MeO	14
3	NO_2	83

[a] CuO nanoparticles (1.26 mol%), benzenethiol (1 mmol), aryl iodide (1.1 mmol), KOH (1.5 mmol), and DMSO (1 mL) were stirred for 5 h at 80°C under a nitrogen atmosphere. [b] Yield of the isolated product.

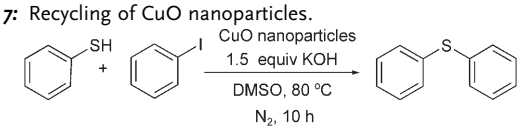
83% yield after a reaction time of 5 h (Table 6, entry 3). When iodobenzene and 4-iodoanisole were treated with benzenethiol under the same conditions for 5 h, the corresponding products were obtained in 71 and 14% yield, respectively (Table 6, entries 1 and 2). The observed decrease in reactivity in the order 1-iodo-4-nitrobenzene > iodobenzene > 4-iodoanisole suggests that these reactions proceed by oxidative addition followed by reductive elimination (Scheme 3).



Scheme 3. Proposed reaction pathway for the CuO-nanoparticle-catalyzed C–S cross-coupling of iodobenzene with thiols in the presence of KOH. R = alkyl, aryl.

The catalyst was found to be recyclable without loss of activity (Table 7). After the reaction of benzenethiol with iodobenzene had reached completion, the catalyst was recovered from the reaction mixture by centrifugation and

Table 7: Recycling of CuO nanoparticles.



Run	Catalyst recovery [%]	Product yield [%]
1[a]	96	95
2[b]	93	89
3[b]	88	81

[a] CuO nanoparticles (1.26 mol%), benzenethiol (1 mmol), iodobenzene (1.1 mmol), KOH (1.5 mmol), and DMSO (1 mL) were stirred for 10 h at 80°C under a nitrogen atmosphere. [b] The recovered catalyst was used under identical reaction conditions to those for the first run.

reused up to three times. Only a slight decrease in catalytic activity was observed.

In conclusion, we have described the C–S cross-coupling of thiols with iodobenzene in the presence of relatively inexpensive air-stable CuO nanoparticles. A variety of thiols could be cross-coupled with iodobenzene in this simple and efficient reaction to give the desired products in high yields. We are currently pursuing the further application of this procedure.

Experimental Section

Typical Procedure: A mixture of iodobenzene (223 mg, 1.1 mmol), benzenethiol (110 mg, 1 mmol), CuO nanoparticles (1.08 mg, 1.26 mol%), and KOH (84 mg, 1.5 mmol) was stirred at 80°C under N_2 in DMSO (1 mL). The progress of the reaction was monitored by TLC (2% ethyl acetate/hexane). When the reaction was complete, the reaction mixture was treated with water (3 mL) and ethyl acetate (10 mL). The organic and aqueous layers were then separated, and the aqueous layer was extracted with ethyl acetate (5 mL). The combined organic solutions were washed with brine (5 mL) and water (5 mL) and dried with Na_2SO_4. The solvent was evaporated, and the residue was passed through a short pad of celite to give analytically pure diphenyl sulfide (176 mg, 95%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.35$–7.24 ppm (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 131.25$, 129.41, 127.71, 127.37 ppm; MS (EI): m/z 186 $[M]^+$.

Received: March 23, 2007
Published online: June 6, 2007

Keywords: aryl halides · C–S coupling · nanoparticles · synthetic methods · thiols

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