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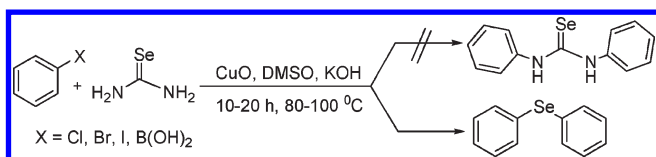
Unexpected C–Se Cross-Coupling Reaction: Copper Oxide Catalyzed Synthesis of Symmetrical Diaryl Selenides via Cascade Reaction of Selenourea with Aryl Halides/Boronic Acids

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Selenourea is used as an effective selenium surrogate in the C–Se cross-coupling reaction catalyzed by copper oxide nanoparticles under ligand free conditions. This protocol has been utilized for the synthesis of a variety of symmetrical diaryl selenides in good to excellent yields from the readily available aryl halides/boronic acids.

Organoselenium compounds are not only important reagents in organic synthesis^{1,2} but also serve as potential drug candidates.³ The biological properties of selenium compounds have attracted increasing attention due to their antioxidant, anticancer, antitumor, and antiviral properties.⁴ In addition, organoselenium compounds offer chemo-, regio-, and stereo-selective reactions and selenium is known as a fundamental

element in life sciences,⁵ and hence, their preparation has also become significant.

Traditional methods for the formation of a C–Se bond require photochemical or harsh reaction conditions, such as the use of polar and toxic solvents like HMPA and high reaction temperatures.⁶ To overcome these difficulties, several metal salts such as palladium-,⁷ nickel-,⁸ copper-,⁹ iron-,¹⁰ indium-,¹¹ and lanthanum-based¹² catalytic systems have been studied for the synthesis of diaryl selenides.

In the present paper, we report the failure of our attempts to transform selenourea (**2**) into the corresponding *N,N'*-disubstituted selenourea (**3**) by the C–N cross-coupling reaction of aryl halides (**1**). However, a very interesting result was obtained from the ¹H NMR spectrum, which showed the formation of a product which no longer contained the NH protons but only aromatic hydrogens. Absorption corresponding to the NH was not observed in the infrared spectrum and comparison with the known compounds. On the basis of these results and the mass spectrum, we propose that the obtained liquid product has the structure **4**.

Recently, heterogeneous catalysts have become attractive both from economic and industrial points of view as compared to homogeneous catalysts. The high surface area and reactive morphologies of nanomaterials allow them to be effective catalysts for organic synthesis.¹³ Furthermore, heterogeneous catalysts have also the advantage of easy product purification and reusability of the catalyst.

In continuation of our interest in the field of cross-coupling reactions,¹⁴ we report herein the CuO nanoparticle-catalyzed unexpected reaction pattern of selenourea and aryl

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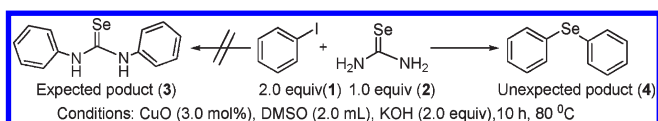
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SCHEME 1. Synthesis of Symmetrical Diphenyl Selenides

TABLE 1. Screening of Copper-Catalyzed Synthesis of Symmetrical Diaryl Selenides^a

entry		copper source	base	solvent	time (h)	temp (°C)	yield ^b (%)
1	Ph-I	Cu ₂ O	Cs ₂ CO ₃	DMF	24	120	15
2		Cu ₂ O	Cs ₂ CO ₃	toluene	24	120	0
3		Cu ₂ O	KOH	DMSO	24	120	20
4		CuO	KOH	DMSO	24	120	25
5		CuO	Cs ₂ CO ₃	toluene	24	120	trace
6		CuO	Cs ₂ CO ₃	DMSO	24	120	18
7		CuO	K ₃ PO ₄	DMSO	24	120	trace
8		CuO	Cs ₂ CO ₃	THF	24	120	0
9		CuO	KOH	DMF	24	120	10
10		CuO	Na ₂ CO ₃	DMF	24	120	10
11		nano CuO	KOH	DMSO	10	80	98
12		nano CuO	KOH	DMSO	10	40	68
13		nano CuO	KOH	DMSO	10	rt	20
14		nano CuO	Cs ₂ CO ₃	DMSO	10	80	89
15		nano CuO	Na ₂ CO ₃	DMSO	10	80	21
16		nano CuO	KOH	toluene	10	80	10
17		nano CuO	K ₃ PO ₄	DMSO	10	80	29
18		nano CuO	KOH	DMF	10	80	41
19				KOH	DMSO	24	80
20		nano CuO		DMSO	24	80	25 ^d
21		nano CuO	KOH	water	24	80	0
22	Ph-B (OH) ₂	nano CuO	KOH	DMSO	10	80	41
23		nano CuO	KOH	DMSO	20	80	60
24		nano CuO	KOH	DMSO	20	100	79

^aReaction conditions: iodobenzene (2.0 mmol), selenourea (1.0 mmol), catalyst (3.0 mol %), base (2.0 equiv), solvent (2.0 mL). ^bIsolated yield. ^cIn the absence of catalyst. ^dIn the absence of base.

halides forming symmetrical diphenyl selenides under ligand-free conditions (Scheme 1). However, to the best of our knowledge, this is the first report on the synthesis of symmetrical diphenyl selenides in the absence of any ligand or cometal catalyst.

Selenourea and iodobenzene were used as model substrates to optimize reaction conditions such as various copper sources, catalysts, bases, solvents, and temperature under nitrogen atmosphere (Table 1). First, several copper oxides were screened (Table 1, entries 1, 4, and 11), and CuO nanoparticles proved to be preeminent for this tandem reaction (Table 1, entry 11). Among various bases screened, KOH and Cs₂CO₃ were found to be excellent bases (Table 1, entries 11, 14). Other bases such as Na₂CO₃ and K₃PO₄ were tested and led to the formation of lesser amounts of the desired product. The effect of solvents was also

TABLE 2. Diaryl Selenides Synthesis from Various Aryl Halides^a

entry	aryl halides	product	yield ^b (%)
1			98
2			61
3			81 ^c
4			trace
5			93
6			76 ^c
7			91
8			95
9			78 ^c
10			78
11			86
12			91
13			84
14			71 ^c
15			90
16			86
17			69 ^c
18			86
19			98

^aReaction conditions: aryl halides (2.0 mmol), selenourea (1.0 mmol), CuO (3.0 mol %), DMSO (2.0 mL), KOH (2.0 equiv), 80 °C. ^bIsolated yield. ^cAfter 20 h.

investigated, and the highest yield was obtained in DMSO (Table 1, entry 11), while reaction in solvents such as toluene, DMF, and water was ineffective (Table 1, entries 16, 18, and 21). The control experiment confirmed that the reaction did not occur in the absence of the catalyst (Table 1, entry 19) as well as the base (Table 1, entry 20). When the reaction was conducted at room temperature and 40 °C, the yields observed were very low (Table 1, entries 12 and 13). The ideal

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TABLE 3. Diaryl Selenide Synthesis from Various Aryl Boronic Acids^a

$$\text{Ar-B(OH)}_2 + \text{H}_2\text{N}-\text{C}(\text{Se})=\text{NH}_2 \xrightarrow[20 \text{ h, } 100^\circ\text{C}]{\text{CuO, DMSO, KOH}} \text{Ar-Se-Ar}$$

entry	boronic acids	product	yield ^b (%)
1			79
2			72
3			76
4			60
5			54
6			61

^aReaction conditions: aryl boronic acid (2.0 mmol), selenourea (1.0 mmol), CuO (3.0 mol %), DMSO (2.0 mL), KOH (2.0 equiv), 100 °C.
^bIsolated yield.

temperature for the reaction was found to be 80 °C. The influence of the amount of catalyst on the yield of the product was evaluated. It is observed that 3.0 mol % of copper oxide is the optimum (Table a, entry 3, Supporting Information).¹⁵ The best result was obtained when the reaction was pursued at 80 °C using 3.0 mol % of the CuO nanoparticles in the presence of KOH (2.0 equiv) and DMSO (2.0 mL).

To explore the scope of copper-catalyzed cascade reaction of selenourea with various aryl halides was investigated under the optimized conditions. In general, all the reactions were very clean, and the diaryl selenides were obtained in high yields (Table 2). This protocol efficiently coupled iodobenzenes having electron-donating groups (e.g., Me, Et, and OMe) with selenourea to produce the corresponding products in excellent yields (Table 2, entries 4, 6, and 7), whereas in the presence of an electron-withdrawing group (NO₂) a slight decrease in the yield of the diaryl selenide (Table 2, entry 9) was observed.

Utilizing these conditions, various heteroaromatic iodides allowed reaction with selenourea to give the corresponding diaryl selenides in excellent yields (Table 2, entries 11, 12, 14, 15, and 17). The reaction of heteroaromatic bromides with selenourea required a longer reaction time to achieve reasonable yields of diaryl selenides (Table 2, entries 13 and 16). Among the 2-iodo/3-iodothiophene and 5-methyl-2-iodothiophenes, the activated ones give a higher yield (Table 2, entries 12, 14, and 15). Iodobenzene was found to be a more reactive substrate than bromo- and chlorobenzenes (Table 2, entries 1–3).

Moreover, the formation of bis(3-bromophenyl)selenane as the major product in the reaction of *m*-bromiodobenzene implied that there was good chemoselectivity between iodo and bromo substituents (Table 2, entry 10). This protocol was also applied for the cross-coupling of alkyl bromide

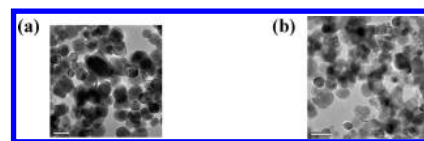
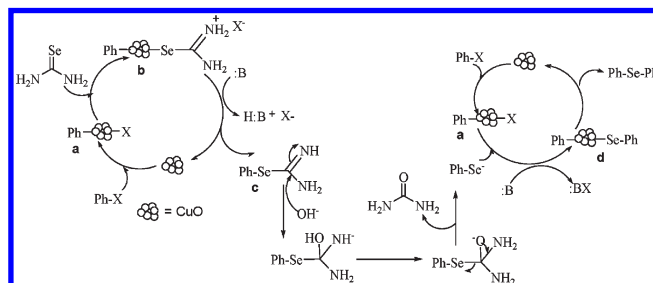


FIGURE 1. TEM images of (a) fresh nano-CuO particles and (b) nano-CuO particles after the fourth cycle.

SCHEME 2. Plausible Mechanism for the CuO Nano Particle Catalyzed C–Se Cross-Coupling of Aryl Halides with Selenourea



(e.g., benzyl bromide) with selenourea, and the corresponding product was obtained in excellent yields (Table 2, entry 18).

This protocol was also applied for the cross-coupling of arylboronic acids with selenourea, and the corresponding diaryl selenides were obtained in high yields with the same catalyst (Table 3). However, the C–Se cross-coupling of various substituted aryl boronic acids with selenourea required longer reaction times and higher temperatures to get reasonable yields of diaryl selenides, whereas shorter reaction times and lower temperatures led to decreased yields (Table 1, entries 22–24).

To check the recyclability of the catalyst, after each cycle, the reaction mixture was allowed to cool and the catalyst was recovered by ultracentrifugation, washed with ethyl acetate and acetone, dried under reduced pressure, and reused for further catalytic reactions. The catalyst maintained its high level of activity even after the fourth cycle as shown in Table b (Supporting Information).¹⁵

These reactions involve a heterogeneous process. TEM images of the catalyst indicated no change before and after the reaction, which further confirmed the heterogeneous nature of the catalyst (Figure 1).

A plausible mechanism for the CuO nanoparticle catalyzed C–Se cross-coupling of aryl halides and selenourea is shown in Scheme 2.¹⁶ Oxidative addition of aryl halide to copper oxide nanoparticles leads to the formation of **a**, which undergoes reaction with selenourea to give the intermediate **b**, which gets transformed to the intermediate Se-arylisoselenourea salt **c** by reductive elimination, and this upon hydrolysis in the reaction mixture produces a benzeneselenate moiety and urea. In this step, urea is hydrolyzed in situ to produce carbon dioxide and ammonia as the final products.¹⁷ Oxidative addition of aryl iodide to copper oxide nanoparticles leads to the formation of **a**, which undergoes reaction with benzeneselenate anion to give the intermediate **d** and that completes the catalytic cycle to produce diaryl selenide by reductive elimination.

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In summary, this is the first reported reaction of aryl halides/boronic acids with selenourea for the synthesis of symmetrical diaryl selenides catalyzed by CuO nanoparticles under ligand-free conditions in the absence of any additive. Various aryl halides/boronic acids underwent cross-coupling with selenourea to give the corresponding products in excellent yields. The catalyst is cheap, air stable, and recyclable and functions under ligand-free conditions.

Experimental Section

General Procedure. To a stirred solution of iodobenzene (2.0 mmol) and selenourea (1.0 equiv) in dry DMSO (2.0 mL) at rt was added nano CuO (3.0 mol %) followed by KOH (2.0 equiv) and the mixture heated at 80 °C for 10 h. The progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was allowed to cool, and a 1:1

mixture of ethyl acetate/water (20 mL) was added. The combined organic extracts were dried with anhydrous Na₂SO₄. The solvent and volatiles were completely removed under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the corresponding coupling product in 98% yield: colorless oil; ¹H NMR (CDCl₃, 200 MHz) δ 7.43–7.41 (m, 4H), 7.24–7.22 (m, 6H); ¹³C NMR (CDCl₃, 50 MHz) δ 132.9, 131.3, 129.2, 127.2.

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Supporting Information Available: Detailed experimental procedures and compound characterization data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.