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LETTERS

A general method for the formation of diaryl selenides using copper(I) catalysts

Rattan K. Gujadhur and D. Venkataraman*

Department of Chemistry, University of Massachusetts, Amherst, 710 North Pleasant Street, Amherst, MA 01003, USA

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Abstract—We report a mild, palladium-free synthetic protocol for the cross coupling reaction of aryl iodides and phenyl selenol using 10 mol% CuI/neocuproine, NaO*t*-Bu or K_2CO_3 as base, in toluene, at 110°C. Using this protocol, we show that a variety of diaryl selenides can be synthesized in good yields from commercially available aryl iodides. © 2002 Elsevier Science Ltd. All rights reserved.

Diaryl selenides have attracted considerable interest because of their potential as anticancer and antioxidant agents.[1] They are also key intermediates in the synthesis of a plethora of biologically and pharmaceutically important selenium compounds such as selenonium salts, selenoxides, selenimines, and selenide dihalides.[2] In recognition of their importance, various synthetic methods for the formation of diaryl selenides have been reported in the literature.[3] Earlier methods often require photochemical or harsh reaction conditions such as the use of polar, toxic solvents such as HMPA and high reaction temperatures.[4] Other reported protocols include the reaction of aryl halide and benzeneselenate anion in liquid ammonia under UV light and the reaction of sodium selenide with arenediazonium salts.[5] In recent years, only a handful of reports have appeared in the literature with synthetic protocols for the formation of aryl–selenium bonds that are general, mild and tolerant. In 1985, Cristau and co-workers first showed that aryl selenides can be obtained by a cross-coupling reaction of aryl halides and sodium benzeneselenolate using Ni(II)-based catalysts.[6] In 2000, Millois and Diaz modified and extended Cristau's method to accommodate diaryl diselenide as a starting material instead of sodium benzeneselenolate.[7] Very recently, the groups of Nishiyama and Beletskaya have independently reported protocols for the cross coupling reaction of aryl iodides and $PhSeSnBu_3$ using palladium-based catalysts.[8]

Table 1. Optimization of the reaction between aryl iodide and phenyl selenol

Entry	Base	GC yield (%)
1	CsF	<5
2	Cs_2CO_3	<5
3	KO*t*-Bu	<10
4	K_2CO_3	70
5	Na_2CO_3	70
6	K_3PO_4	82
7	NaO*t*-Bu	92

In the past 5 years, there has been a resurgence in interest in developing mild synthetic methods based on copper-based catalysts as an alternative to palladium(0) catalysts for the formation of aryl–carbon and aryl–heteroatom bonds. In this regard, the D.V. group[9] and others[10,11] have reported copper-based methods for the formation of aryl–carbon, aryl–nitrogen, aryl–oxygen and aryl–sulfur bonds. In addition to being simple and mild, these protocols also accommodate substrates that do not undergo coupling by palladium catalysis.[12] Moreover, in comparison to palladium, copper-based catalysts are quite attractive from an economic standpoint, especially in large and industrial scale syntheses.[13] We now extend the utility of copper-based catalysts for the formation of aryl-selenium bonds.

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* Corresponding author. Tel.: 413-545-2028; fax: 413-545-4490; e-mail: dv@chem.umass.edu

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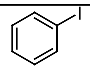
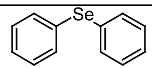
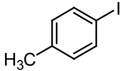
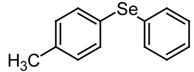
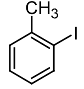
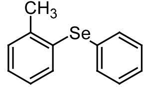
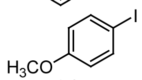
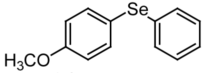
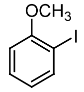
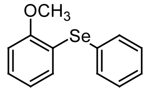
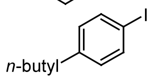
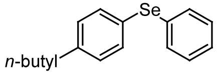
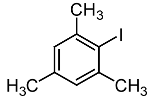
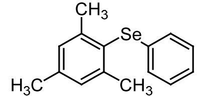
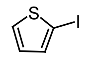
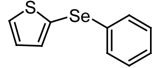
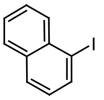
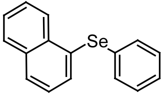
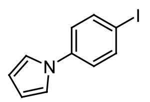
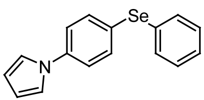
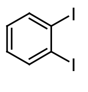
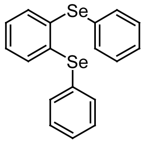
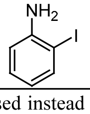
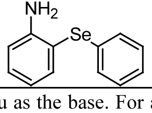
We began the investigation of the cross-coupling reaction between aryl iodides and phenyl selenol using 10 mol% CuI/neocuproine[14] with NaO*t*-Bu as the base and toluene as the solvent. We were pleased to find that using this protocol, in 24 h, the reaction between iodobenzene and phenyl selenol was complete. The ligand, neocuproine, was found to be essential for the reaction, since its absence gave no conversion to the desired product. If in the reaction protocol neocuproine was replaced by phenanthroline, diphenyl selenide was obtained in a lower yield (70% by GC). Moreover, the reaction with the well-defined complex Cu(neocuproine)(PPh_3)Br showed complete conversion to the product after the same period of time. We chose to use CuI/neocuproine as our catalyst instead of the well-defined Cu(neocuproine)(PPh_3)Br, since it gave identical results and dispenses with the need to synthesize the complex. After having established the efficacy of the CuI/neocuproine catalytic system for the formation of aryl–selenium bonds, we then studied the effect of the base on these reactions (see Table 1).

We found that NaO*t*-Bu was the most effective base for this reaction. In contrast, KO*t*-Bu was not an effective base in our protocol, similar to what we had observed for the formation of aryl–sulfur bonds. Milder bases such as K_3PO_4, K_2CO_3 and Na_2CO_3 provided diphenyl selenide in moderate yields. Other mild bases such as CsF and Cs_2CO_3 were ineffective. In our protocol, we then replaced iodobenzene with bromobenzene. By GC, in addition to both the starting materials, significant amount of diphenyl diselenide was observed, presumably from the oxidation of phenyl selenol. This indicated that the reaction was selective to iodides.

Using our protocol,[†] we were able to couple phenyl selenol with electron-rich aryl iodides in very good yields (Table 2). We were able to couple sterically hindered iodides such as those with *ortho*-functionalities (entries 3, 5, 7 and 11), as well as aryl iodides containing heteroatoms (entry 8 and 10). When *o*-iodoaniline was used as the aryl halide, in addition to the desired selenide, we observed products arising from the self-coupling of *o*-iodoaniline. This problem also persisted with K_3PO_4. However, when K_2CO_3 was used

Table 2. Reaction of electron-rich aryl iodides and phenyl selenol

Entry	Aryl Iodide	Product	Isolated Yield (%)
1			90
2			84
3			80
4			88
5			78
6			80
7			82
8			68
9			82
10			76
11			81
12			60*

*K_2CO_3 was used instead of NaO*t*-Bu as the base. For all entries, catalyst loading: 10 mol% CuI & 10 mol% neocuproine, solvent: toluene, temperature: 110°C

[†] **General procedure**: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar, was charged with sodium *tert*-butoxide (Acros, 3.0 mmol), CuI (10 mol% with respect to the aryl iodide), and neocuproine (10 mol% with respect to the aryl iodide). The tube was then sealed with a rubber septum, taken out of the glove box and phenol selenol (2.2 mmol), the aryl iodide (2.00 mmol) and toluene (4.0 mL) were injected into the tube through the septum. The contents were then stirred at 110°C for 24 h. The reaction mixture was then cooled to room temperature and filtered to remove any insoluble residues. The filtrate was concentrated in vacuo; the residue was purified by flash column chromatography on silica gel to obtain the analytically pure product.

Spectroscopic data for selected products from Table 2.

Entry 6: The general procedure was used to convert 4-*n*-butyliodobenzene and phenyl selenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a transparent oil (464 mg, 80% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.31 (m, 4H), 7.18–7.13 (m, 3H), 7.03–6.99 (m, 2H), 2.53 (t, 2H), 1.53–1.18 (m, 4H), 0.87 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.56, 133.65, 132.14, 131.93, 129.49, 129.17, 127.0, 126.86, 32.25, 33.46, 22.31, 13.92 (C_8). Anal. calcd for $C_{16}H_{18}Se$: C, 66.43; H, 6.27; Found C, 66.68; H, 6.54%.

Entry 10: The general procedure was used to convert 1-(4-iodophenyl)pyrrole and phenyl selenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a white solid (450 mg, 76% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.38 (m, 3H), 7.26–7.19 (m, 6H), 7.07 (t, J=4.3, 2H), 6.28 (t, J=4.3, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.54 (C_3), 133.35, 132.68, 131.85, 129.40, 127.38, 125.0, 121.16, 119.13, 110.70. Anal. calcd for $C_{16}H_{13}NSe$: C, 64.43; H, 4.39. Found C, 64.35; H, 4.56. Melting point: 86–88°C. All other compounds reported in Tables 2 and 3 are known.

as the base, we were able to isolate 1-amino-2-phenylselanyl-benzene in 60% yield (entry 12). With electron-poor aryl iodides, in addition to the desired diaryl selenides, we observed diaryl diselenides if NaO*t*-Bu or K_3PO_4 was used. In addition, with NaO*t*-Bu, transesterifcation products were observed when aryl halides with ester groups were used. We found that these problems can be avoided if K_2CO_3 was used instead of NaO*t*-Bu or K_3PO_4. Using this modified protocol we were able to obtain a variety of diaryl selenides from electron-poor aryl halides (Table 3). The protocol tolerates even base sensitive groups such as esters and ketones (entries 3, 4, and 6).

In summary, we have reported a general synthetic protocol for the formation of diaryl selenides, using copper(I) catalysts. In this protocol, we recommend the use of 10 mol% CuI, 10 mol% neocuproine, NaO*t*-Bu as the base, and toluene as the solvent for electron-rich aryl iodides. For electron-poor aryl iodides, we recommend the use of K_2CO_3 in the place of NaO*t*-Bu. Our protocol is palladium-free and avoids the use of expensive and/or air-sensitive ligands, and makes use of readily available phenyl selenols. We are in the process of expanding the scope of these reactions and will be reporting on them shortly.[15]

Acknowledgements

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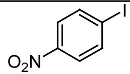
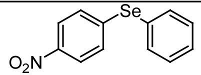
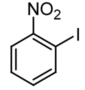
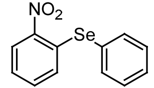
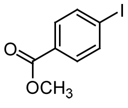
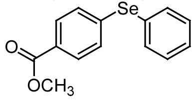
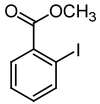
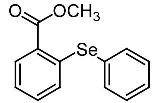
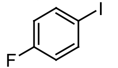
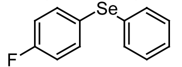
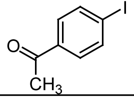
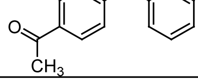
Table 3. Reaction of electron-poor aryl iodides and phenyl selenol

Entry*	Aryl Iodide	Product	Isolated Yield (%)
1			75
2			81
3			78
4			76
5			92
6			78

*For all entries, catalyst loading: 10 mol% CuI & 10 mol% neocuproine, solvent: toluene, temperature: 110°C.

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14. Neocuproine is 2,9-dimethyl-1,10-phenanthroline.
15. During our recent investigations we found that phenyl boronic acid can be coupled with phenyl selenol to form diphenyl selenide, using the methodology developed by Lam and Chan. This methodology uses copper(II) acetate in stoichiometric amounts, with triethylamine as the base and dichloromethane as the solvent.