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Copper-Catalyzed Domino One-Pot Synthesis of 2-(Arylselanyl)arylcyanamides

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Keywords: Copper / Selenium / Heterocycles / Cross-coupling / Domino reactions

Domino C–Se cross-coupling of 2-(iodoaryl)selenoureas with aryl iodides has been accomplished in the presence of a copper(I)–1,1-phenanthroline complex at moderate temperature. The reactions involve intra- and intermolecular C–Se cross-coupling to give the substituted 2-(arylselanyl)arylcyanamides. Aryl iodides having electron-donating and -withdrawing substituents are compatible, affording the target selanyl ethers in high yield.

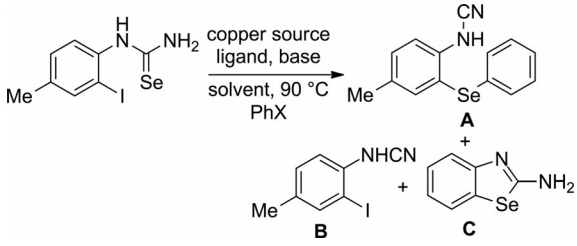
Introduction

The cross-coupling reactions of aryl halides with heteroatom nucleophiles using transition metal catalysts are powerful tools for the construction of carbon–heteroatom bonds that are important in biological, materials, and pharmaceutical sciences.[1] Recently, the formation of C–N, C–O, and C–S bonds have made considerable progress. Subsequently, a few studies have focused on the construction of C–Se bonds, as this moiety is present in many biologically and pharmaceutically active compounds.[2,3] Selenides also play an important role in synthetic chemistry as versatile reagents for synthesis.[4] Similarly, cyanamides have attracted much attention in biological and pharmaceutical sciences because of their unique structure.[5,6] For example, cyanamides serve as important intermediates for the synthesis of minoxidil[7] and herbicides.[8] They also find use as tumor inhibitors.[9] The development of methods for the synthesis of compounds having these two aforementioned moieties will be thus useful in organic synthesis. In this contribution, we wish to report a novel copper(I)-catalyzed one-pot domino C–Se cross-coupling reaction of 2-(iodoaryl)selenoureas with aryl iodides to afford substituted 2-(arylselanyl)arylcyanamides at moderate temperature in high yield. The reactions are efficient and take place via intra- and intermolecular C–Se cross-coupling reactions. Aryl iodides having electron donating and -withdrawing substituents are compatible. To the best of our knowledge, this is the first example available for the synthesis of 2-(arylselanyl)arylcyanamides.

Results and Discussion

First, the reaction conditions were optimized with *N*-(2-iodo-4-methylphenyl)selenourea and iodobenzene as model substrates (Table 1). Among the set of ligands examined,

Table 1. Optimization of the reaction conditions.



Entry	[Cu] Source	Ligand	Solvent	X	Time [h]	% Yield[a,b] A	B	C
1	$CuSO_4·5H_2O$	–	DMSO	I	1	–	95	–
2	CuI	–	DMSO	I	3	30	20	45
3	CuI	**L7**	DMSO	I	1	95	–	–
4[c]	CuI	**L7**	DMSO	I	3	43	15	37
5[d]	CuI	**L7**	DMSO	I	3	53	16	26
6	CuI	**L7**	DMF	I	3	49	15	35
7	CuI	**L7**	toluene	I	1	–	94	–
8	CuI	**L7**	1,4-dioxane	I	1	–	94	–
9	CuI	**L1**	DMSO	I	3	45	15	35
10	CuI	**L2**	DMSO	I	1	–	92	–
11	CuI	**L3**	DMSO	I	3	25	25	45
12	CuI	**L4**	DMSO	I	3	37	23	35
13	CuI	**L5**	DMSO	I	3	25	10	60
14	CuI	**L6**	DMSO	I	3	35	18	45
15[e]	CuI	**L7**	DMSO	I	4	62	–	33
16[f]	CuI	**L7**	DMSO	I	4	49	–	46
17[g]	CuI	**L7**	DMSO	I	3	50	–	45
18	CuBr	**L7**	DMSO	I	3	55	15	25
19	Cu_2O	**L7**	DMSO	I	1	–	95	–
20	CuI	**L7**	DMSO	Br	6	20	–	75
21	CuI	**L7**	DMSO	Cl	6	–	–	94

[a] Substrate (0.5 mmol), copper source (5 mol-%), **L1**–**7** (5 mol-%), Cs_2CO_3 (0.75 mmol), and iodobenzene (0.5 mmol) were stirred in solvent (1 mL) at 90 °C. [b] Isolated yield. [c] K_2CO_3 used. [d] K_3PO_4 used. [e] T = 80 °C. [f] Cs_2CO_3 (1 equiv.) used. [g] Catalyst (2.5 mol-%) used.

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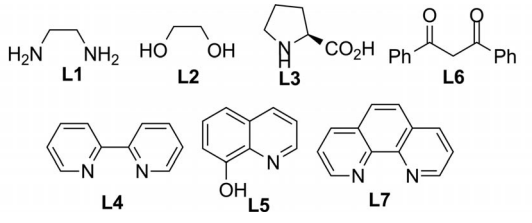
1,10-phenanthroline (**L7**) afforded the best results, giving selectively product **A** in 99% yield (Table 1, Entry 3). In contrast, ethylene diamine (**L1**), ethylene glycol (**L2**), L-proline (**L3**), 2,2′-bipyridine (**L4**), 8-hydroxyquinoline (**L5**), and dibenzoylmethane (**L6**) were found to be less selective, giving **B** or **C** or both as byproducts along with target molecule **A**. Recrystallization of **A** in MeOH gave single crystals whose X-ray analysis is presented in Figure 1. A control experiment confirmed that a mixture of **A**, **B**, and **C** were detected without the aid of ligand **L7** (Table 1, Entry 2). The catalytic activity of different copper sources was evaluated, and CuI was found to be superior to CuBr, Cu_2O, and $CuSO_4·5H_2O$. DMSO was found to be the solvent of choice, whereas DMF, toluene, and 1,4-dioxane gave inferior results. Of the screened bases, K_2CO_3, K_3PO_4, and Cs_2CO_3, Cs_2CO_3 gave the best results. Reaction temperature was another important factor that affected the results, and 90 °C was found to be the optimum temperature. A blank reaction run without a copper salt gave **B** as the sole product and the formation of **A** was not observed. This result suggests that, in the absence of a copper(I) complex, the base-promoted deselenization takes place to afford cyanamide **B**.



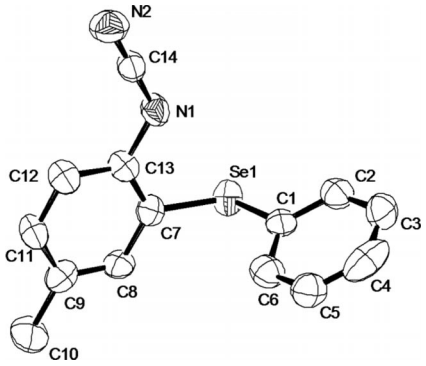
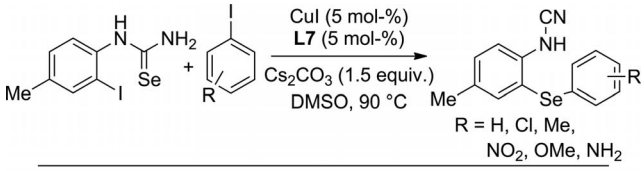
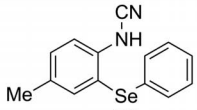
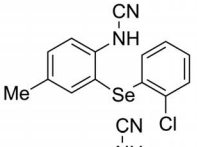
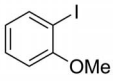
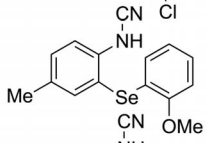
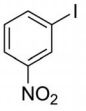
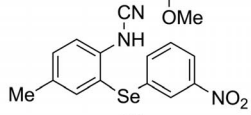
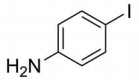
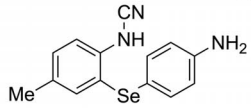
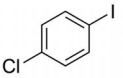
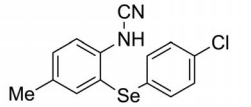
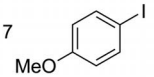
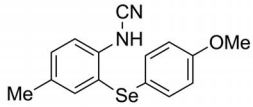
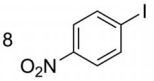
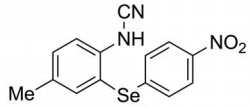
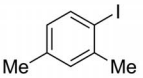
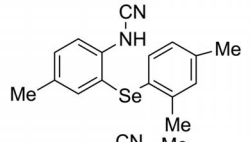
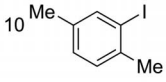
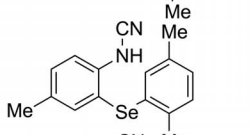
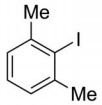
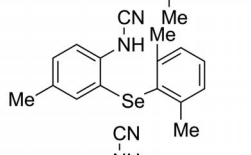
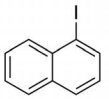
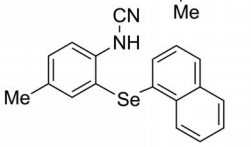


Figure 1. ORTEP diagram of 2-(phenylselanyl)-4-methylphenylcyanamide with 50% ellipsoids.[10] H atoms are omitted for clarity.

The reactivities of other aryl halides were further compared. The reactions with bromobenzene and chlorobenzene gave **C** as the only product. Likewise, reaction of *N*-(2-bromo-4-methylphenyl)selenourea with iodobenzene gave a 4:15 mixture of 2-bromo-4-methylphenylcyanamide and **C** in >99% yield, whereas *N*-(2-chloro-4-methylphenyl)selenourea did not undergo any cross-coupling with iodobenzene and afforded 2-chloro-4-methylphenylcyanamide as the sole product in >99% yield. In summary, the optimal conditions in DMSO consist of the combination of CuI (5 mol-%) and **L7** (5 mol-%) along with the presence of Cs_2CO_3 (1.5 equiv.) at 90 °C for 1 h.

Table 2. The cross-coupling of *N*-(2-iodo-4-methylphenyl)-selenourea with substituted aryl iodides.[a]



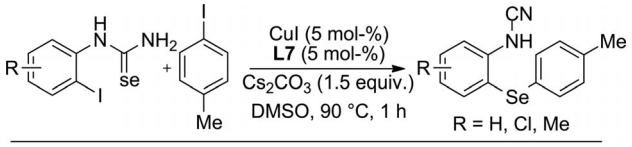
Entry	Aryl iodide	Time [h]	Product	Yield [%][b]
1		1		95
2		1.5		85
3		2		89
4		1.5		85
5		2		87
6		1.5		89
7		2		91
8		1.5		75
9		1		92
10		1		94
11		1.5		88
12		1.5		93

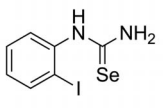
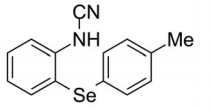
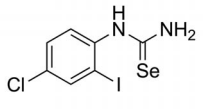
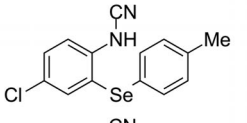
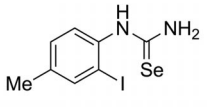
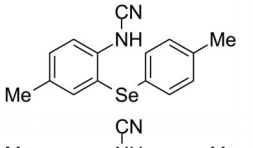
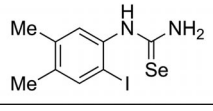
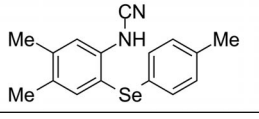
[a] *N*-(2-Iodo-4-methylphenyl)selenourea (0.5 mmol), aryl iodide (0.5 mmol), CuI (5 mol-%), 1,10-phenanthroline (5 mol-%), and Cs_2CO_3 (0.75 mmol) were stirred at 90 °C in DMSO (1 mL) in air. [b] Isolated yield.

Next, to reveal the scope of the procedure, the reaction of a series of substituted aryl iodides was explored with *N*-(2-iodo-4-methylphenyl)selenourea (Table 2). Aryl iodides having 2-Cl, 2-OMe, 3-NO_2, 4-NH_2, 4-Cl, 4-OMe, and 4-NO_2 substituents readily participated in the C–Se domino cross-coupling reaction to give 2-(aryl selanyl)arylcyanamides in 1–2 h with yields ranging from 75 to 95%. Similarly, aryl iodides with 2,4-Me, 2,5-Me, and 2,6-Me groups and 1-naphthyl iodide gave the corresponding 2-(arylselanyl)arylcyanamides in high yield.

Finally, the reactions of the substituted *N*-(2-iodo-4-methylphenyl)selenoureas with aryl iodides were studied (Table 3). For example, *N*-(2-iodo-4-methylphenyl)selenourea having 4-Cl, 4-Me, and 4,5-Me substituents underwent domino C–Se cross-coupling with 1-iodo-4-methylbenzene to afford the respective substituted 2-(arylselanyl)-arylcyanamides in 1 h with 90–95% yields. These results clearly suggest that the present protocol can be used for the one-pot synthesis of 2-(arylselanyl)arylcyanamides.

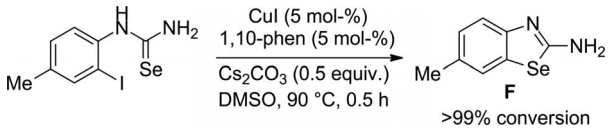
Table 3. The cross-coupling of substituted selenoureas with 1-iodo-4-methylbenzene.[a]



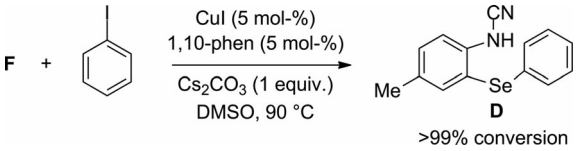
Entry	*N*-(2-Iodoaryl)selenourea	Product	Yield [%][b]
1			95
2			91
3			95
4			90

[a] *N*-(2-Iodoaryl)selenourea (0.5 mmol), 1-iodo-4-methylbenzene (0.5 mmol), CuI (5 mol-%), **L7** (5 mol-%), and Cs_2CO_3 (0.75 mmol) were stirred at 90 °C for 1 h in DMSO (1 mL). [b] Isolated yield.

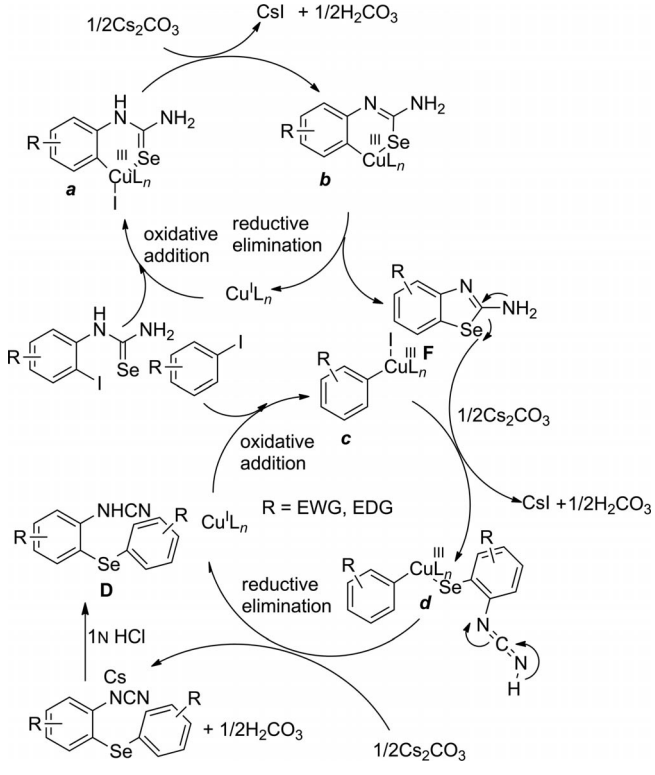
Regarding the mechanism, control experiments were pursued. The cyclization of (2-iodo-4-methylphenyl)selenourea was studied with 0.5 equiv. of Cs_2CO_3 in the absence of an aryl iodide (Scheme 1). The cyclization occurred to give 2-aminobenzoselenazole **F** in 0.5 h with 100% selectivity. Next, the reaction of **F** was studied with iodobenzene in the presence of 1 equiv. of Cs_2CO_3 (Scheme 2). Benzoselenazole **F** underwent reaction in the presence of Cu^I–1,10-phenanthroline to give **D** in quantitative yield. The intramolecular cyclization was found to be faster than the intermolecular reaction. These results suggest that the process involves intramolecular followed by intermolecular C–Se domino cross-coupling reactions (Scheme 3). Thus, the selenourea may undergo chelation followed by oxidative addition with copper(I)–1,10-phenanthroline to give metallocycle ***b***, which could lead to the formation of **F** by reductive elimination. The cross-coupling of **F** with ***c*** may afford intermediate ***d***, which could complete the catalytic cycle by reductive elimination of target molecule **D**.



Scheme 1.



Scheme 2.



Scheme 3. Proposed catalytic cycle.

Conclusions

In conclusion, a novel copper-catalyzed domino C–Se cross coupling of (2-iodoaryl)selenoureas with aryl iodides has been developed to afford the substituted (2-selanylaryl)-

arylcyanamides. The procedure involves intra- and intermolecular C–Se cross-coupling reactions at moderate temperature.

Experimental Section

General Procedure for the Synthesis of 2-(Arylselanyl)arylcyanamides: To a stirred solution of 1,10-phenanthroline (5 mol-%) and CuI (5 mol-%) in DMSO (1 mL) was added the *N*-(2-iodoaryl)-selenourea (0.5 mmol), aryl iodide (0.5 mmol), and Cs_2CO_3 (244 mg, 0.75 mmol) at ambient temperature, and the mixture was allowed to stir at 90 °C for the appropriate time. Progress of the reaction was monitored by TLC (ethyl acetate/hexane). The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (10 mL). The solution was washed successively with 1 N HCl (1 × 3 mL) and water (3 × 3 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography (ethyl acetate/hexane) to afford the 2-(arylselanyl)arylcyanamide in analytically pure form.

Supporting Information (see footnote on the first page of this article): Characterization data and copies of the ^1H and ^{13}C NMR spectra of the 2-(arylselanyl)arylcyanamides.

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[10] Recrystallization of 2-(phenylselanyl)-4-methylphenylcyanamide in MeOH afforded single crystals whose X-ray data were collected with a Bruker SMART APEX equipped with a CCD area detector using Mo-K_α radiation in the scan range 1.20–28.31°. $C_{14}H_{12}N_2Se$, Mw = 287.22, orthorhombic; space group $Pna2_1$, a = 8.0688(3) Å, b = 19.6845(9) Å, c = 15.9556(7) Å; α = 90°, β = 90°, γ = 90°, V = 2534.23(19) Å^3, Z = 8, $\rho_{calcd.}$ = 1.506 mg/m^3; T = 296(2) K, crystal dimension 0.3 × 0.2 × 0.2 mm^3; 3786 reflections; $F(000)$= 1152.0, Final [$I > 2\sigma(I)$]; R_1 = 0.0636, wR_2 = 0.1617, R Indices (all data) R_1 = 0.0771, WR_2 = 0.1721, GOF (on F^2) = 0.905. CCDC-779997 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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