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# Microwave-assisted Synthesis of Diaryl Selenides. Elucidation of Cu(I)-catalyzed Reaction Mechanism

Irina P. Beletskaya,*[1] Alexander S. Sigeev,[1] Alexander S. Peregudov,[2] Pavel V. Petrovskii,[2] and Victor N. Khrustalev[2]
[1]*Department of Chemistry, Moscow State University, GSP-3, Moscow 119899, Russia*
[2]*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Science, Vavilova str. 28, V-344, Moscow 119991, Russia*

(Received April 12, 2010; CL-100355; E-mail: beletska@org.chem.msu.ru)

A novel microwave-assisted cross-coupling of trialkyltin arylselenides **1** with arylbromides using $[(phen)CuI]_2$ afforded unsymmetrical diarylselenides **3** in high to excellent yields. A plausible catalytic cycle for Cu(I)-catalysed cross-coupling has been proposed. A key intermediate in this catalytic cycle was synthesized and its structure was determined by X-ray diffractometry.

The microwave-assisted organic synthesis has received wide recognition in recent years since it provides drastic decrease in reaction times.[1] This can significantly influence the selectivity and yields of products in some reactions.[2]

Compounds containing arylchalcogenide structural motif have attracted considerable attention due to their various practical and scientific applications. They include substances of pharmaceutical[3] and material[4] interest. Earlier, we have shown that easily available trialkyltin arylselenides $ArSeSnAlk_3$[5] are an excellent source of ArSe-group in the cross-coupling reactions with aryl,[6] alkyl,[7] and acylhalogenides.[8] At the same time these compounds can disproportionate in the presence of palladium complexes at temperatures more than 90 °C with formation of $Ar_2Se$ and $(Alk_3Sn)_2Se$.

$$ArSeSnBu_3 \xrightarrow{[M],\Delta} Ar_2Se + (Bu_3Sn)_2Se \qquad (1)$$

In contrast, Cu(I) complexes with bidentate N,N-ligands (2,2′-bipyridine (bpy), 1,10-phenanthroline (phen)) turned out to be excellent catalysts for this reaction leading to unsymmetrical diarylselenides in high yields.[6b]

In the present work we have carried out the reaction of 4-$ClC_6H_4SeSnBu_3$ (**1a**) with various aryl and hetarylbromides in the presence of 5% $[(phen)CuI]_2$ under microwave (MW) irradiation (Table 1).[10] The microwave activation drastically decreased the reaction time: from 6–30 h to 15–50 min.

The yields of diarylselenides were also higher in the case of the microwave-assisted reactions. If for active ArBr **2a**–**2c** the increase in yield was not more than 2–6% (Entries 1–3), for deactivated aryl bromides **2g** and **2h** it was more significant (15–26%) (Entries 7 and 8). In the case of 4-bromoaniline (**2h**), the difference in results of MW and conventional heating was connected with ammonolysis of **1a** by aniline with formation of ArSeH which was unreactive under conventional heating conditions (Entry 8).

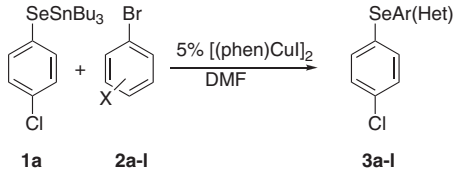
For deactivated arylbromides **2i** and **2l** with steric hindrances the increase in yields was more than 30% (Entries 9 and 12). Even for very unreactive 3-bromo-2-*tert*-butylimidazo[1,2*a*]pyrimidine (**2l**), diarylselenide **3l** was obtained in moderate yield (48%) after 50 min of MW heating.

In contrast, conventional heating leads mainly to the disproportion product: $(4\text{-}ClC_6H_4)_2Se$ (>30%, GC). The yield of cross-coupling product **3l** was very low (<15%, GC) (Entry 12).

In the case of several bromine atoms in arylbromide, selective substitution can be performed (Table 2).[10]

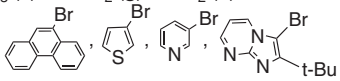
The selective monosubstitution in 2,6-dibromopyridine (**2m**) in the microwave-assisted reaction proceeds with high selectivity (Entry 1) with the use of 0.95 equiv of **1a** vs. 1.1 equiv in the standard protocol and leads to a monosubstituted product in 85% yield. Although under the conventional heating conditions the overall substitution yield being almost the same,

**Table 1.** Cross-coupling of arylbromides with **1a**: Conventional heating vs. microwave assistance

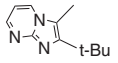



**1a** **2a-l** **3a-l**

X = 4-$NO_2$ (**a**), 4-CN (**b**), 3,4,5-$Cl_3$ (**c**), 4-Ac (**d**) 3-$CF_3$ (**e**), 4-$NMe_2$ (**g**), 4-$NH_2$ (**h**), 2-Me-4-$NH_2$ (**i**)

ArBr = 

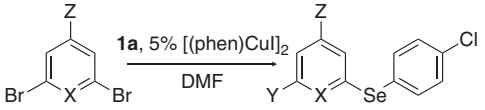

(**f**) (**j**) (**k**) (**l**)

| Entry | Ar(Het) | MW, 140 °C | | 110 °C | |
|---|---|---|---|---|---|
| | | *t*/min | Yield[a]/% | *t*/h | Yield[a]/% |
| 1 | 4-$NO_2C_6H_4$ | 12 | 96 | 6 | 90 |
| 2 | 4-$NCC_6H_4$ | 15 | 93 | 6 | 89 |
| 3 | 3,4,5-$Cl_3C_6H_2$ | 15 | 97 | 6 | 95 |
| 4 | 4-$AcC_6H_4$ | 15 | 91 | — | — |
| 5 | 3-$CF_3C_6H_4$ | 20 | 90 | — | — |
| 6 |  | 18 | 87 | — | — |
| 7 | 4-$Me_2NC_6H_4$ | 25 | 87 | 14 | 72 |
| 8 | 4-$NH_2C_6H_4$ | 25 | 82[b] | 16 | 56[c] |
| 9 | 4-$NH_2$-2-$MeC_6H_3$ | 25 | 65 | 18 | 31 |
| 10 | 3-Thienyl | 15 | 88 | 5 | 81 |
| 11 | 3-Py | 20 | 88 | — | — |
| 12 |  | 50 | 48 | 30 | (15)[d] |

[a]Isolated yield. The GC yield is given in parentheses. [b]<4% of $(4\text{-}ClC_6H_4Se)_2$ by GC. [c]ca. 12% of $(4\text{-}ClC_6H_4Se)_2$ by GC. [d]>30% $(4\text{-}ClC_6H_4)_2Se$ by GC.

**Table 2.** Cross-coupling with di- and tribromides

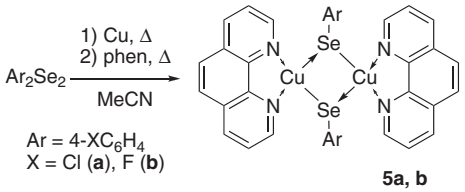



**2m**: X = N, Z = H
**2n**: X = CH, Z = Br

**4a**: X = N, Y = Br, Z = H
**4b**: X = N, Y = 4-ClC$_6$H$_4$Se, Z = H
**4c**: X = CH, Y = Z = Br
**4d**: X = CH, Y = 4-ClC$_6$H$_4$Se, Z = Br
**4e**: X = CH, Y = Z = 4-ClC$_6$H$_4$Se

| Entry | 2 | 1a/equiv | 4 | MW, 140 °C | | 110 °C | |
|---|---|---|---|---|---|---|---|
| | | | | $t$/min | Yield[a]/% | $t$/h | Yield[a]/% |
| 1 | **m** | 0.95 | **4a** | 15 | 85[b] | 5 | 68[c] |
| 2 | **m** | 2.2 | **4b** | 20 | 90 | 7 | 85 |
| 3 | **n** | 0.8 | **4c** | 15 | (40)[d] | — | — |
| 4 | **n** | 2.2 | **4d** | 30 | 85 | — | — |
| 5 | **n** | 3.5 | **4e** | 60 | 80 | — | — |

[a]Isolated yield. The GC yield is given in parentheses. [b]<5% of **4b** by GC. [c]ca. 10% of **4b** by GC. [d]ca. 20% of **4d** by GC.




**Scheme 1.** Synthesis of [(phen)CuSeAr]$_2$.

the yield of **4a** was markedly lower. Thus, in the microwave mode the selectivity of monosubstitution was significantly higher: the ratio of **4a**/**4b** was 17:1 vs. 6.8:1 in the case of the conventional heating (Entry 1).

For 1,3,5-tribromobenzene (**2n**), the monosubstitution was not selective. Even with the use of 0.8 equiv of **1a** we observed the formation of significant quantities of disubstituted product **4d** (ca. 20% by GC). The yield of **4c** was ca. 40% by GC (Entry 3). In contrast, the disubstitution with 2 equiv of **1a** was highly selective and led to the corresponding bis-selenide **4d** in 85% yield (Entry 4). The trisubstitution proceeds significantly slower but selectively gives selenide **4e** in high yield (80%) (Entry 5).

To elucidate the Cu(I)-catalyzed cross-coupling mechanism, we have synthesized the most probable reaction intermediate **5** (Scheme 1).[10]

Copper(I) arylselenolate was obtained by the reaction of the corresponding diaryldiselenide with a freshly prepared copper powder. The reaction of CuSeAr with 1 equiv of phenanthroline afforded the corresponding copper complex **5** in almost quantitative yield. Such type of complexes is well known.[9] There are two types of these complexes described in literature: the neutral binuclear complexes [LCuX]$_2$ and ionic [L$_2$Cu]$^+$X$^-$. The formation of the first type of complexes is specific for strong $\pi$-acidic ligands such as CN, SCN.[9f–9h] In contrast, in the case of noncoordinated $ClO_4$[9d] an ionic complex formed. Halogen ligands can form both types of the complexes depending on the solvent and nature of halogen.[9c,9e]

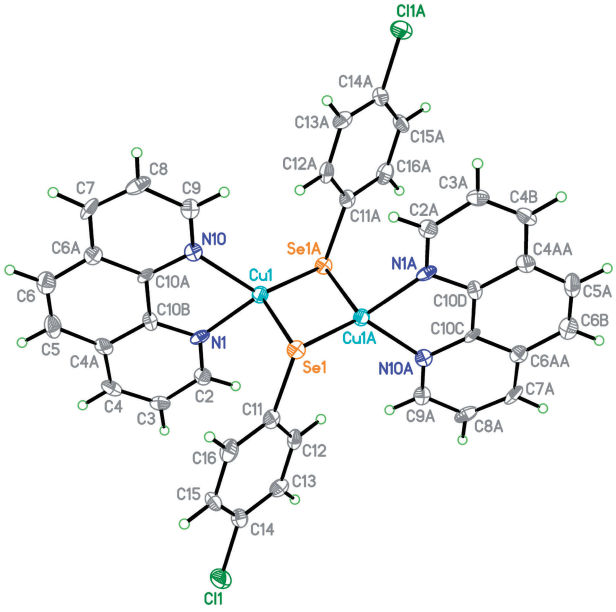
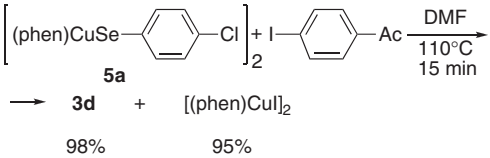



**Figure 1.** Molecular structure of **5a** (50% ellipsoids). Selected bond lengths (Å) and angles (°): Se1–Cu1 2.5083(9), Se1–Cu1A 2.3876(9), Se1–C11 1.907(5), Cu1···Cu1A 2.6054(14), Cu1–N1 2.056(5), Cu1–N10 2.097(4), Cu1–Se1–Cu1A 64.25(3), Se1–Cu1–Se1A 115.75(3), Se1–Cu1–N1 106.63(12), Se1–Cu1–N10 103.61(12), N1–Cu1–Se1A 114.98(12), N10–Cu1–Se1A 128.90(12), N1–Cu1–N10 80.68(17).

The structure of **5a** was unambiguously established by single-crystal X-ray diffraction study and is shown in Figure 1 along with the atomic numbering scheme and selected bond lengths and angles.[11] Compound **5a** is a dimer formed by two bridging *p*-chlorophenylselenolate ligands. It crystallizes in the monoclinic space group $P2_1/n$ and resides on a crystallographic inversion center. Consequently, the Cu and Se atoms in **5a** constitute a strictly planar $Cu_2Se_2$ central core representing a parallelogram with the unequal Cu–Se distances (2.3876(9) and 2.5083(9) Å). The Cu···Cu distance of 2.6054(14) Å is in accord with the +1 oxidation states of the copper centers.[12] The geometry around each Cu atom is distorted tetrahedral.

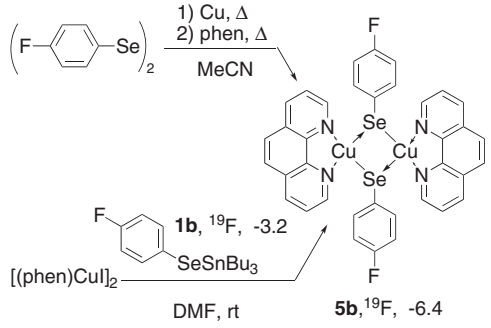
We believe that **5** is one of the key intermediates in Cu(I)-catalyzed coupling. The reaction of **5a** with 4-iodoacetophenone affords **3d** in almost quantitative yield after 15 min at 110 °C.



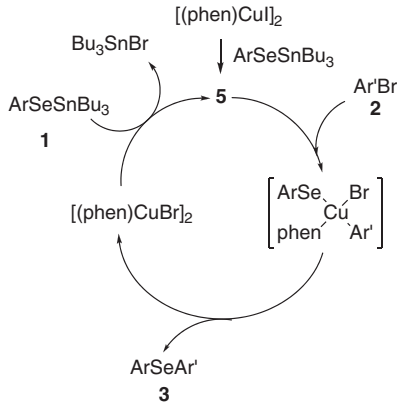

(2)

[(phen)CuI]$_2$ formed has low solubility in DMF and can be separated in 95% yield. Catalytic activities of the complex obtained and an authentic sample of [(phen)CuI]$_2$ in the cross-coupling reaction were identical.

Using catalytic amounts of [(phen)CuI]$_2$ in the reaction of FC$_6$H$_4$SeSnBu$_3$ (**1b**) with PhI we observed fast anion exchange with quantitative formation of complex **5b** ($^{19}$F NMR) even at room temperature (Scheme 2). Thus the predominant form of copper(I) in reaction mixture was arylselenolate complex **5** instead of [(phen)CuHal]$_2$.

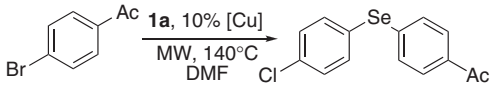



**Scheme 2.**




**Scheme 3.** A plausible Cu(I)-catalysed cross-coupling mechanism.

**Table 3.** Reuse of copper catalyst




**2d** **3d**

| Entry | Cycle | Time/min | GC yield/% |
|---|---|---|---|
| 1 | $[(phen)CuI]_2$ | 15 | 95 |
| 2 | 1 | 18 | 96 |
| 3 | 2 | 25 | 95 |
| 4 | 3 | 25 | 92 |
| 5 | 4 | 30 | 94 |

A plausible mechanism of cross-coupling involving formation of copper(I) intermediate 5 is presented in Scheme 3. In contrast to the palladium catalysis, in the Cu(I)-catalyzed cross-coupling the formation of arylselenolate complex **5** is followed by oxidative addition of ArX.

The proposed mechanism seems to be general for the Cu(I)-catalyzed cross-couplings with S, Se, and Te nucleophiles.

As stated above, $[(phen)CuHal]_2$ can be easily isolated due to low solubility and retain the catalytic activity. It will be of great interest to test the reusability of the complex in catalytic conditions. We used the cross-coupling of **2d** with **1a** as a model system (Table 3).

For five cycles of reuse the yield of diarylselenide **3d** remained unchanged (Table 3). The reaction time, however, gradually increased from 15 to 30 min. This decrease of catalytic activity for the reused complex is attributed to the destruction of complex **5** with formation of inert $Cu_2Se$ leading to reducing the catalyst concentration.

In conclusion, we developed a novel microwave-assisted Cu(I)-catalyzed cross-coupling reaction of trialkyltin arylselenides with aryl bromides affording unsymmetrical diarylselenides in high to excellent yields. We synthesized a key intermediate, determined its structure by X-ray and propose a plausible mechanism for this reaction.

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