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Palladium-catalyzed phenyl-selenylation with *n*-$Bu_3SnSePh$ in one-pot two-step reactions

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Abstract—We have studied the Pd-catalyzed cross-coupling reaction of a stannane derived from selenium *n*-$Bu_3SnSePh$ (**1**) with aryl and perfluoroalkyl iodides. Herein a very efficient *one-pot two-step* selenylation reaction to form a C–Se bond is reported. Ph_2Se_2 reacts with Na metal in liquid ammonia yielding $PhSe^-$ ions. To this solution *n*-Bu_3SnCl was added to afford **1**, which was introduced in the palladium-catalyzed coupling reaction without isolation. These reactions afford functionalized diarylselenides and phenylperfluroalkyl selenides from good to high yields (38–98%).

Transition metal-catalyzed reactions of aryl halides or triflates with organoheteroatom compounds are widely used for the synthesis of different heteroatom-contained compounds.[1] Organotin compounds are extensively used in cross-coupling reactions.[2] Although organostannanes having a Sn–Se bond are known, the synthetic applications of these organostannylselenides are few.[2g] The biological and medicinal roles of organoselenium compounds are progressively more important due to their antioxidant, antitumor, antimicrobial, and antiviral properties.[3] Ar_2Se in particular have attracted considerable attention and several synthetic methods are available for their synthesis.[4] In addition, Ar_2Se can be obtained by coupling of ArI catalyzed by Ni(II)[5] or by Cu(I).[6] However, most of these methods require the handling of unstable reagents and a two-step procedure. A relative new alternative includes organostannylselenides, since it has been shown that the trialkylstannylarylselenides ($R_3SnSeAr$) are an excellent source of arylselenyl groups.[7] The reason for this is that they are more convenient to handle than most commonly used selenols because of their stability to air and moisture. Approaches to the preparation of $R_3SnSeAr$ from distannane $(R_3Sn)_2$ and diselenide $(RSe)_2$,[8] or by the reaction of R_3SnCl with PhSeNa were described.[9] $R_3SnSeAr$ were also used as a source of a arylselenyl group in the arylselenylation of aryl halide and/or triflates catalyzed by Pd,[10,11] Ni,[12] and Cu.[13] Recently, Pd pincer-complexes were used in selenylation of organohalides.[14]

Herein, we report our results on the Pd-catalyzed cross-coupling reaction of *n*-$Bu_3SnSePh$ (**1**) with ArI in one-pot two-step reactions to form unsymmetric diaryl selenides. The in situ generation of the *n*-$Bu_3SnSePh$ eliminates the tedious isolation and purification of the tin reagent. To extend the applications of this methodology, we studied the Pd-catalyzed cross-coupling reaction of **1** with perfluoroalkyl iodides ($R_{fn}I$). To the best of our knowledge, this is the first report of the Pd(0) catalyzed reaction for heteroatom–R_{fn} bond formation. Only the introduction of a R_{fn} group on olefinic and acetylenic carbons by the Pd-catalyzed reaction between organotin and $R_{fn}I$ was reported.[15] Synthetic routes to perfluoroalkyl aryl selenides are not numerous.[16] Recently, aryl and alkyl perfluoroalkyl selenides were obtained from diselenides in the presence of sodium hydroxymethanesulfinate from fair to good yields (28–80%).[17] Perfluoroalkyl selenylation of olefins has also been performed.[18]

Concerning the Pd-catalyzed cross-coupling reaction of **1** with ArI, the generation and subsequent use of **1** was in accordance with the procedure previously

Keywords: Organostannylselenides; Selenylation; Pd catalysis; Perfluoroalkyl iodides.

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reported by us for the synthesis of tertiary phosphanes,[2e] arsanes, and stibanes[2h] by Pd-catalyzed reaction of the corresponding organotin reagents. A typical procedure involves the formation of $PhSe^-$ anions from Ph_2Se_2 (1 mmol) and Na metal (2 mmol) in liquid ammonia (Eq. 1), then n-Bu_3SnCl (2 mmol) was added to obtain **1** (Eq. 2). The ammonia was allowed to evaporate and the organic solvent was added. The Pd-catalyzed cross-coupling reaction was performed with the solution of **1** and the ArI (1.4 mmol) in the presence of $(PPh_3)_2PdCl_2$ (1.5 mol %) (Eq. 3).

$$Ph_2Se_2 \xrightarrow[NH_3]{2\,Na} 2\,PhSe^- \qquad (1)$$

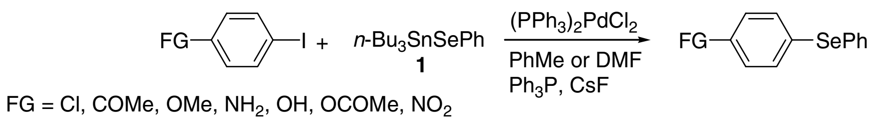
$$PhSe^- \xrightarrow{n\text{-}Bu_3SnCl} \xrightarrow[PhMe]{NH_3} \underset{\mathbf{1}}{n\text{-}Bu_3SnSePh} \qquad (2)$$

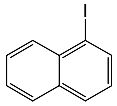
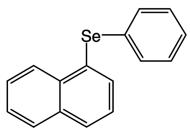
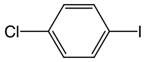
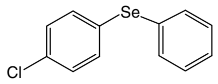
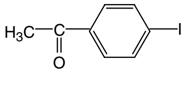
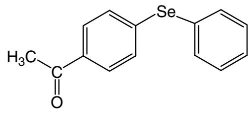
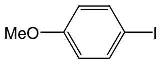
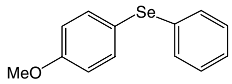
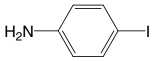
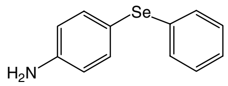
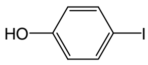
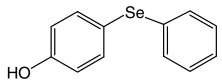
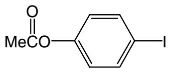
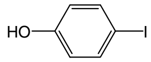
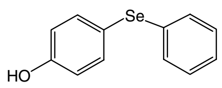
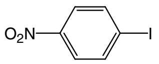
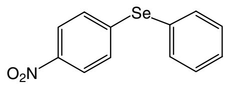
$$\mathbf{1} + ArI \xrightarrow[PhMe]{Pd(0)} PhSeAr \qquad (3)$$

The results of the Pd-catalyzed selenylation with ArI are presented in Table 1. The reaction of **1** with 1-iodonaphthalene (**2a**) catalyzed by $(PPh_3)_2PdCl_2$, afforded the 1-naphthylphenylselenide (**2b**) with total selectivity in 94% yield within 24 h (entry 1). By contrast, when the procedure was carried out without the Pd catalyst, there was almost no reaction (entry 2). By performing the reaction with only $PhSe^-$ anions without **1**, we found only 8% of product **2b** (entry 3). When 4-chloroiodobenzene (**3a**) was allowed to react, the selenide **3b** was obtained in 96% yield (entry 4). The redox-sensitive aryl iodide **4a**, bearing a carbonyl group, was directly transformed into the selenide **4b** in high yields (entry 5). 4-Methoxyiodobenzene (**5a**) did not react under the conditions above described (entry 6). Lewis-basic additives have been shown to facilitate certain Stille reactions, presumably by generating hypervalent stannane complexes.[19] Considering this and the fact that the addition of F^- ions could provide a more efficient cross-coupling reaction, we used CsF as an activator of the organotin reagent.[20] In the presence of 3 equiv of CsF, the cross-coupling reaction of substrate **5a** produced selenide **5b** in good yields (entry 7). The transformation of the 4-iodoaniline (**6a**) to the selenide **6b** was successfully carried out. When the reaction was performed in toluene at 100 °C (entry 8), the yields of selenide **6b** were lower (50%) but they improved at a higher temperature (entry 9). It should be noticed that, in the cross-coupling selenylation carried out by Beletskaya et al.,[11] no reaction occurs with **6a**, and Sonoda et al. reported lower yields with this substrate in a related system.[10] When 4-iodophenol (**7a**) was allowed to react with **1** in toluene at 80 °C, the yield of the diarylselenide **7b** was only 6% (entry 10). With the addition of 3 equiv of CsF, we found that the reaction provided the product **7b** with 15% yield (entry 11). The observation of an important ligand effect in the Stille reaction, and in particular the catalytic activity displayed by a Pd catalyst employing phosphanes as ancillary ligands,[2a] encouraged us to undertake the reaction with PPh_3 as ligand. When PPh_3 (4:1 with respect to the catalyst) and also CsF were added to the cross-coupling reaction in DMF at 120 °C, the system became more efficient giving **7b** in moderate yield (entry 12). Apparently, a more polar solvent as DMF may not only favor the selenylation through a faster oxidative addition, but also increase the solubility of CsF.[21] This still low yield may be due to a tendency of the hydroxy group to coordinate the Pd metal or the intrinsic acidity of the phenol group, thus reducing its activity and/or retarding the transmetalation. To further optimize the reaction, we carried it out protecting this group as an acetoxy. Initially, in the reaction of 4-iodophenyl acetate (**8a**) with **1** conducted at 80 °C in toluene, the hydrolyzed product **7a** was formed in 25% yield and 75% of the substrate was recovered (entry 13). In the presence of CsF, the reaction of **8a** provided the coupling product with deprotection of the hydroxyl group **7b** in low yield, with a similar ratio of the coupling protective product (entry 14). The yields improved when PPh_3 was added as ancillary ligand (entry 15). When examining the possibility that added phosphanes increase yields, four different reaction conditions could be considered: nonpolar solvent with or without added phosphane, and polar solvent with or without added phosphane. We have already examined the first two of these conditions. When the reaction of **8a** was carried out in DMF at a higher temperature, with CsF, only 10% yield of **7b** was obtained (entry 17). However, in the presence of CsF and PPh_3, **7b** was obtained in 95% yield (entry 18). In conclusion, the yield increase resulted from a combination of the change of the solvent and the addition of phosphane. Also, under these conditions, the catalyst system was more effective and the cross-coupling reaction appeared to be faster than the deprotection of the **8a**. The electron-withdrawing and reducible 4-iodonitrobenzene (**9a**) was found to be compatible with these selenylation conditions, and reduction products of the substrate were not observed. When we attempt the reaction of **9a** in toluene at 80 °C, the reaction did not proceed (entry 18). The use of PPh_3 and CsF in DMF allowed the reaction to proceed; however, **9b** was obtained in only 38% yield (entry 19). In summary, there are two different general conditions for the cross-coupling reaction with ArI and **1**. For ArI with electron-withdrawing groups, the reactions proceeded to high yields in toluene at 80 °C. On the other hand, ArI with electron-donating groups required the use of PPh_3 and CsF in DMF at 120 °C to give comparable yields.

Next, we turned our attention to the cross-coupling of **1** with $R_{fn}I$. In an initial attempt, we performed the reaction of **1** with perfluorooctyl iodide (**10a**) (Eq. 4) whose results are shown in Table 2. It was found that, although the reaction did not proceed in toluene at 80 °C, when CsF and 10 mol % of the catalyst were added we obtained 10% yield of **10b** (entries 1 and 2). Adding PPh_3 as ligand the results did not improve (entry 3). However, with 3 equiv of CsF, **10b** was formed in 30% yield (entry 4). Using DMF as solvent and at a higher temperature the selenylation reaction proceeded in a similar way as in toluene (entry 5). Nevertheless, the use of 10 mol % of the catalyst led to a significantly more active catalyst system, allowing the reaction to

Table 1. Selenylation of ArI with **1** in the presence of $(PPh_3)_2PdCl_2$[a]



Entry	Substrate		Conditions	Product		Yield (%)[b]
1		**2a**	Toluene (80 °C)		**2b**	94
2			Without catalyst			5
3			Without **1**[c]			8
4		**3a**	Toluene (80 °C)		**3b**	96
5		**4a**	Toluene (80 °C)		**4b**	98 (92)
6		**5a**	Toluene (80 °C)		**5b**	—
7			Toluene (80 °C), CsF[d]			83
8		**6a**	Toluene (100 °C)		**6b**	50
9			Toluene (116 °C)			78
10		**7a**	Toluene (80 °C)		**7b**	6
11			Toluene (80 °C), CsF[d]			15
12			DMF (120 °C), CsF, PPh_3[e]			50
13		**8a**	Toluene (80 °C)		**7a**	**7a**: 25
14			Toluene (80 °C), CsF[d]		**7b**	**7b**: 19
15			Toluene (80 °C), CsF, PPh_3[f]			**7b**: 38
16			DMF (120 °C), CsF[d]			**7b**: 10
17			DMF (120 °C), CsF, PPh_3[f]			**7b**: 95
18		**9a**	Toluene (80 °C)		**9b**	—
19			DMF (120 °C), CsF, PPh_3[e]			38

[a] Reaction conditions: $PhSe^-$ anion was prepared in 300 mL of liquid ammonia from Ph_2Se_2 (1 mmol) and Na metal (2 mmol) and then n-Bu_3SnCl (2 mmol) was added. The coupling reaction was carried out with the aryl halide (1.4 mmol) and $(PPh_3)_2PdCl_2$ (1.5 mol %) for 24 h.

[b] CG yields. Isolated yields in branches. The other selenides were isolated with yields ca. 10–15% lowers than the CG ones. These yields were not optimized.

[c] Reaction was carried out without adding n-Bu_3SnCl.

[d] 3 equiv of CsF were added.

[e] The coupling reaction was carried out with the ArI (1.0 mmol), $(PPh_3)_2PdCl_2$ (5 mol %), CsF (3.0 mmol), and PPh_3 (Pd–L, 1:4) for 24 h. Without the addition of CsF and PPh_3 there were not reaction and 85% of the reduction product.

[f] The coupling reaction was carried out with the ArI (1.4 mmol) and $(PPh_3)_2PdCl_2$ (5 mol %), CsF (4.2 mmol), PPh_3(Pd:L, 1:4).

proceed to 70% yield (entry 6). Likewise, the Pd-catalyzed selenylation of the perfluorodecyl iodide (**11a**) with **1** could be successfully carried out. $PhSeC_{10}F_{21}$ (**11b**) was obtained in 90% yield (entry 7). To the best of our knowledge, this is the first example of the synthesis of $PhSeR_{fn}$ by Pd-catalyzed cross-coupling reaction and also the first report of a reaction for heteroatom–R_{fn} bond formation using $R_{fn}I$ as electrophiles.

Table 2. Pd-catalyzed cross-coupling of **1** with $R_{fn}I$ as electrophile[a]

Entry	Substrate	$(PPh_3)_2PdCl_2$ (mol %)	Solvent	Ligand:PPh_3 (Pd:L)	Additive: CsF (equiv)	Product	Yield (%)
1	**10a**	1.5	Toluene	—	—	**10b**	<2
2	**10a**	10	Toluene	—	1.1	**10b**	10
3[b]	**10a**	10	Toluene	1:4	1.1	**10b**	7
4	**10a**	10	Toluene	1:4	3	**10b**	30
5	**10a**	1.5	DMF	1:4	3	**10b**	35
6	**10a**	10	DMF	1:4	3	**10b**	70
7	**11a**	10	DMF	1:4	3	**11b**	90

[a] Reaction conditions: $PhSe^-$ ion was prepared in 300 mL of liquid ammonia from Ph_2Se_2 (1 mmol) and Na metal (2 mmol) and then n-Bu_3SnCl (2 mmol) was added. The coupling reaction was carried out with $R_{fn}I$ (1.4 mmol) and $(PPh_3)_2PdCl_2$ for 24 h at 80 °C when toluene was used and 120 °C when DMF was used.

[b] CG yields.

$$
\begin{array}{llcl}
n\text{-}Bu_3SnSePh \;+\; R_{fn}I & & \xrightarrow{(PPh_3)_2PdCl_2} & PhSeR_{fn} \\
R_{fn} = C_8F_{17} & \mathbf{10a} & & \mathbf{10b} \\
\qquad\;\; C_{10}F_{21} & \mathbf{11a} & & \mathbf{11b}
\end{array}
\tag{4}
$$

In conclusion, we have reported a very efficient one-pot two-step selenylation by Pd-catalyzed cross-coupling reaction to obtain a wide range of functionalized organoselenides. This methodology has some notable features: (i) the use of a stable organoselenium reagent against air and moisture; (ii) the feasibility of a one-pot reaction; (iii) a high yield preparation method of functionalized aryl selenides; (iv) a high functional group compatibility. Particularly noteworthy is the fact that perfluoroalkyl iodides were viable electrophiles in the Pd-catalyzed cross-coupling and that the synthesis of $PhSeR_{fn}$ by this reaction proved a new versatile tool.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.106.

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