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3-Iodoselenophene derivatives: a versatile substrate for Negishi cross-coupling reaction

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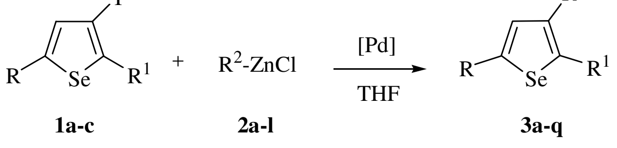
Abstract—3-Iodoselenophene derivatives undergo a direct Negishi cross-coupling reaction with several organozinc compounds in the presence of a catalytic amount of $Pd(PPh_3)_4$ in THF at room temperature. This cross-coupling reaction proceeded cleanly under mild conditions and permitted the formation of polyaromatic compounds in good yields.

Transition-metal catalyzed cross-coupling reactions between Csp^2-centers have been extensively used for preparing pharmaceuticals and agrochemical intermediates.[1] In this context, there have been developments in palladium-catalyzed coupling systems as a consequence of the great interest in the development of coupling substrates that are more economic, more easily accessible, and reactive even under mild conditions. In this line, the palladium-catalyzed cross-coupling of organozinc compounds with organic electrophiles, known as the Negishi reaction, has become an extremely powerful tool for the construction of carbon–carbon bonds.[2] Functionalized organozinc compounds are also important tools for allowing easy access to polyfunctional aromatic and heteroaromatic compounds.[3] On the other hand, chalcogenide compounds have found such wide utility because their effects on an extraordinary number of very different reactions, including many carbon–carbon bond formations, under relatively mild reaction conditions[4] and useful biological activities.[5] Among chalcogenide compounds, the chalcogenophene derivatives play an important role in organic synthesis because many of them show biological activities.[6] Halochalcogenophenes are important derivatives that provide an opportunity for further functionalization. In particular, 2-iodo- and bromoselenophenes are useful as substrates in a variety of C–C, C–N, and C–S bond forming reactions.[7]

To the best of our knowledge no Negishi cross-coupling reaction using 3-haloselenophene as substrate in the preparation of sp^2–sp^2 or sp^2–sp carbon–carbon bond has been described so far. Our continuing interest in the palladium-catalyzed Negishi cross-coupling reactions of organochalcogen[8] prompted us to examine the cross-coupling reaction of 3-iodoselenophenes **1a–c** with organozinc chlorides **2a–l** to obtain selenophene derivatives **3a–q** (Scheme 1).

The starting 3-iodoselenophene was readily available by using the electrophilic cyclization protocol of (*Z*)-selenoenynes. The treatment of (*Z*)-selenoenyne with iodine in CH_2Cl_2 lead to the formation of the 3-iodoselenophene **1a**, isolated in 93% yield after purification (Scheme 2).[9]



R = R^1 = alkyl, aryl; R^2= aryl, heteroaryl, alkynyl

Scheme 1.

Keywords: Palladium; Negishi reaction; Cross-coupling; Haloselenophene.

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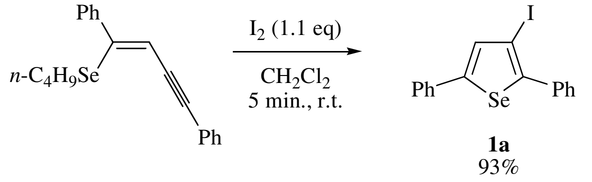


Scheme 2.

Our initial efforts were devoted to the selection of a suitable catalyst system for an efficient coupling. In this way, 2,5-diphenyl-3-iodoselenophene **1a** and *p*-tolylzinc chloride **2a** were used as standard substrates. Thus, a mixture of 3-iodoselenophene **1a** (0.25 mmol), *p*-tolylzinc chloride **2a** (0.75 mmol) (prepared in situ by reaction of 4-bromotoluene with *n*-BuLi in THF at −78 °C followed by the addition of $ZnCl_2$) in THF, at room temperature was reacted with different palladium catalysts and the results are shown in Table 1.

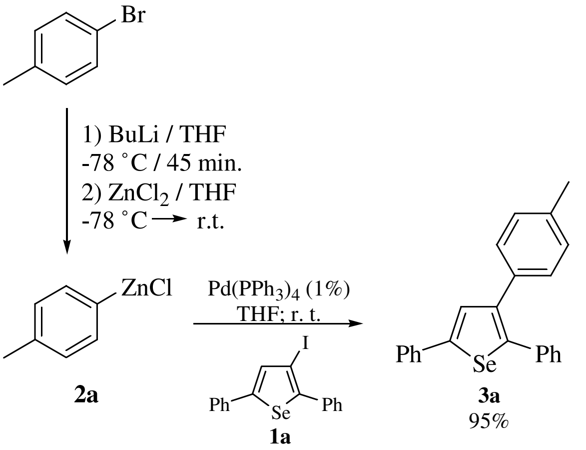
As shown in Table 1, all catalysts of Pd(0) and Pd(II) tested, such as $PdCl_2(PhCN)_2$, $PdCl_2(PPh_3)_2$, $PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd(dba)_2$, and $Pd(dppe)_2$, in 10 mol % exhibit a poor to good catalytic activity but the best result was obtained using $Pd(PPh_3)_4$ which gave the desired product **3a** in 88% yield (Table 1, entry 7). It is important to note that when the amount of catalyst is reduced from 10 to 1 mol %, an increase in the yield was observed (Table 1, entries 7–9). The influence of other parameters such as the amount of the organozinc compound in this reaction was also investigated. We observed that this cross-coupling reaction required the use of an excess of organozinc reagent (3 equiv). When 1.5 or 2 equiv of compound **2a** was used unsatisfactory yields of **3a** were obtained (Table 1, entries 10 and 11).

Thus, the careful analysis of the optimized reactions revealed that the optimum conditions for the cross-coupling were found to be the use of 2,5-diphenyl-3-iodoselenophene **1a** (0.25 mmol) and *p*-tolylzinc chloride **2a** (0.75 mmol), $Pd(PPh_3)_4$ (1 mol %), in THF (3 mL), at room temperature. Under these conditions we were able to prepare 2,5-diphenyl-3-*p*-tolylselenophene **3a** in 95% yield (Scheme 3).[10]

Table 1. Reaction conditions optimization[a]

Entry	Catalyst (mol %)	R^2-ZnCl (equiv)	Yield **3a** (%)
1	$Pd(OAc)_2$ (10)	3	50
2	$PdCl_2(PPh_3)_2$ (10)	3	55
3	$PdCl_2$ (10)	3	45
4	$PdCl_2(PhCN)_2$ (10)	3	60
5	$Pd(dba)_2$ (10)	3	33
6	$Pd(dppe)_2$ (10)	3	20
7	$Pd(PPh_3)_4$ (10)	3	88
8	$Pd(PPh_3)_4$ (5)	3	90
9	$Pd(PPh_3)_4$ (1)	3	95
10	$Pd(PPh_3)_4$ (1)	2	82
11	$Pd(PPh_3)_4$ (1)	1.5	40

[a] Reactions were performed in the presence of **1a** (0.25 mmol), using THF (3 mL) as solvent at room temperature for 24 h.



Scheme 3.

To demonstrate the efficiency of this cross-coupling reaction, we explored the generality of our method extending the coupling reaction to other aryl, heteroaryl, and alkynylzinc chlorides as well as to other 3-iodoselenophenes and the results are summarized in Table 2.

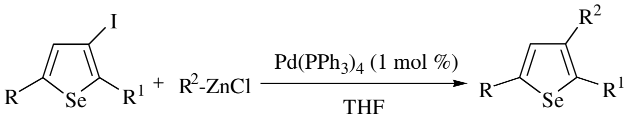
Inspection of Table 2 shows that the reaction worked well for a variety of organozinc chlorides. A closer inspection of the results revealed that the reaction is not sensitive to the electronic effects in organozinc chloride. A wide range of groups attached to the arylzinc chloride, such as electron-rich, neutral, and poor groups were cross-coupled efficiently under these conditions and produced the functionalized products in good to excellent yields. However, the reaction was sensitive to the steric effect of the aromatic ring attached in the arylzinc chloride. For example, arylzinc chloride bearing *o*-tolyl and naphthyl groups gave a lower yield of the desired products (Table 2, entries 2 and 6). Organozinc reagents having heteroaromatics such as 2-furyl and 2-thienyl groups afforded the corresponding products **3i** and **3j** in satisfactory isolated yields (Table 2, entries 9 and 10).

Alkynylzinc compounds could also be coupled in good yields (Table 2, entries 11 and 12).

In an attempt to broaden the scope of our methodology, the possibility of performing the reaction using other 3-iodoselenophenes was also investigated. As illustrated in Table 2, the cross-coupling reaction of **1b–c** with arylzinc chlorides, under the same reaction conditions, led to the corresponding coupling products **3m–q** in good yields (Table 2, entries 13–17).

The 3-alkynylselenophenes obtained by this protocol appear highly promising as intermediates for the preparation of more highly substituted selenophenes. In this context, we have carried out the synthesis of vinylic telluride **4** using compound **3r** as a starting material, which was obtained using the procedure described here in 58% yield. Many classes of organotellurium compounds have been prepared and studied to date, vinylic tellurides are certainly the most useful and promising

Table 2. Coupling products using 3-iodoselenophenes **1a**–**c** and organozinc reagents **2a**–**l**[a]



1a-c **2a-l** **3a-q**

$R = R^1$ = alkyl, aryl; R^2 = aryl, heteroaryl, alkynyl

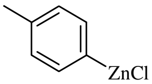
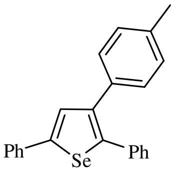
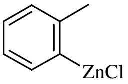
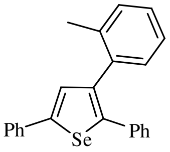
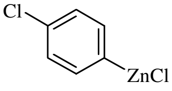
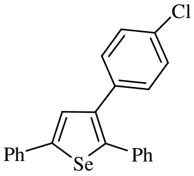
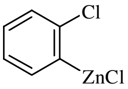
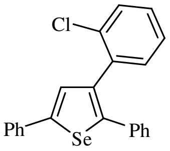
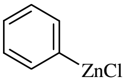
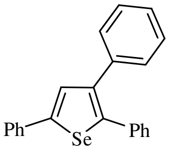
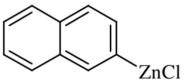
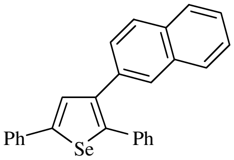
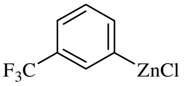
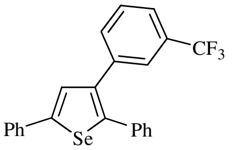
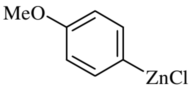
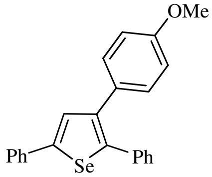
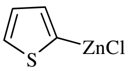
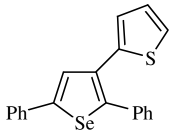
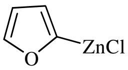
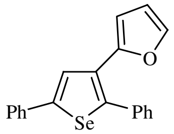
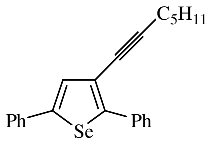
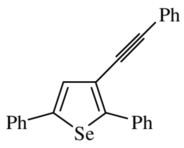
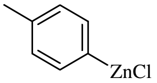
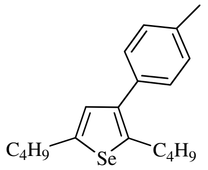
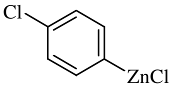
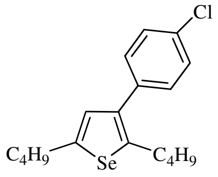
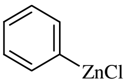
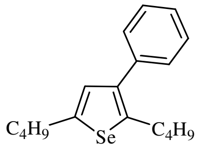
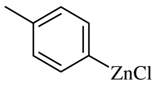
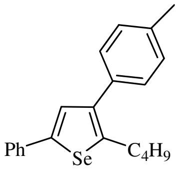
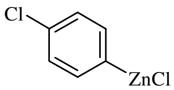
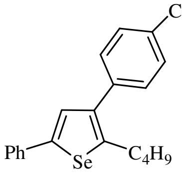
Entry	R^2-ZnCl	Product **3**	Yield[b] (%)
1	 **2a**	 **3a**	95
2	 **2b**	 **3b**	65
3	 **2c**	 **3c**	70
4	 **2d**	 **3d**	82
5	 **2e**	 **3e**	71
6	 **2f**	 **3f**	35
7	 **2g**	 **3g**	70
8	 **2h**	 **3h**	60
9	 **2i**	 **3i**	93
10	 **2j**	 **3j**	72
11	$C_5H_{11}-\equiv-ZnCl$ **2k**	 **3k**	75
12	$Ph-\equiv-ZnCl$ **2l**	 **3l**	75
13	 **2a**	 **3m**	70[c]
14	 **2c**	 **3n**	76[c]
15	 **2e**	 **3o**	70[c]

Table 2 (*continued*)

Entry	R^2-ZnCl	Product **3**	Yield[b] (%)
16	 **2a**	 **3p**	73[c]
17	 **2c**	 **3q**	90[c]

[a] Reactions were performed in the presence of **1a–c** (0.25 mmol), **2a–l** (0.75 mmol), using THF (3 mL) as solvent at room temperature for 24 h.

[b] The yields are given for isolated products.

[c] Reaction time 30 h.

compounds in view of the usefulness in the organic synthesis, including in the synthesis of natural products.[11] Thus, 3-alkynylselenophene **3r** was reacted with NaOH in toluene under reflux for 4 h. Then the terminal alkyne generated in situ reacts with BuTeTeBu and $NaBH_4$ in ethanol, under reflux, to give the corresponding vinylic telluride **4** (Scheme 4).[12]

In summary, we have explored the Negishi cross-coupling reaction of 3-iodoselenophene derivatives with several organozinc compounds in the presence of catalytic amount of $Pd(PPh_3)_4$ under mild reaction conditions (room temperature) and established a new route to obtain polyaromatic compounds in good to excellent yields. Analysis of the ^1H and ^{13}C NMR spectra showed that all the obtained products presented data in full agreement with their assigned structures.

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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.2007.11.070.

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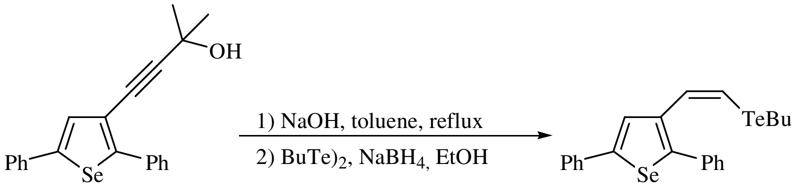
9. Alves, D.; Luchese, C.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2007**, *72*, 6726.
10. *General procedure for the cross-coupling reaction*. A 10 mL Schlenk tube, equipped with a magnetic bar, rubber septum and argon, containing previously prepared the organozinc compound (0.75 mmol),[8] was charged sequentially with the 3-iodoselenophene derivative (0.25 mmol) and $Pd(PPh_3)_4$ (0.0028 g, 0.0025 mmol). The yellow mixture was stirred at room temperature and the reaction time



3r **4**

Scheme 4.

was determined monitoring the reaction by TLC. The reaction mixture was then quenched with aqueous NH_4Cl (5 mL), washed with CH_2Cl_2 (3 × 5 mL), dried with $MgSO_4$ and the solvent removed under vacuum. The products were purified by column chromatography. Selected spectral and analytical data for **3c**: yield: 0.068 g (70%). ^1H NMR: (400 MHz, $CDCl_3$): δ 7.57–7.53 (m, 4H), 7.44 (s, 1H), 7.39–7.22 (m, 10H). ^{13}C NMR: (100 MHz, $CDCl_3$): δ 148.83, 144.45, 139.50, 136.04, 135.92, 135.84, 132.78, 130.43, 129.20, 128.96, 128.90, 128.53, 127.57, 127.49, 126.19, 126.02. MS (relative intensity) m/z: 358 (100), 282 (71), 204 (35), 128 (63), 111 (44), 77 (29). HRMS calcd for $C_{22}H_{15}ClSe$: 394.0027. Found: 394.0032.

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