

Palladium-Catalyzed Cross-Coupling Reaction of 3-Iodoselenophenes with Boronic Acids

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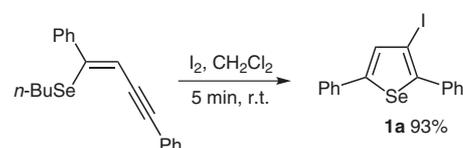
Abstract: The Suzuki cross-coupling of 3-iodoselenophenes with boronic acids in the presence of catalytic amount of palladium salt is described. This cross-coupling reaction proceeded cleanly under mild conditions and was performed with aryl boronic acids bearing electron-withdrawing, electron-donating, and neutral substituents, furnishing the correspondents products in moderate to good yields.

Key words: palladium, Suzuki cross-coupling, selenophene, boronic acid

The palladium-catalyzed cross-coupling reactions of aryl halides or triflates with boronic acids, commonly referred to Suzuki reactions, are a powerful, versatile, and popular tool for selective construction of carbon–carbon bonds.¹ The palladium-catalyzed Suzuki cross-coupling reaction of aryl halides with boronic acids and esters has become a common and convenient synthetic method in organic chemistry for biaryl compounds.² Many examples of Suzuki coupling reactions, between heterocyclic halides and phenyl boronic acids, have appeared in the literature over the past two decades,³ and as the key stage in the synthesis of many currently interesting heterocycle-incorporated compounds, have proved to proceed generally and effectively.⁴ More recently, significant advances have been made in the use of organoboron reagents as coupling partners in a number of palladium-mediated carbon–carbon bond formation. Among them, the use of potassium organotrifluoroborates, as the organoboron coupling partner, has some advantages in comparison to boronic acids and boronic esters, such as be more nucleophilic, stable in the air, crystalline as solids, and easily prepared.⁵ Our continuing interest in the synthesis⁶ and applications⁷ of organochalcogenides in organic synthesis prompted us to examine the cross-coupling reaction of 3-iodoselenophenes **1a–c** with boronic acids **2a–k** in the presence of

palladium salt to obtain 3-arylselenophenes **3a–t** (Scheme 1).

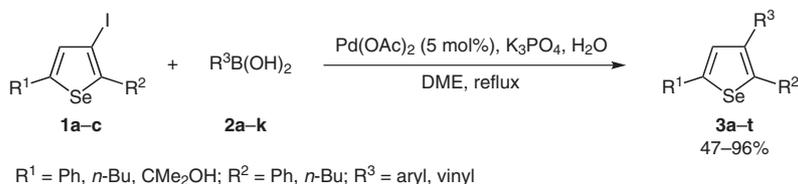
The starting 3-iodoselenophene was readily available by using the electrophilic cyclization protocol of *Z*-selenoenynes. The treatment of *Z*-selenoenyne with iodine in CH₂Cl₂ leads to the formation of 3-iodoselenophene **1a**, isolated in 93% yield after purification (Scheme 2).⁸



Scheme 2

Our initial studies have focused on the development of an optimum set of reaction conditions. In this way, 2,5-diphenyl-3-iodoselenophene (**1a**), and 4-methyl phenylboronic acid (**2a**) were used as standard substrates. Thus, a mixture of 3-iodoselenophene **1a** (0.25 mmol), boronic acid **2a** (0.35 mmol), solution of K₃PO₄ (1.2 mmol) in H₂O (0.6 mL), using DME (2.5 mL) as a solvent with different palladium catalysts (Table 1).

As shown in Table 1, catalysts of Pd(0) and Pd(II) with different ligands tested, exhibited a moderate to good catalytic activity, but the best result was obtained using Pd(OAc)₂ (5 mol%) which gave the desired product **3a** in excellent yield (Table 1, entry 6). It is important to note that when the amount of catalyst is reduced from 5 mol% to 1 mol%, a decrease in the yield was observed (Table 1, entries 6–8). We also observed that the nature of the base was critical for the success of the coupling. The reaction of 3-iodoselenophene **1a** with *p*-tolylboronic acid **2a** using Pd(OAc)₂ (5 mol%) in DME was refluxed with differ-



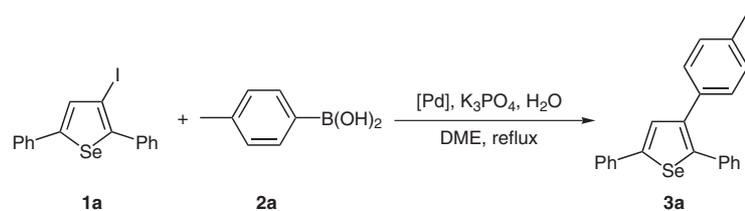
Scheme 1

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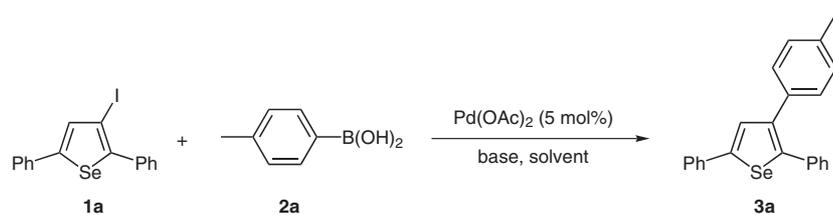
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Table 1 Influence of Catalyst in the Reaction of **1a** and **2a**^a

Entry	[Pd] (mol%)	Yield of 3a (%)
1	Pd(PPh ₃) ₄ (5)	87
2	Pd(dba) ₂ (5)	89
3	PdCl ₂ (PPh ₃) ₂ (5)	71
4	PdCl ₂ (PhCN) ₂ (5)	77
5	PdCl ₂ (5)	n.r.
6	Pd(OAc) ₂ (5)	95
7	Pd(OAc) ₂ (2.5)	trace
8	Pd(OAc) ₂ (1)	n.r.

^a Reactions were performed in the presence of **1a** (0.25 mmol), **2a** (0.35 mmol), K₃PO₄ (1.2 mmol) in H₂O (0.6 mL), DME (2.5 mL) as solvent, under reflux, during 15 h.

Table 2 Optimization of Reactions Conditions^a

Entry	Base	Solvent	Yield of 3a (%)
1	K ₃ PO ₄	DME–H ₂ O	95
2	K ₂ CO ₃	DME–H ₂ O	86
3	Na ₂ CO ₃	DME–H ₂ O	70
4	Cs ₂ CO ₃	DME–H ₂ O	73
5	KOH	DME–H ₂ O	88
6	K ₃ PO ₄	DME	57
7	K ₃ PO ₄	THF	72
8	K ₃ PO ₄	DMF	73
9	K ₃ PO ₄	1,4-dioxane	76
10	K ₃ PO ₄	MeOH	38
11	K ₃ PO ₄	CH ₂ Cl ₂	55
12	K ₃ PO ₄	toluene	50

^a Reactions were performed by using **1a** (0.25 mmol), **2a** (0.35 mmol), Pd(OAc)₂ (5 mol%), basic solution (1.2 mmol) in H₂O (0.6 mL) with different solvents (2.5 mL), under reflux, during 15 h.

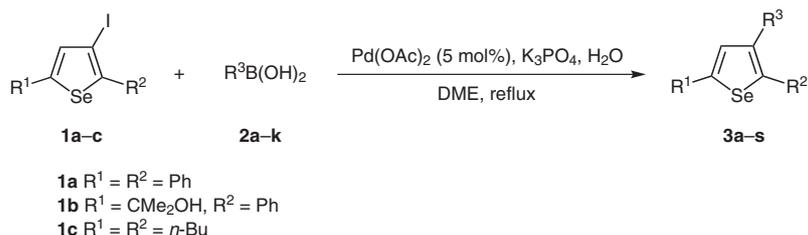
ent bases as shown in Table 2. When the reaction was carried out with inorganic bases such, K_3PO_4 , K_2CO_3 , Na_2CO_3 , Cs_2CO_3 , and KOH afforded coupling product in good yields (Table 2, entries 1–5). Gratifyingly, the use of K_3PO_4 , an inexpensive base, resulted in the coupled product in 95% yield (Table 2, entry 1). It is also important to mention that when dry base was used in place of an aqueous solution, only 57% of product was obtained (Table 2; entry 6). Regarding the influence of the solvent, optimal results were achieved using DME (Table 2, entry 1). By using DMF, THF, and 1,4-dioxane (Table 2, entries 7–9) moderate yields were obtained, while other solvents such as MeOH, CH_2Cl_2 , and toluene (Table 2, entries 10–12) furnished a small amount of the desired product **3a**.

Careful analysis of the optimized reactions revealed that the optimum conditions for this coupling reaction were found to be the use of $Pd(OAc)_2$ (5 mol%), 3-iodoselenophene **1a** (0.25 mmol) and *p*-tolylboronic acid (0.35 mmol) in DME (2.5 mL) at room temperature. After 30 minutes at this temperature, the solution of K_3PO_4 (1.2 mmol) in H_2O (0.6 mL) was added, then the mixture was refluxed for 15 hours. Using this reaction conditions we were able to prepare 2,5-(diphenyl)-3-(*p*-tolyl)selenophene (**3a**) in 95%.⁹ In order to demonstrate the efficiency of this protocol, we explored the generality of our method extending the conditions to other aryl or vinylbo-

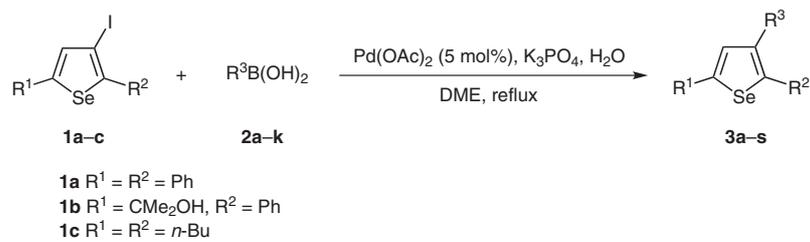
ronic acids and other 3-iodoselenophenes, the results are summarized in Table 3.

Inspection of Table 3 shows that the reaction worked well for a variety of arylboronic acids. A closer inspection of the results revealed that the reaction is sensitive to the electronic effect of an aromatic ring attached in the arylboronic acid. For example, arylboronic acid bearing electron-donating group (Me and OMe) at the *para* position gave a better yield than the arylboronic acids bearing electron-withdrawing group and electron-neutral group (Table 3, entries 1 and 2 vs. 3, 8–11). We have found that steric effects had a little influence on the coupling reaction. Boronic acids containing a 2-methylphenyl, mesityl, and naphthyl group, gave lower yields of product **3** compared to unsubstituted arylboronic acids (Table 3, entries 3 vs. 4–6). Differentiation in the reactivity between chlorine and boron atoms of boronic acids can be seen by coupling of 4-chlorophenylboronic acid with 3-iodoselenophene to provide only the Suzuki product in 70% and 72% yields, without any homo-coupling product observed (Table 3, entries 8 and 15). To the best of our knowledge, aryl chloride could react with boronic acids to afford biaryl products using palladium catalysts.¹⁰ In our case, the chlorine substituent was not affected.

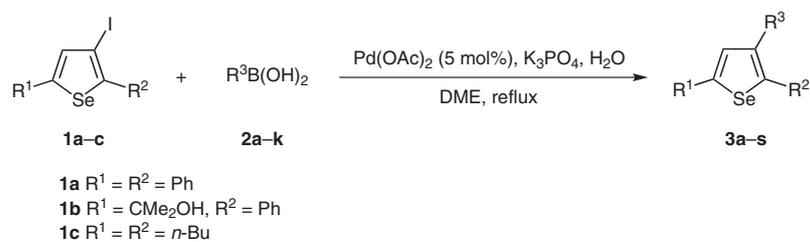
Table 3 Coupling Products Using 3-Iodoselenophenes **1a–c** and Boronic Acids **2a–k**^a



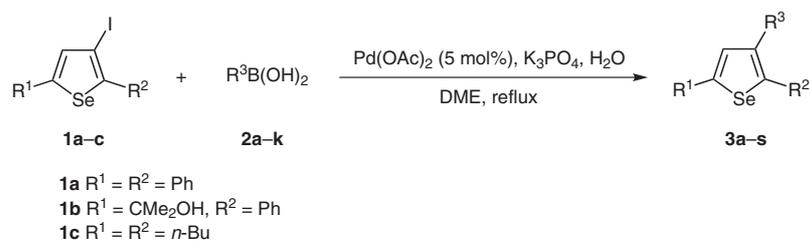
Entry	Substrate	R ²	Product yield (%)
1	1a		 3a 95
2	1a		 3b 90
3	1a		 3c 80

Table 3 Coupling Products Using 3-Iodoselenophenes **1a–c** and Boronic Acids **2a–k^a** (continued)

Entry	Substrate	R ²	Product yield (%)
4	1a		 3d 66
5	1a		 3e 74
6	1a		 3f 73
7	1a		 3g 88
8	1a		 3h 70
9	1a		 3i 71
10	1a		 3j 67

Table 3 Coupling Products Using 3-Iodoselenophenes **1a–c** and Boronic Acids **2a–k^a** (continued)

Entry	Substrate	R ²	Product yield (%)
11	1a		 3k 68
12	1a	2a	 3l 86
13	1b	2b	 3m 88
14	1b	2f	 3n 78
15	1b	2h	 3o 72
16	1b	2k	 3p 96

Table 3 Coupling Products Using 3-Iodoselenophenes **1a–c** and Boronic Acids **2a–k^a** (continued)

Entry	Substrate	R ²	Product yield (%)
17	1b	2c	<p style="text-align: center;">3q 72</p>
18	1c	2b	<p style="text-align: center;">3r 52</p>
19	1c	2c	<p style="text-align: center;">3s 54</p>
20	1c	2k	<p style="text-align: center;">3t 47</p>

^a Reactions were performed by using **1a–c** (0.25 mmol), **2a–k** (0.35 mmol), Pd(OAc)₂ (5 mol%), K₃PO₄ (1.2 mmol) in H₂O (0.6 mL), DME (2.5 mL) as solvent, under reflux, during 1–15 h.

In an attempt to broaden the scope of our methodology, the possibility of performing the reaction with other 3-iodoselenophenes was also investigated. Then the substrate **1b**, which has a hydroxyl group in the side chain, was cross-coupled efficiently under these conditions with electron-rich and electron-poor arylboronic acids producing the coupled products in good yields (Table 3, entries 12–16). Additionally, the substrate **1c**, which has an alkyl group, gave the Suzuki products in moderate yields (Table 3, entries 18–20).

In summary, we have explored the Suzuki cross-coupling reaction of aryl- or vinylboronic acids with symmetrical 3-iodoselenophenes using a catalytic amount of Pd(OAc)₂. The reaction proceeded cleanly under mild reaction conditions and was performed with aryl boronic acids bearing electron-withdrawing, electron-donating, and neutral substituents. In addition, by this protocol unsym-

metrical 3-iodoselenophenes having an alkyl or hydroxyl group in the side chain gave the Suzuki products in good yields. Analysis of the ¹H NMR and ¹³C NMR spectra showed that all the obtained products presented data in full agreement with their assigned structures.

Acknowledgment

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- (9) **General Procedure for the Cross-Coupling Reaction**
To a solution of appropriate 3-iodoselenophene (0.25 mmol) in DME (2.5 mL) was added Pd(OAc)₂ (0.003 g, 5 mol%) and boronic acid (0.35 mmol) under argon. The resulting solution was stirred for 30 min at r.t. After this time, a solution of K₃PO₄ (1.2 mmol, 0.254 g) in H₂O (0.6 mL) was added. The mixture was then heated at reflux during 1–15 h, cooled to r.t., diluted with CH₂Cl₂ (20 mL), and washed with brine (2 × 20 mL). The organic phase was separated, dried over MgSO₄, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using hexane as eluent. **Selected Spectral and Analytical Data for 2,5-(Diphenyl)-3-(p-tolyl)selenophene (3a)**
Yield 0.088 g (95%). ¹H NMR (400 MHz, CDCl₃): δ = 7.59–7.57 (m, 3 H), 7.39–7.35 (m, 2 H), 7.30–7.19 (m, 8 H), 7.10–7.08 (m, 2 H), 2.33 (s, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 148.25, 140.84, 136.57, 136.32, 136.17, 134.71, 129.58, 129.25, 129.21, 129.05, 129.01, 128.92, 128.38, 127.64, 127.19, 126.02, 21.19 ppm. MS: m/z (%) = 373 (100), 281 (65), 296 (45), 220 (42), 128 (72), 91 (65). HRMS: m/z calcd for C₂₃H₁₈Se: 374.0574; found: 374.0580.
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