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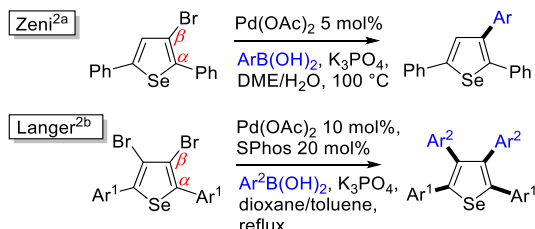
Unprecedented access to β -arylated selenophenes via palladium-catalysed direct arylation

Aymen Skhiri,^[a,b] Ridha Ben Salem,^{*,[b]} Jean-François Soulé,^{*,[a]} Henri Doucet^{*,[a]}

Abstract: Several methods allow the access to α -arylated selenophenes; whereas the synthesis of β -arylated selenophenes remains very challenging. We demonstrated that the Pd-catalysed coupling of benzenesulfonyl chlorides with selenophenes affords regiospecifically the β -arylated selenophenes. The reaction proceeds with easily accessible catalyst, base and substrates, and tolerates a variety of substituents both on the benzene and selenophene moieties. This transformation allows the programmed synthesis of polyarylated selenophenes with potential applications in pharmaceutical and material chemistry, as the installation of aryl groups at the desired positions can be achieved.

(Hetero)arylated selenophenes are important structures with several applications such as in the fields of pharmaceutical chemistry and organo-electronics.^[1] If the biological or physical properties of several 2-(hetero)arylselenophenes have been studied in detail, on the other hand, 3-arylselenophenes have attracted less attention. This is certainly due to the lack of convenient synthetic methods for the preparation of such structures.^[2] Currently, β -arylated selenophenes can be prepared via Suzuki coupling using 3-bromoselenophene derivatives^[3] (Scheme 1) or via Negishi coupling.^[4]

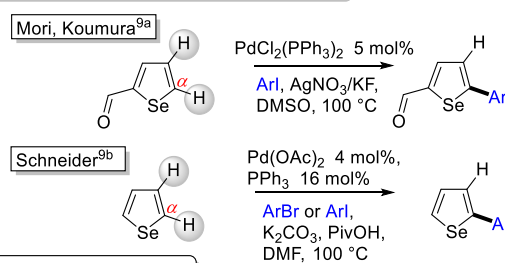
Pd-catalysed β -arylations via Suzuki coupling



Scheme 1. Reported pathways for the synthesis of β -arylated selenophenes from selenophenes.

Since one decade, the metal-catalysed functionalization of C-H bonds has emerged as a very powerful method for the simpler access to molecules useful to materials or biological applications. β -specific C-H bonds of (hetero)arenes can be coupled with arenes, provides one of the simplest way for access to bi(hetero)aryls.^[5] From thiophene derivatives, by tuning the reaction conditions, both the α - and β -arylated thiophenes can be easily obtained using Pd-catalysed direct arylation.^[7,8] In contrast, relatively little effort has been expended toward developing such metal-catalysed direct arylations for the synthesis of arylated selenophenes. In 2008, Mori and Kounmura et al. reported the first Pd-catalysed direct arylation of selenophene derivative (Scheme 2, top). Using aryl iodides as aryl source and $\text{PdCl}_2(\text{PPh}_3)_2$ catalyst, they obtained regioselectively the C5-arylated 2-formylselenophenes.^[9a] Then, in 2014, Schneider et al. reported condition allowing the access to 2-arylselenophenes from selenophene and aryl halides (Scheme 2, middle). To our knowledge the metal-catalysed direct arylation at β -position of selenophene has not been reported so far (Scheme 2, bottom).^[9b] Therefore, it was of particular interest to us to achieve an arylation at the 3- or 4-positions of selenophenes.

Previous work: Pd-catalysed direct α -arylations



Scheme 2. Pd-catalysed direct arylation of selenophenes.

Dong et al. reported in 2009 an example of Pd-catalysed direct arylation, via a desulfative coupling, of a quinoline using p -TolSO₂Cl as aryl source.^[10,11] Following this seminal result, the use of ArSO₂Cl as aryl source for the Pd-catalysed direct arylations has been extended to a variety of heteroarenes by several groups.^[12,13] In 2014, we described a novel access to β -arylated thiophenes from thiophenes and ArSO₂Cl, using desulfative Pd-catalysed direct arylation.^[14] However, to our knowledge, the desulfative direct arylation of selenophenes with ArSO₂Cl has not been reported.

Herein, we describe an environmentally benign general protocol allowing the completely regioselective access to β -arylated selenophenes, using Pd-catalysed desulfative direct arylation, from selenophenes and ArSO₂Cl (Scheme 2, bottom). The influence of

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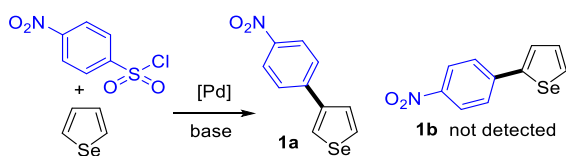
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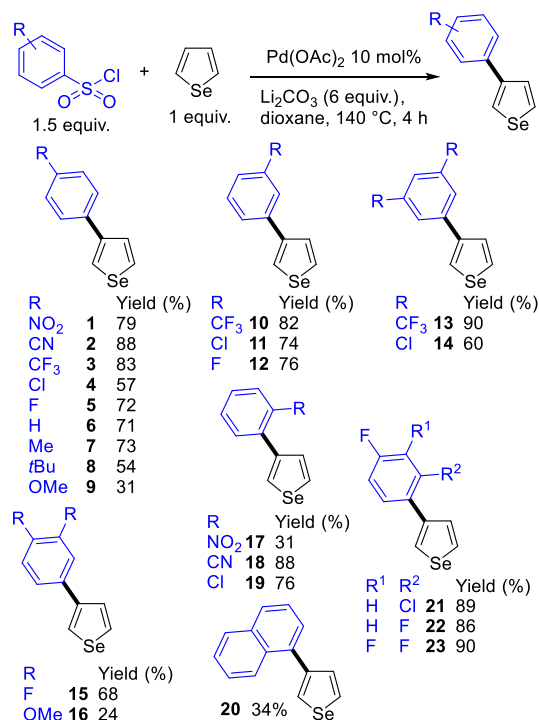
the ArSO₂Cl and selenophenes substituents is reported. The high yielding programmed synthesis of a tetraarylselenophene is also described.

Based on our previous results as a starting point,^[14] we first examined the influence of several reaction conditions on the product formation for the reaction of 1.5 equiv. of 4-nitrobenzenesulfonyl chloride with selenophene at 140 °C during 4 h (Scheme 3 and Table 1 in SI). Using 10 mol% Pd(OAc)₂ catalyst and 3 equiv. of Li₂CO₃ as the base in 1,4-dioxane, the C3-arylated selenophene **1a** was regiospecifically obtained in 56% yield. No formation of the C2-arylated selenophene derivative **1b** was observed by GC/MS and ¹H NMR analysis of the crude mixture. The use of PdCl₂(C₃H₅)₂(dppb), PdCl₂, PdCl₂(MeCN)₂ or Pd(PPh₃)₄ catalysts also led regiospecifically to product **1a**, but in lower yields. On the other hand, in the presence of a larger excess (6 equiv.) of Li₂CO₃ base, product **1a** was obtained 79% yield. Then, we examined the influence of other bases such as Na₂CO₃, K₂CO₃, Cs₂CO₃, K₃PO₄ or KOAc; however, lower yields in **1a** were obtained.



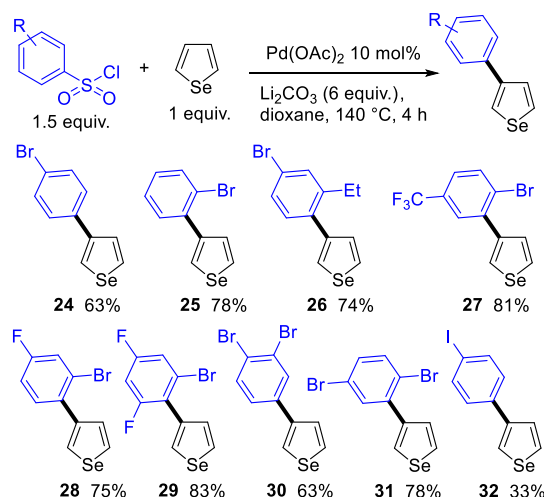
Scheme 3. Influence of the reaction conditions.

Then, the influence of the *para*-substituents on ArSO₂Cl for reaction with selenophene was examined using 10 mol% Pd(OAc)₂ catalyst and 6 equiv. of Li₂CO₃ in dioxane (Scheme 4). First we employed electron-deficient ArSO₂Cl. Cyano- and trifluoromethyl-substituents on ArSO₂Cl gave regiospecifically the C3-arylated selenophenes **2** and **3** in 88% and 83% yields, respectively. Relatively good yields were also obtained for the coupling of 4-chloro and 4-fluoro-benzenesulfonyl chlorides with selenophene, as the desired products **4** and **5** were isolated in 57% and 72% yields, respectively. It should be noted that no cleavage of the C-Cl bond was observed allowing further transformations. Good yields of 71% and 73% in **6** and **7** were also obtained from PhSO₂Cl and *p*-TolSO₂Cl; whereas, lower yields of 54% and 31% in **8** and **9** were produced from the electron-rich 4-*tert*-butyl- and 4-methoxybenzenesulfonyl chlorides. The influence of *meta*-substituents on the ArSO₂Cl partner was also evaluated. ArSO₂Cl bearing CF₃, Cl or F *meta*-substituents were successfully coupled with selenophene, affording regiospecifically the desired C3-arylated selenophenes **10-12** in 74-82% yields. ArSO₂Cl containing two CF₃, Cl or F substituents also gave the expected products **13-15** in good to high yields; whereas, the electron-rich 3,4-dimethoxybenzenesulfonyl chloride afforded **16** in only 24% yield. ArSO₂Cl containing cyano or chloro *ortho*-substituents were also tolerated affording **18** and **19** in 88% and 76% yields, respectively; whereas a nitro *ortho*-substituent gave **17** in only 31% yield. Polyfluorinated molecules are ubiquitous in medicinal chemistry, owing to fluorine atom properties which induce a dramatic change in the molecules behaviour. The use of ArSO₂Cl containing fluorine atoms should offer a straightforward route to (poly)fluorinated 3-arylselenophenes. Indeed, from ArSO₂Cl containing one to three fluoro substituents, the 3-arylselenophenes **21-23** were produced in 86-90% yields.



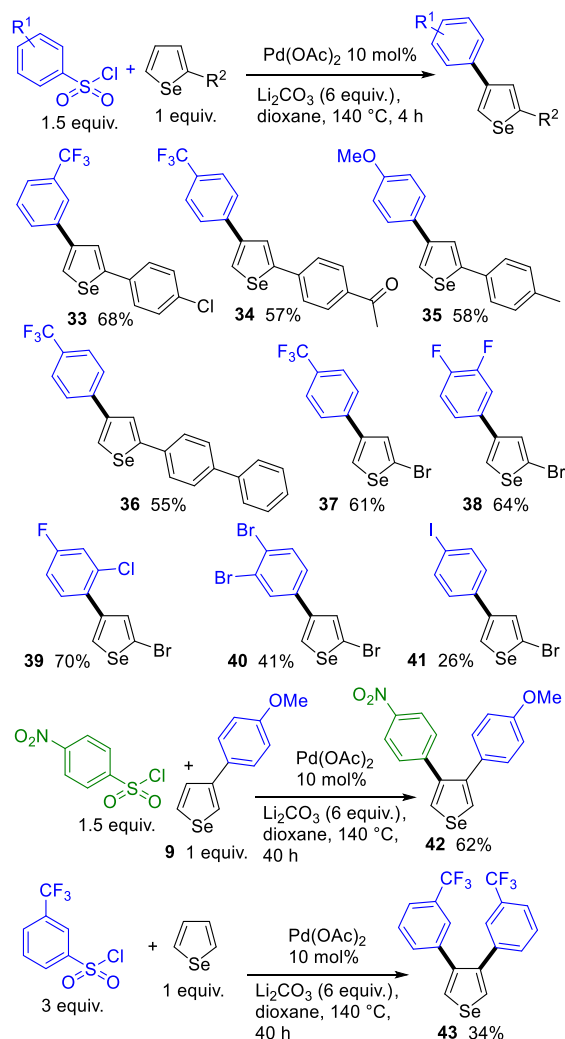
Scheme 4. Influence of the substituents on ArSO₂Cl.

As the use of ArSO₂Cl as coupling partners in Pd-catalyzed direct arylations tolerates bromo and iodo substituents,^[14b] the behaviour of several (poly)halobenzenesulfonyl chlorides for coupling with selenophene was investigated (Scheme 5). Satisfactory yields in **24** and **25** were obtained in the presence of ArSO₂Cl containing 2- or 4-bromo-substituents. An additional *ortho*-ethyl-substituent exhibits a minor influence, as with 2-ethyl-4-bromobenzenesulfonyl chloride, a high yield of 74% in the target product **26** was obtained. 2-Bromobenzenesulfonyl chloride bearing CF₃ or F substituents also led to the expected 3-arylate selenophenes **27-29** in 75-83% yield. The reactivity of two dibromobenzenesulfonyl chlorides, which can be easily obtained by reaction of dibromobenzenes with chlorosulfonic acid, is also described in the scheme 5. In both cases, the target products **30** and **31** were obtained in good yields, without cleavage of both C-Br bonds. Then, although C-I bonds on benzene rings are known to be very reactive in the presence of palladium catalysts, we examined the reactivity of 4-iodobenzenesulfonyl chloride in the presence of selenophene. The reaction affords **32** in only 33% yield, but without cleavage of the C-I bond.



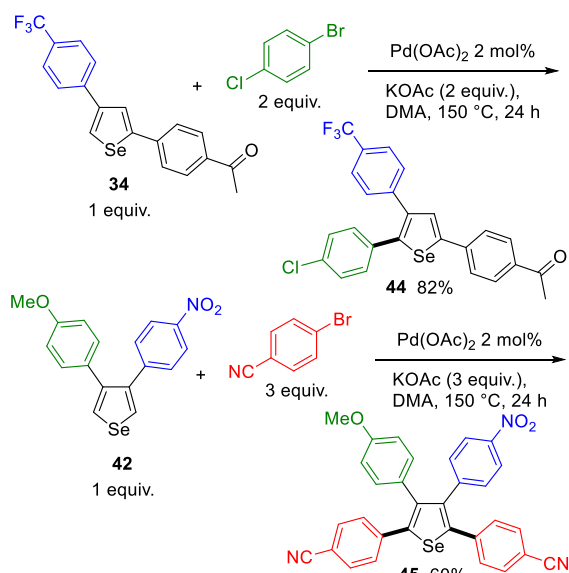
Scheme 5. Influence of bromo- or iodo-substituents on ArSO_2Cl .

The regioselectivity of the arylation of 2- or 3-substituted selenophenes was also determined (Scheme 6). We first examined the reactivity of 2-arylselenophenes, which could be easily obtained *via* direct arylation of selenophene by aryl bromides using reported conditions.^[9b] High yields in **33-36** were obtained from four 2-arylselenophenes using CF_3 - or MeO -substituted ArSO_2Cl as aryl source. In all cases, a complete regioselectivity in favour of the arylation at C4-position of the 2-arylselenophene was observed. A bromo-substituent at C2-position on selenophene was also tolerated, affording the 4-aryl-2-bromoselenophenes **37-39** in 61-70% yields, without cleavage of the selenophenyl C-Br bond. Moreover, in the presence of 3,4-dibromobenzenesulfonyl chloride and 4-iodobenzenesulfonyl chloride, the 4-arylated 2-bromoselenophene derivatives **40** and **41** were obtained in moderate yields, but without cleavage of the C-halo bonds on both coupling partners. The reaction of 3-(4-methoxyphenyl)selenophene **9** with 4-nitrobenzenesulfonyl chloride regioselectively affords the 3,4-diarylselenophene **42**, which contains two different aryl groups, in 62% yield (Scheme 6, bottom). It was also possible to directly prepare the 3,4-diarylselenophene **43**, bearing two identical aryl groups, by reaction of selenophene with 3 equiv. of benzenesulfonyl chloride derivative.



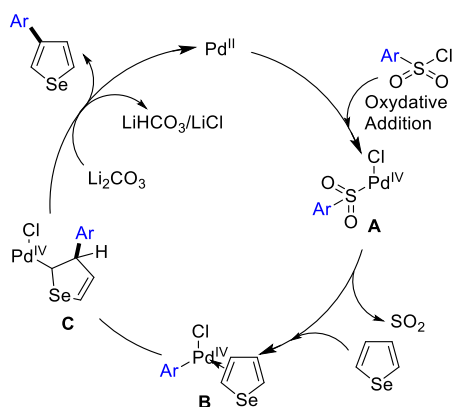
Scheme 6. Influence of substituents on selenophene.

Then, from the previously obtained 2,4-diarylselenophene **34** and 4-bromochlorobenzene in the presence of 2 mol% $\text{Pd}(\text{OAc})_2$ catalyst the 2,3,5-triarylselenophene **44** containing three different aryl groups was obtained in 82% yield (Scheme 7, top). Finally, the tetraarylated selenophene **45** could be obtained by reaction of the 3,4-diarylselenophene **42** with 3 equiv. of 4-bromobenzonitrile in the presence of $\text{Pd}(\text{OAc})_2$ catalyst (Scheme 7, bottom).



Scheme 7. Programmed polyarylations of selenophene.

Although the mechanism cannot yet be elucidated, a catalytic cycle shown on scheme 8 can be proposed. The first step is probably the oxidative addition of the ArSO_2Cl to Pd(II) to afford the Pd(IV) intermediate **A** as for Dong reaction.^[10] Then, after elimination of SO_2 , the coordination of selenophene gives **B**, which affords **C** after migration of the aryl group to the β -carbon atom of selenophene.^[15] Finally, base-assisted proton abstraction gives the β -arylated selenophene with regeneration of the Pd(II) species. However, an Heck-type Pd(0)/Pd(II) mechanism, with carbo-palladation followed by an anti- β -hydride elimination or a base-assisted E2 elimination is also possible.^[16]



Scheme 8. Proposed catalytic cycle

In summary, we report here the first procedure promoting the hard-to-achieve arylation at β -position of selenophene derivatives. The reaction proceeds with easily accessible phosphine-free Pd(OAc)_2 catalyst and Li_2CO_3 as base and tolerates a wide variety of substituents both on the ArSO_2Cl and selenophene coupling partners. Moreover, this procedure allows the programmed synthesis of polyarylated selenophenes as the installation of aryl groups at the desired positions can be achieved. Due to the wide availability of diversely functionalised ArSO_2Cl , this strategy (no expensive base and ligand) should be very attractive to synthetic or material chemists for access to β -arylated and polyarylated selenophenes.

Keywords: Palladium • catalysis • C-H functionalization • selenophenes • benzenesulfonyl chlorides

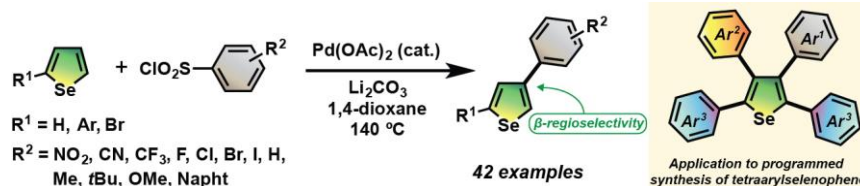
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***β*-regioselectivity**

Aymen Skhiri, Ridha Ben Salem,* Jean-François Soulé,* Henri Doucet * **Page – Page**

Unprecedented access to *β*-arylated selenophenes via palladium-catalysed direct arylation



The palladium-catalysed coupling of benzenesulfonyl chlorides with selenophene derivatives allows the access to *β*-arylated selenophenes with complete regioselectivity. The reaction proceeds with easily accessible catalyst, base and substrates, without oxidant and tolerates a variety of substituents both on the benzene and selenophene moieties.