Unprecedented Access to β-Arylated Selenophenes through Palladium-Catalysed Direct Arylation

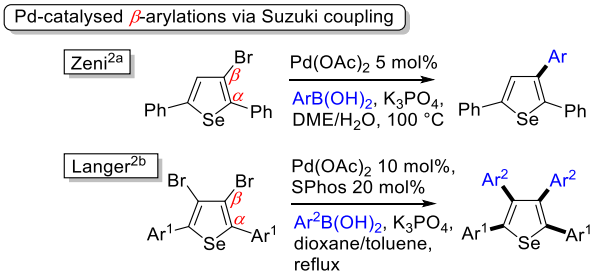
Aymen Skhiri, Ridha Ben Salem, Jean-François Soulé, Henri Doucet

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]



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

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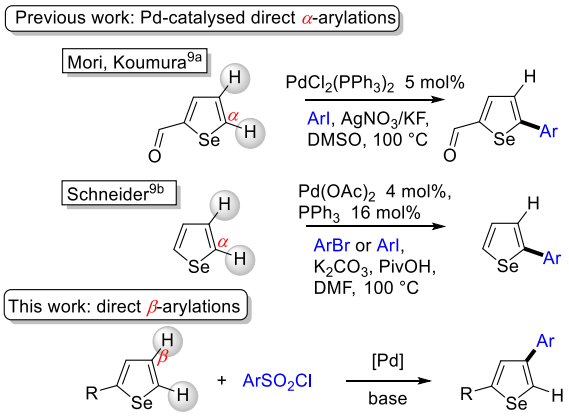
Since one decade, the metal-catalysed functionalization of C-H bonds has emerged as a very powerful method for the simpler acces to molecules useful to materials or biological applications. *specific* C–H bonds of (hetero)arenes can be coupled with arenes, provides one of the simplest way for access to bi(hetero)aryls.[5] From thiophene derivatives, by tuning the reaction conditions, bot the α- and β-arylated thiophenes can be easily obtained using Pd catalysed direct arylation.[7,8] In contrast, relatively little effort ha been expended toward developing such metal-catalysed direc arylations for the synthesis of arylated selenophenes. In 2008, Mor Koumura et al. reported the first Pd-catalysed direct arylation of selenophene derivative (Scheme 2, top). Using aryl iodides as ary source and $PdCl_2(PPh_3)_2$ catalyst, they obtained regioselectively th C5-arylated 2-formylselenophenes.[9a] Then, in 2014, Schneider et a reported condition allowing the access to 2-arylselenophenes fror selenophene and aryl halides (Scheme 2, middle). To our knowledg the metal-catalysed direct arylation at β-position of selenophene has not been reported so far (Scheme 2, bottom).[9b] Therefore, was of particular interest to us to achieve an arylation at the 3- or 4 positions of selenophenes.



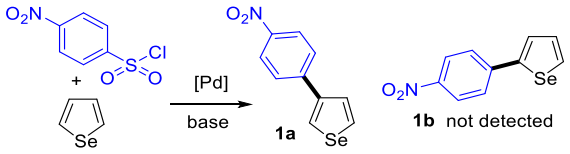
Scheme 2. Pd-catalysed direct arylation of selenophenes.

Dong et al. reported in 2009 an example of Pd-catalysed direc arylation, via a desulfitative coupling, of a quinoline using *p* $TolSO_2Cl$ as aryl source.[10,11] Following this seminal result, the us of $ArSO_2Cl$ 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 $ArSO_2Cl$, using desulfitative Pd-catalysed direct arylation.[14] However, to our knowledge, the desulfitative direct arylation of selenophenes with $ArSO_2Cl$ has not been reported.

Herein, we describe an environmentally benign general protocol allowing the completely regioselective access to β-arylated selenophenes, using Pd-catalysed desulfitative direct arylation, from selenophenes and $ArSO_2Cl$ (Scheme 2, bottom). The influence of

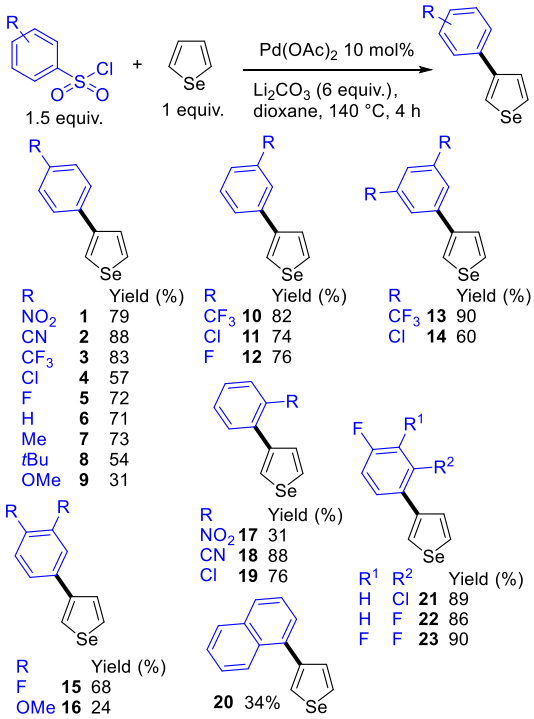
the $ArSO_2Cl$ and selenophenes substituents is reported. The high yielding programmed synthesis of a tetraarylselenophene is also described.

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 Li_2CO_3 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 $PdCl(C_3H_5)(dppb)$, $PdCl_2$, $PdCl_2(MeCN)_2$ or $Pd(PPh_3)_4$ 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 Li_2CO_3 base, product **1a** was obtained 79% yield. Then, we examined the influence of other bases such as Na_2CO_3, K_2CO_3, Cs_2CO_3, K_3PO_4 or KOAc; however, lower yields in **1a** were obtained.



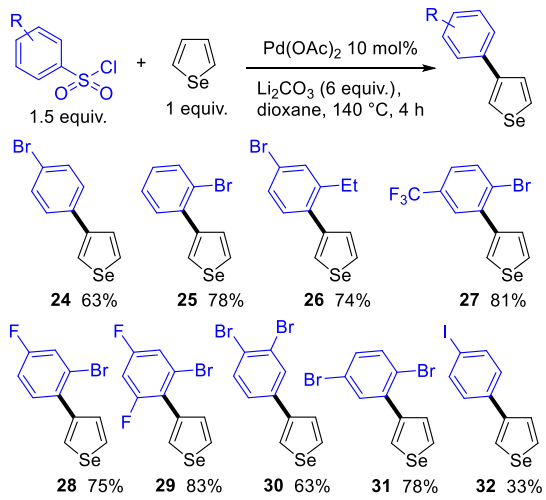
Scheme 3. Influence of the reaction conditions.

Then, the influence of the *para*-substituents on $ArSO_2Cl$ for reaction with selenophene was examined using 10 mol% $Pd(OAc)_2$ catalyst and 6 equiv. of Li_2CO_3 in dioxane (Scheme 4). First we employed electron-deficient $ArSO_2Cl$. Cyano- and trifluoromethyl-substituents on $ArSO_2Cl$ 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 $PhSO_2Cl$ and *p*-$TolSO_2Cl$; whereas, lower yields of 54% and 31% in **8** and **9** were produced from the electron-rich 4-*tert*-butyl- and 4-methoxy-benzenesulfonyl chlorides. The influence of *meta*-substituents on the $ArSO_2Cl$ partner was also evaluated. $ArSO_2Cl$ bearing CF_3, Cl or F *meta*-substituents were successfully coupled with selenophene, affording regiospecifically the desired C3-arylated selenophenes **10**-**12** in 74-82% yields. $ArSO_2Cl$ containing two CF_3, 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. $ArSO_2Cl$ 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 $ArSO_2Cl$ containing fluorine atoms should offer a straightforward route to (poly)fluorinated 3-arylselenophenes. Indeed, from $ArSO_2Cl$ containing one to three fluoro substituents, the 3-arylselenophenes **21**-**23** were produced in 86-90% yields.



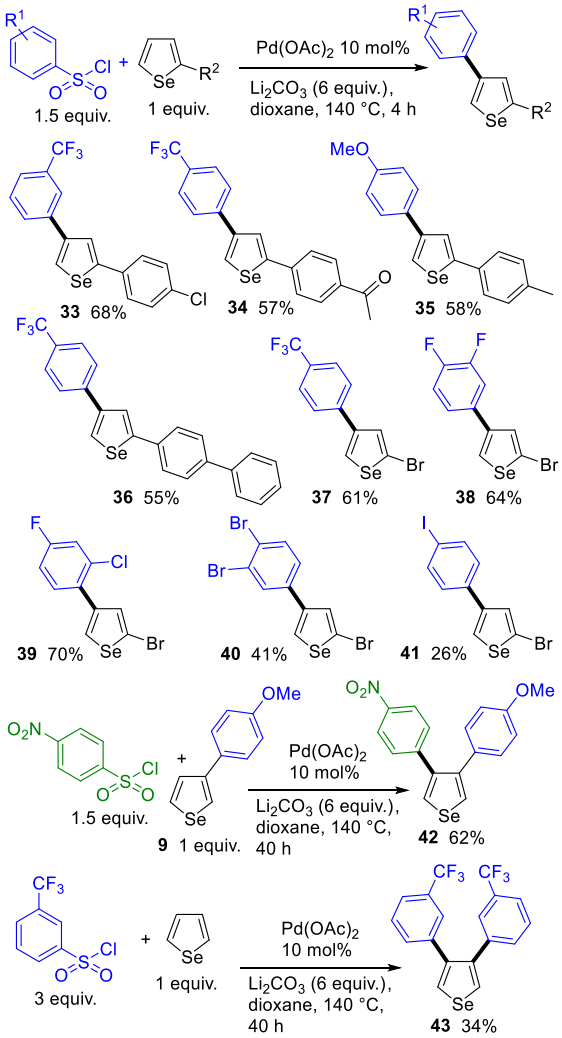
Scheme 4. Influence of the substituents on $ArSO_2Cl$.

As the use of $ArSO_2Cl$ as coupling partners in Pd-catalyse direct arylations tolerates bromo and iodo substituents,[14b] th behaviour of several (poly)halobenzenesulfonyl chlorides fc coupling with selenophene was investigated (Scheme 5 Satisfactory yields in **24** and **25** were obtained in the presence c $ArSO_2Cl$ containing 2- or 4-bromo-substituents. An additiona *ortho*-ethyl-substituent exhibits a minor influence, as with 2-ethyl-4 bromobenzenesulfonyl chloride, a high yield of 74% in the targe product **26** was obtained. 2-Bromobenzenesulfonyl chloride bearing CF_3 or F substituents also led to the expected 3-arylate selenophenes **27**-**29** in 75-83% yield. The reactivity of tw dibromobenzenesulfonyl chlorides, which can be easily obtained b reaction of dibromobenzenes with chlorosulfonic acid, is als described in the scheme 5. In both cases, the target products **30** an **31** were obtained in good yields, without cleavage of both C-B bonds. Then, although C-I bonds on benzene rings are known to b very reactive in the presence of palladium catalysts, we examine the reactivity of 4-iodobenzenesulfonyl chloride in the presence c selenophene. The reaction affords **32** in only 33% yield, but withou cleavage of the C-I bond.



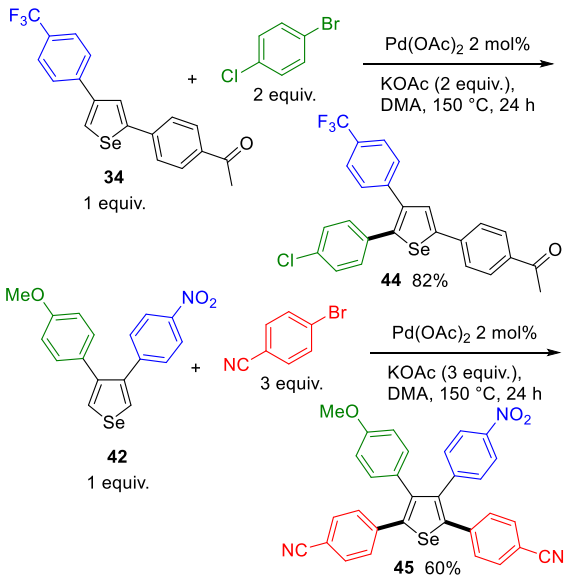
Scheme 5. Influence of bromo- or iodo-substituents on $ArSO_2Cl$.

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.



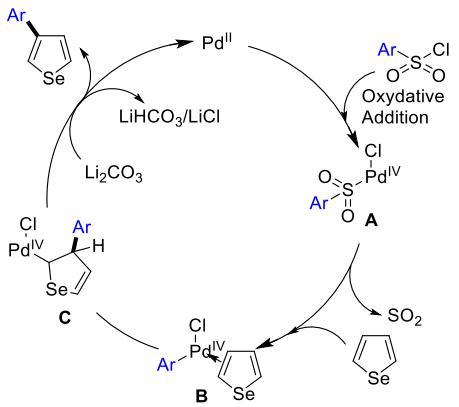
Scheme 6. Influence of substituents on selenophene.

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

[1] a) E. G. A. Notaras, N. T. Lucas, M. G. Humphrey, A. C. Willis, A. D. Rae, *Organometallics* **2003**, *22*, 3659-3670; b) C. W. Nogueira, G. Zeni, J. B. T. Rocha, *Chem. Rev.* **2004**, *104*, 6255-6285; c) B. A. Trofimov, E. Y. Schmidt, A. I. Mikhaleva, C. Pozo-Gonzalo, J. A. Pomposo, M. Salsamendi, N. I. Protzuk, N. V. Zorina, A. V. Afonin, A. V. Vashchenko, E. P. Levanova, G. G. Levkovskaja, *Chem. Eur. J.* **2009**, *15*, 6435-6445; d) S. S. Zade, N. Zamoshchik, M. Bendikov, *Chem. Eur. J.* **2009**, *15*, 8613-8624; e) C. Sanmartín , D. Plano, A. K. Sharma, J. A. Palop. *J. Mol. Sci.* **2012**, *13*, 9649-9672.

[2] C. R. B. Rhoden, G. Zeni, *Org. Biomol. Chem.* **2011**, *9*, 1301-1313.

[3] For C3-arylation of selenophenes via Suzuki coupling: a) D. A. Barancelli, D. Alves, P. Prediger, E. C. Stangherlin, C. W. Nogueira, G. Zeni, *Synlett* **2008**, 119-125; b) D. T. Tung, A. Villinger, I Langer, *Adv. Synth. Catal.* **2008**, *350*, 2109-2117; c) D. A. Barancell C. I. Acker, P. H. Menezes, G. Zeni, *Org. Biomol. Chem.* **2011**, 1529-1537; d) P. Ehlers, T. T. Dang, T. Patonay, A. Villinger, I Langer, *Eur. J. Org. Chem.* **2013**, 2000-2007.

[4] For C3-arylation of selenophenes via Negishi coupling: R. I Schumacher, D. Alves, R. Brandao, C. W. Nogueira, G. Zen *Tetrahedron Lett.* **2008**, *49*, 538-542.

[5] For reviews: a) C. B. Bheeter, L. Chen, J-F. Soulé, H. Doucet, *Cat. Sc Technol.* **2016**, *6*, 2005-2049; b) R. Rossi, M. Lessi, C. Manzini, C Marianetti, F. Bellina, *Tetrahedron* **2016**, *72*, 1795-1837.

[6] a) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200-205; b) B.-J. Li, S D. Yang, Z.-J. Shi, *Synlett* **2008**, 949-957; c) L. Ackermann, F Vicente, A. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826; d) C L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677-685; e) I Ackermann, *Chem. Rev.* **2011**, *111*, 1315-1345; f) J. Yamaguchi, A D. Yamaguchi, K. Itami, *Angew. Chem., Int. Ed.* **2012**, *51*, 8960-900 g) J. Wencel-Delord, F. Glorius, *Nature Chem.* **2013**, *5*, 369-375; h) Rossi, F. Bellina, M. Lessi, C. Manzini, *Adv. Synth. Catal.* **2014**, *35* 17-117.

[7] a) A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A Miyafuji, T. Nakata, N. Tani, Y. Aoyagi, *Heterocycles* **1990**, *3* 1951-1958; b) J. Roger, F. Požgan, H. Doucet *Green Chem.* **2009**, *1* 425-432.

[8] For Pd-catalysed direct β-arylations of thiophenes: a) T. Okazawa, Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.*, **2002**, *124*, 528 5287; b) S. Kirchberg, T. Vogler, A. Studer, *Synlett* **2008**, 2841-284 c) S. Yanagisawa, K. Ueda, H. Sekizawa, K. Itami, *J. Am. Chem. So* **2009**, *131*, 14622-14623; d) S. Kirchberg, S. Tani, K. Ueda, Yamaguchi, A. Studer, K. Itami, *Angew. Chem. Int. Ed.* **2011**, *5* 2387-2391; e) I. Schnapperelle, S. Breitenlechner, T. Bach, *Org. Let* **2011**, *13*, 3640-3643; f) K. Funaki, T. Sato, S. Oi, *Org. Lett.* **2012**, *1* 6186-6189: g) D.-T. D. Tang, K. D. Collins, F. Glorius, *J. Am. Chem Soc.* **2013**, *135*, 7450-7453; h) I. Schnapperelle, T. Bacl *ChemCatChem* **2013**, *5*, 3232-3236; i) D.-T. D. Tang, K. D. Collins, Glorius, *J. Am. Chem. Soc.*, **2013**, *135*, 7450-7453; j) D. T. D. Tan K. D. Collins, J. B. Ernst, F. Glorius, *Angew. Chem. Int. Ed.*, **2014**, *5* 1809-1813.

[9] For Pd-catalysed direct α-arylations of selenophenes: a) S. Tamba, F Fujii, A. Mori, K. Hara, N. Koumura, *Chem. Lett.* **2011**, *40*, 922-92 b) D. S. Rampon, L. A. Wessjohann, P. H. Schneider, *J. Org. Chem* **2014**, *79*, 5987-5992.

[10] a) X. Zhao, E. Dimitrijevic, V. M. Dong, *J. Am. Chem. Soc.* **200** *131*, 3466-3467; b) X. Zhao, V. M. Dong, *Angew. Chem., Int. Ed* **2010**, *50*, 932-934.

[11] For a review: L. Wang, W. He, Z. Yu, *Chem. Soc. Rev.* **2013**, *42*, 599-621.

[12] For a review: K. Yuan, J.-F. Soulé, H. Doucet, *ACS Catal.* **2015**, *5*, 978-991.

[13] For Pd-catalysed desulfitative couplings with heteroarenes: a) M. Zhang, S. Zhang, M. Lui, J. Cheng, *Chem. Commun.* **2011**, *47*, 11522-11524; b) R. Chen, S. Liu, X. Liu, L. Yang, G.-J. Deng, *Org. Biomol. Chem.* **2011**, *9*, 7675-7679; c) B. Liu, Q. Guo, Y. Cheng, J. Lan, J. You, *Chem. Eur. J.* **2011**, *17*, 13415-13419; d) O. Y. Yuen, C. M. So, W. T. Wong, F. Y. Kwong, *Synlett* **2012**, *23*, 2714-2718; e) T. Miao, P. Li, G.-W. Wang, L. Wang, *Chem. Asian J.* **2013**, *8*, 3185-3190; f) R.

Jin, K. Yuan, E. Chatelain, J.-F. Soulé, H. Doucet, *Adv. Synth. Catal.* **2014**, *356*, 3831-3841.

[14] a) K. Yuan, H. Doucet, *Chem. Sci.*, **2014**, *5*, 392-396; b) A. Skhiri, A. Beladhria, K. Yuan, J.-F. Soulé, R. Ben Salem, H. Doucet, *Eur. J. Org. Chem.* **2015**, 4428-4436.

[15] For mechanistic studies on the regioselectivity of the carbopalladation of thiophenes and relative deprotonation rates, see: M. Steinmetz, K. Ueda, S. Grimme, J. Yamaguchi, S. Kirchberg, K. Itami, A. Studer, *Chem. Asian J.* **2012**, *7*, 1256-1260.

[16] C. Colletto, S. Islam, F. Julia-Hernandez, I. Larrosa, *J. Am. Chem. Soc.* **2016**, *138*, 1677-1683.

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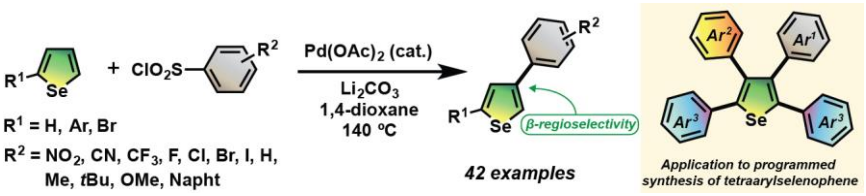
***β*-regioselectivity**

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.