



Direct Arylation

Direct Arylations of Heteroarenes with Benzenesulfonyl Chlorides Using Pd/C Catalyst

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Abstract: The reactivity of heteroaromatics in direct arylation with benzenesulfonyl chlorides using 10 % Pd/C as catalyst was explored. With (benzo)thiophenes, (benzo)furans, pyrroles and selenophenes, high yields in arylated heteroarenes were obtained. These arylations were performed using only 5 mol-% Pd/C and Li₂CO₃ as inexpensive base. The regioselectivities are similar to those observed with homogeneous palladium catalysts. Better yields were obtained with electron-deficient benzenesulfonyl chlorides than with the electron-rich ones. Notably, useful substituents such as bromo or iodo on the benzenesulf

onyl chloride were tolerated, as no cleavage of the C–Br or C–I bonds was observed under these conditions. The use of Pd/C presents several advantages compared to the previously employed homogeneous palladium catalysts, as it can be easily removed by filtration at the end of the reaction. The major side-products of the reaction are HBr associated to Li₂CO₃. Therefore, this new protocol affords a very attractive synthetic scheme in terms of cost, simplicity and low environmental impact for the access to arylated heteroaromatics.

Introduction

Many drugs contain an aryl substituent on a 5-membered ring heteroarene (Figure 1). For example, Atorvastatin which is used to prevent cardiovascular diseases is one of the most prescribed drugs. Canagliflozin is a medication used to treat type 2 diabetes. Saprisartan is an AT1 receptor antagonist. Raloxifene is a medication used to prevent and treat osteoporosis, and Lapatinib is an orally active drug used against breast cancer and other solid tumors. In addition, aryl-substituted heteroarenes are ubiquitous units in organic material science.^[1] Therefore, the development of new procedures using easily accessible and easy to handle inexpensive reagents that allow access to such structures in a few steps is of great interest to pharmacochemists as well as to researchers working in the field of organic materials.

The Pd-catalyzed reactions such as Stille, Suzuki and Negishi cross-couplings are very effective tools for the access to aryl-substituted heteroarenes. These coupling reactions tolerate many useful functional groups and high yields in target products are often obtained. However, one of the major drawback of such couplings is that they require the preliminary synthesis of organometallic or boron derivatives.^[2] In 1985, Ohta et al. described the Pd-catalyzed arylation of heteroarenes via the cleavage of C–H bonds using aryl bromides as aryl sources^[3] Since this seminal report, the so-called "direct arylations" of heteroarenes using Pd-catalysis was demonstrated to be a very

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Figure 1. Representative examples of drugs containing an aryl-substituted heteroarene.

effective method for the preparation of arylated heteroarenes (Scheme 1, a).^[4–7] For these arylations, in addition to aryl halides, a variety of aryl sources such as benzenesulfonyl chlorides can be employed. The use of benzenesulfonyl chlorides is very attractive as in some cases, the regioselectivity of the arylation

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is modified and as they allow the synthesis of molecules containing several halo-substituents including iodo, due to the C-halo bond tolerance of the reactions performed with these substrates.^[8–10] To the best of our knowledge, in all cases the Pd-catalyzed direct arylations of heteroarenes by benzenesulfonyl chlorides were performed using homogeneous catalysts (Scheme 1, b).^[8]



Scheme 1. Pd-catalyzed direct arylations of heteroarenes.

Pd/C catalyst displays several advantages over homogeneous palladium catalysts:^[11] 1) it is easy to handle because it is not sensitive to air or moisture, 2) it is readily available on a large scale and at an affordable cost, 3) it can be removed by simple filtration, 4) recycling of the recovered Pd/C residues is possible in some cases or they can be reconditioned. However, to date the Pd-catalyzed direct arylation of heteroarenes using Pd/C is limited to the reactions with aryl halides.^[12–15] A few other heterogeneous Pd-catalysts such as Pd(OH)₂, zeolites or nanoparticles have also been successfully employed for the direct arylation of heteroaromatics with aryl halides.^[16,17]

As the efficacy of the Pd/C catalyst in direct heteroarene arylations by benzenesulfonyl chlorides has not yet been described, we investigated its potential using a set of heteroarenes (Scheme 1, bottom).

Results and Discussion

Using reaction conditions similar to those employed with homogeneous palladium catalyst,^[9] we first studied the reactivity of 2-methylthiophene (1.5 equiv.) using 4-(trifluoromethyl)-benzenesulfonyl chloride (1 equiv.) as the aryl source in the presence of 5 mol-% Pd/C (10 %) (Scheme 2). With Li₂CO₃ as the base at 150 °C, the C4-arylated thiophene **1** was regioselectively obtained in 79 % yield. It should be noted that this regioselectivity of C4-arylation) is different from the regioselectivity observed with aryl bromide and Pd/C (C5-arylations). This difference of regioselectivity for the arylation of thiophenes using benzene-sulfonyl chlorides or aryl bromides had already been observed with homogeneous Pd-catalysts.^[9] The use of a lower reaction temperature of 130 °C, or the use of cyclopentyl methyl ether

as the solvent afforded the desired coupling product **1** in lower yields of 68 % and 15 %, respectively. We also studied the possibility of recycling the Pd/C catalyst. The Pd/C recovered by filtration through filter paper was used for a second run which afforded **1** in a lower yield of 44 %.



Scheme 2. Pd/C-catalyzed coupling of 2-methylthiophene with benzenesulfonyl chlorides.

The mechanism of the direct arylations of heteroarenes using Pd/C catalyst has not yet been elucidated. In 2003 Conlon et al. studied the mechanism of the Suzuki–Miyaura reaction using Pd/C.^[18a] They suggested that this reaction might have a homogeneous component due to the formation of soluble palladium-species coming from the desorption of the palladium from Pd/C to produce soluble Pd^{II} species. Such desorption may occur after the oxidative addition of the aryl halide on the Pd/C surface. The direct arylation of heteroarenes might proceed via a similar mechanism.

In order to better understand the mechanism of the coupling using benzenesulfonyl chlorides with Pd/C, the mercury poisoning test was applied to this reaction. When a drop of Hg was added to the reaction mixture, no formation of product **1** was detected by GC/MS, and ¹H NMR analysis of the crude mixture (Scheme 2). Such reaction inhibition is generally observed when the catalytic cycle involves heterogeneous species including colloidal Pd⁰.^[19a] However, in a few cases, Hg⁰ interaction with soluble molecular Pd complexes was also found to inhibit catalytic reactions.^[19b,19c]

The kinetics of the formation of product 1 using both Pd/C and Pd(OAc)₂ catalysts was measured (Scheme 3, a). With Pd/C, an induction period was observed with <1 % yield in 1 after 15 minutes. Conversely, with Pd(OAc)₂ after 15 minutes 4 % of 1 was obtained. At 4 h the yields in 1 with Pd/C and Pd(OAc)₂ were 17 % and 33 %, respectively; whereas after 16 h, similar yield in 1 were obtained with these two catalysts. The induction period for the Pd/C catalyzed reaction might come from a slow leaching to produce catalytically active palladium clusters or nanoparticles. In order to confirm the formation of soluble clusters or nanoparticles, a hot filtration test^[20] was performed (Scheme 3, b). The yield in 1 with Pd/C at 150 °C after 4 h was 13 %; then, the reaction mixture was filtered through a pad of Celite, and 1 equiv. of Li₂CO₃ was added to the solution which was heated again at 150 °C during 4 h. The filtrate was catalytically active, as after 8 h the reaction progressed to 21 % yield.





This result supports the formation of catalytically active soluble clusters or nanoparticles from Pd/C.^[21]



Scheme 3. Kinetics of the direct arylation of 2-methylthiophene with 4-(tri-fluoromethyl)benzenesulfonyl chloride using Pd/C or Pd(OAc)₂ catalysts and hot filtration test.

Then, a set of benzenesulfonyl chlorides was treated with 2methylthiophene using Pd/C (Scheme 4). From benzenesulfonyl chlorides bearing chloro or fluoro *para*-substituents, the desired products **2** and **3** were obtained in 62 % and 77 % yield, respectively. By contrast, the reaction of electron-rich 4-methoxybenzenesulfonyl chloride gave the product **5** in only 21 % yield, due to a low conversion of this benzenesulfonyl chloride. As the use of benzenesulfonyl chlorides in Pd-catalyzed direct arylations tolerates bromo-substituents,^[8] the behavior of 3-bromoand 4-bromo-benzenesulfonyl chlorides was also investigated. With 4-bromobenzenesulfonyl chloride, a moderate yield in the target product **6** was obtained due to a poor conversion. Conversely, the use of 3-bromobenzenesulfonyl chloride afforded the product **7** in 79 % yield. In both cases, no cleavage of the C–Br bond was observed.



Scheme 4. Pd/C-catalyzed coupling of 2-methylthiophene with benzenesulfonyl chlorides.

Under the same reaction conditions using Pd/C, the direct arylation of benzothiophene with benzenesulfonyl chlorides regioselectively gave the C3-arylated benzothiophenes (Scheme 5). Again, the use of benzenesulfonyl chlorides as the aryl source instead of aryl bromides modifies the regioselectivity of the arylation. In the presence of aryl bromides and Pd/C, regioselective C2-arylations of benzothiophene had been previously observed.^[9] The reaction tolerates a range of substituents on the benzenesulfonyl chloride. However, again higher yields in desired coupling products were obtained in the presence of electron-withdrawing groups such as trifluoromethyl or chloro than with 4-methoxybenzenesulfonyl chlorides, the halocontaining 3-arylbenzothiophenes **13** and **14** were obtained in moderate yields.



Scheme 5. Pd/C-catalyzed coupling of benzothiophene with benzenesulfonyl chlorides.

The reactivity of Menthofuran, which is a natural compound found in mint oil, using Pd/C was then investigated (Scheme 6). The influence of nitro and bromo *para*-substituents on the benzenesulfonyl chloride was examined, and both reactions produced the expected C5-arylated Menthofuran derivatives **15** and **16** in high yields.



Scheme 6. $\mathsf{Pd}/\mathsf{C}\text{-catalyzed}$ coupling of menthofuran with benzenesulfonyl chlorides.

The regioselective Pd-catalyzed direct arylation of benzofuran with aryl halides is a challenging reaction. Such couplings generally led to mixtures of C2- and C3-arylation products together with C2,C3-diarylation products, as C2- and C3-positions of benzofuran display quite similar reactivity.^[22] We have reported a few years ago that the use of benzenesulfonyl chlorides instead of aryl halides using the homogeneous catalyst PdCl₂(MeCN)₂ allows to control the regioselectivity of the Pdcatalyzed arylation of benzofurans in favor of C2-position.^[22] When Pd/C was used for the direct arylation of benzofuran with benzenesulfonyl chlorides, the C2-arylated benzofurans were



also regioselectively produced (Scheme 7). At 150 °C after 16 h, the 2-arylbenzofurans **17–20** were obtained in 57–73 % yields, from benzenesulfonyl chlorides bearing nitro, trifluoromethyl, chloro or fluoro *para*-substituents. Similar yields in products **21** and **22** were obtained from benzenesulfonyl chloride and 4methoxybenzenesulfonyl chloride. Notably, from 4-bromobenzenesulfonyl chloride, the bromo-substituted 2-arylbenzofuran **23** was isolated in 81 % yield.



Scheme 7. Pd/C-catalyzed coupling of benzofuran with benzenesulfonyl chlorides.

Then, the reactivity of pyrrole derivatives with benzenesulfonyl chlorides using Pd/C was examined (Scheme 8). For these reactions, an excess (3 equiv.) of pyrrole derivative was employed in order to avoid the formation of 2,5-diarylated pyrrole derivatives. From 1-methylpyrrole and 4-nitro-, 4-methoxy- and 3-bromo-benzenesulfonyl chlorides, the C2-arylated pyrroles **24–26** were obtained in 71–92 % yields. The reaction also tolerated benzyl or fluorobenzene substituents on the nitrogen atom of pyrrole, providing the products **27** and **28** in good yields. Under these conditions, no debenzylation was observed.



Scheme 8. Pd/C-catalyzed coupling of pyrrole derivatives with benzenesulfonyl chlorides.

In the presence of aryl halides, the Pd-catalyzed direct arylation of selenophene proceed at C2-position;^[18] whereas with benzenesulfonyl chlorides using the homogeneous catalyst Pd(OAc)₂, C3-arylated selenophenes had been obtained.^[19] We observed that using Pd/C and benzenesulfonyl chlorides, the arylation of selenophene also occurred regioselectively at C3position of selenophene (Scheme 9). Nitro and bromo *para*substituents on the benzenesulfonyl chloride were successfully employed affording the products **29** and **30** in 56 % and 70 % yield, respectively. A 4-iodo substituent on the benzenesulfonyl chloride was also tolerated giving rise to the 3-arylselenophene **31** in 77 % yield.





Scheme 9. Pd/C-catalyzed coupling of selenophene with benzenesulfonyl chlorides.

Conclusion

Pd/C catalyst was successfully employed to promote the direct arvlation of a range of heteroaromatics using benzenesulfonvl chlorides as the aryl source. To the best of our knowledge these are the first examples of desulfitative direct arylations of heteroaromatics using a heterogeneous pre-catalyst. These couplings likely proceed via the formation of homogeneous catalytically active soluble clusters or nanoparticles from Pd/C. Good to high yields in arylated heteroaromatics were obtained using a variety of benzenesulfonyl chlorides. With (benzo)thiophenes and selenophene, the arylation occurred at β -positions; whereas, with (benzo)furans and pyrroles α -arylated compounds were obtained. These regioselectivities are similar to those observed with the homogeneous palladium catalysts Pd(OAc)₂ or PdCl₂(MeCN)₂ when benzenesulfonyl chlorides were employed as the aryl sources. This protocol is attractive as 1) Pd/C can be easily removed by simple filtration, 2) the catalyst, base and reactants are air-stable and easily available, 3) the reaction tolerates useful functional groups such as nitro, trifluoromethyl, methoxy or even bromo and iodo substituents. For these reasons, this new procedure provides an economically viable and environmentally very attractive access to arylated heteroaromatics.

Experimental Section

1,4-Dioxane (99 %) and $\rm Li_2CO_3$ (99 %) were purchased from Fischer. 10 % Pd/C was purchased from Aldrich (Reference 205699 which is expect to conform to the following: approximately 90 % <60 μm and 10 % <5 μm with an average particle size of 15 μm). These compounds were not purified before use.

Typical Experiment for Coupling Reactions: The reaction of the benzenesulfonyl chloride (1 mmol), heteroaromatic (1.5 or 3 mmol) (see schemes) and Li_2CO_3 (0.222 g, 3 mmol) in the presence of 10 % Pd/C (0.055 g, 5 mol-%) in 1,4-dioxane under argon at 150 °C during 16 h, affords the corresponding product after cooling, evaporation of the solvent and filtration through silica gel (pentane/ ether).

2-Methyl-4-[4-(trifluoromethyl)phenyl]thiophene (1):^[9] 4-(Trifluoromethyl)benzenesulfonyl chloride (0.245 g, 1 mmol) and 2-methylthiophene (0.147 g, 1.5 mmol) affords **1** in 79 % (0.191 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.65 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 1.4 Hz, 1H), 7.07 (d, *J* = 1.4 Hz, 1H), 2.54 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 141.2, 140.5, 139.4,





128.6 (q, J = 32.6 Hz), 126.5, 125.7 (q, J = 3.2 Hz), 124.3, 124.0 (q, J = 271.6 Hz), 119.6, 15.4. LRMS calcd. for M⁺ C₁₂H₉F₃S 242, found 242.

4-(4-Chlorophenyl)-2-methylthiophene (2):^[9] 4-Chlorobenzenesulfonyl chloride (0.211 g, 1 mmol) and 2-methylthiophene (0.147 g, 1.5 mmol) affords **2** in 62 % (0.129 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.50 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 1.4 Hz, 1H), 7.04 (d, *J* = 1.4 Hz, 1H), 2.55 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 140.9, 140.8, 134.6, 132.7, 128.8, 127.4, 124.4, 118.3, 15.4. LRMS calcd. for M⁺ C₁₁H₉ClS 208, found 208.

4-(4-Fluorophenyl)-2-methylthiophene (3):^[9] 4-Fluorobenzenesulfonyl chloride (0.194 g, 1 mmol) and 2-methylthiophene (0.147 g, 1.5 mmol) affords **3** in 77 % (0.148 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.50 (dd, *J* = 8.3, 5.6 Hz, 2H), 7.13 (d, *J* = 1.4 Hz, 1H), 7.06 (t, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 1.4 Hz, 1H), 2.53 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 162.0 (d, *J* = 245.4 Hz), 141.0, 140.7, 132.3 (d, *J* = 3.3 Hz), 127.6 (d, *J* = 8.1 Hz), 124.5, 117.7, 115.5 (d, *J* = 21.3 Hz), 15.3. LRMS calcd. for M⁺ C₁₁H₉FS 192, found 192.

2-Methyl-4-phenylthiophene (4):^[9] Benzenesulfonyl chloride (0.177 g, 1 mmol) and 2-methylthiophene (0.147 g, 1.5 mmol) affords **4** in 75 % (0.131 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.58 (d, *J* = 8.3 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 1.4 Hz, 1H), 7.08 (d, *J* = 1.4 Hz, 1H), 2.55 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 142.0, 140.5, 136.1, 128.7, 126.9, 126.2, 124.6, 118.0, 15.5. LRMS calcd. for M⁺ C₁₁H₁₀S 174, found 174.

4-(4-Methoxyphenyl)-2-methylthiophene (5):^[9] 4-Methoxybenzenesulfonyl chloride (0.206 g, 1 mmol) and 2-methylthiophene (0.147 g, 1.5 mmol) affords **5** in 21 % (0.043 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.49 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 1.4 Hz, 1H), 7.00 (d, *J* = 1.4 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 2H), 3.83 (s, 3H), 2.52 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 158.7, 141.7, 140.3, 129.0, 127.3, 124.6, 116.6, 114.1, 55.3, 15.4. LRMS calcd. for M⁺ C₁₂H₁₂OS 204, found 204.

4-(4-Bromophenyl)-2-methylthiophene (6):^[9] 4-Bromobenzenesulfonyl chloride (0.255 g, 1 mmol) and 2-methylthiophene (0.147 g, 1.5 mmol) affords **6** in 38 % (0.096 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.49 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 1.4 Hz, 1H), 7.02 (d, *J* = 1.4 Hz, 1H), 2.53 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 140.9, 140.8, 135.0, 131.8, 127.8, 124.3, 120.8, 118.4, 15.4. LRMS calcd. for M⁺ C₁₁H₉BrS 252, found 252.

4-(3-Bromophenyl)-2-methylthiophene (7):^[23] 3-Bromobenzenesulfonyl chloride (0.255 g, 1 mmol) and 2-methylthiophene (0.147 g, 1.5 mmol) affords **7** in 79 % (0.200 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.71 (s, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 1.4 Hz, 1H), 7.03 (d, *J* = 1.4 Hz, 1H), 2.53 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 141.1, 140.6, 138.2, 130.4, 129.9, 129.4, 124.9, 124.5, 123.0, 119.1, 15.6. LRMS calcd. for M⁺ C₁₁H₉BrS 252, found 252.

3-[4-(Trifluoromethyl)phenyl]benzo[*b***]thiophene (8):^[9]** 4-(Trifluoromethyl)benzenesulfonyl chloride (0.245 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **8** in 71 % (0.197 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.98–7.92 (m, 1H), 7.91–7.85 (m, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.48 (s, 1H), 7.45–7.38 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 140.7, 139.6, 137.4, 136.6, 129.5 (q, *J* = 32.6 Hz), 128.8, 125.7 (q, *J* = 4.0 Hz), 124.7, 124.6 (m), 124.1 (q, *J* = 271.8 Hz), 123.1, 122.5. LRMS calcd. for M⁺ C₁₅H₉F₃S 278, found 278.

3-(4-Chlorophenyl)benzo[b]thiophene (9):^[9] 4-Chlorobenzenesulfonyl chloride (0.211 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **9** in 63 % (0.154 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.97–7.90 (m, 1H), 7.90–7.83 (m, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.43–7.37 (m, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 140.7, 137.6, 136.8, 134.4, 133.5, 129.9, 128.9, 124.5, 124.4, 123.7, 123.0, 122.6. LRMS calcd. for M⁺ C₁₄H₉ClS 244, found 244.

3-(4-Fluorophenyl)benzo[*b***]thiophene (10):^[24]** 4-Fluorobenzenesulfonyl chloride (0.194 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **10** in 60 % (0.137 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.97–7.90 (m, 1H), 7.89–7.82 (m, 1H), 7.55 (dd, *J* = 8.3, 5.6 Hz, 2H), 7.43–7.38 (m, 2H), 7.38 (s, 1H), 7.18 (t, *J* = 8.3 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 162.5 (d, *J* = 246.6 Hz), 140.8, 138.0, 137.1, 132.2, 130.4 (d, *J* = 8.1 Hz), 124.6, 124.5, 123.6, 123.1, 122.8, 115.8 (d, *J* = 21.5 Hz). LRMS calcd. for M⁺ C₁₄H₉FS 228, found 228.

3-Phenylbenzo[b]thiophene (11):^[9] Benzenesulfonyl chloride (0.177 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **11** in 61 % (0.128 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.98–7.90 (m, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.51 (t, *J* = 7.9 Hz, 2H), 7.44–7.38 (m, 4H). ¹³C NMR (100 MHz, CDCl₃): δ = 140.7, 138.1, 137.9, 136.0, 128.7, 128.5, 127.5, 124.4, 124.3, 123.4, 122.9. LRMS calcd. for M⁺ C₁₄H₁₀S 210, found 210.

3-(4-Methoxyphenyl)benzo[b]thiophene (12):^[9] 4-Methoxybenzenesulfonyl chloride (0.206 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **12** in 41 % (0.098 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.97–7.90 (m, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.43–7.36 (m, 2H), 7.35 (s, 1H), 7.04 (d, *J* = 8.3 Hz, 2H), 3.89 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 159.1, 140.6, 138.1, 137.7, 129.8, 128.5, 124.3, 124.2, 122.9, 122.8, 122.5, 114.1, 55.3. LRMS calcd. for M⁺ C₁₅H₁₂OS 240, found 240.

3-(4-Bromophenyl)benzo[*b***]thiophene (13)**:^[9] 4-Bromobenzenesulfonyl chloride (0.255 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **13** in 45 % (0.130 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.97–7.90 (m, 1H), 7.90–7.82 (m, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.43–7.36 (m, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 140.7, 137.5, 136.8, 134.8, 131.9, 130.2, 124.6, 124.5, 123.7, 123.0, 122.6, 121.6. LRMS calcd. for M⁺ C₁₄H₉BrS 288, found 288.

3-(4-Iodophenyl)benzo[b]thiophene (14): 4-Iodobenzenesulfonyl chloride (0.302 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **14** in 54 % (0.181 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.97–7.89 (m, 1H), 7.89–7.83 (m, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.45–7.37 (m, 3H), 7.33 (d, *J* = 8.3 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 140.7, 137.9, 137.5, 136.9, 135.5, 130.5, 124.6, 124.5, 123.8, 123.0, 122.6, 93.1. Anal. Calcd for C₁₄H₉IS (336.19): C, 50.02; H, 2.70; found C, 67.34; H, 3.80.

3,6-Dimethyl-2-(4-nitrophenyl)-4,5,6,7-tetrahydrobenzofuran (15):^[10b] 4-Nitrobenzenesulfonyl chloride (0.221 g, 1 mmol) and menthofuran (0.225 g, 1.5 mmol) affords **15** in 82 % (0.222 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 8.22 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 2.80–2.60 (m, 1H), 2.50–2.24 (m, 3H), 2.23 (s, 3H), 2.00–1.80 (m, 2H), 1.50–1.30 (m, 1H), 1.12 (d, *J* = 7.5 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 152.4, 145.1, 145.0, 138.4, 124.3, 124.2, 121.2, 121.1, 31.6, 31.2, 29.2, 21.5, 120.0, 10.5. LRMS calcd. for M⁺ C₁₆H₁₇NO₃ 271, found 271.

2-(4-Bromophenyl)-3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran (16):^[10b] 4-Bromobenzenesulfonyl chloride (0.255 g, 1 mmol) and menthofuran (0.225 g, 1.5 mmol) affords **16** in 84 % (0.256 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.50 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 2.80–2.70 (m, 1H), 2.50–2.20 (m, 3H), 2.15 (s, 3H), 2.10–1.85 (m, 2H), 1.50–1.35 (m, 1H), 1.12 (d, *J* = 7.5 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 150.1, 145.9, 131.7, 131.5, 126.5, 120.2, 119.7,





117.0, 31.6, 31.4, 29.8, 21.7, 20.2, 10.1. LRMS calcd. for $M^+\,C_{16}H_{17}BrO$ 304, found 304.

2-(4-Nitrophenyl)benzofuran (17):^[22] 4-Nitrobenzenesulfonyl chloride (0.221 g, 1 mmol) and benzofuran (0.177 g, 1.5 mmol) affords **17** in 57 % (0.136 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 8.34 (d, *J* = 8.6 Hz, 2H), 8.03 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.27 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 155.6, 153.4, 147.4, 136.4, 128.8, 126.0, 125.3, 124.5, 123.7, 121.8, 111.6, 105.2. LRMS calcd. for M⁺ C₁₄H₉NO₃ 239, found 239.

2-[4-(Trifluoromethyl)phenyl]benzofuran (18):^[22] 4-(Trifluoromethyl)benzenesulfonyl chloride (0.245 g, 1 mmol) and benzofuran (0.177 g, 1.5 mmol) affords **18** in 63 % (0.165 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.96 (d, *J* = 7.8 Hz, 2H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.14 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 155.3, 154.3, 133.8, 130.2 (q, *J* = 32.5 Hz), 129.0, 126.0 (q, *J* = 2.1 Hz), 125.2, 125.1, 124.1 (q, *J* = 271.8 Hz), 123.4, 111.5, 103.4. LRMS calcd. for M⁺ C₁₅H₉F₃O 262, found 262.

2-(4-Chlorophenyl)benzofuran (19):^[22] 4-Chlorobenzenesulfonyl chloride (0.211 g, 1 mmol) and benzofuran (0.177 g, 1.5 mmol) affords **19** in 60 % (0.137 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.79 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.01 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 155.0, 154.9, 134.4, 129.2 (2C), 129.1, 126.3, 124.7, 123.2, 121.1, 111.3, 101.9. LRMS calcd. for M⁺ C₁₄H₉ClO 228, found 228.

2-(4-Fluorophenyl)benzofuran (20):^[22] 4-Fluorobenzenesulfonyl chloride (0.194 g, 1 mmol) and benzofuran (0.177 g, 1.5 mmol) affords **20** in 73 % (0.155 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.87 (dd, *J* = 5.8, 5.5 Hz, 2H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 2H), 6.98 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 163.0 (d, *J* = 248.7 Hz), 155.1, 155.0, 129.3, 126.9, 126.8 (d, *J* = 8.3 Hz), 124.4, 123.2, 121.0, 116.1 (d, *J* = 21.7 Hz), 111.3, 101.1 (d, *J* = 1.7 Hz). LRMS calcd. for M⁺ C₁₄H₉FO 212, found 212.

2-Phenylbenzofuran (21):^[22] Benzenesulfonyl chloride (0.177 g, 1 mmol) and benzofuran (0.177 g, 1.5 mmol) affords **21** in 65 % (0.126 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.89 (d, *J* = 7.8 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.04 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 156.0, 155.0, 130.6, 129.3, 128.9, 128.7, 125.1, 124.4, 123.1, 121.0, 111.3, 101.4. LRMS calcd. for M⁺ C₁₄H₁₀O 194, found 194.

2-(4-Methoxyphenyl)benzofuran (22):^[22] 4-Methoxybenzenesulfonyl chloride (0.206 g, 1 mmol) and benzofuran (0.177 g, 1.5 mmol) affords **22** in 57 % (0.128 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.80 (d, *J* = 7.8 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 2H), 6.89 (s, 1H), 3.87 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 160.1, 156.2, 154.8, 129.6, 126.6, 123.9, 123.5, 123.0, 120.7, 114.4, 111.1, 99.8, 55.5. LRMS calcd. for M⁺ C₁₅H₁₂O₂ 224, found 224.

2-(4-Bromophenyl)benzofuran (23):^[22] 4-Bromobenzenesulfonyl chloride (0.255 g, 1 mmol) and benzofuran (0.177 g, 1.5 mmol) affords **23** in 81 % (0.221 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.73 (d, *J* = 7.8 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.02 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 155.0, 154.9, 132.1, 129.5, 129.2, 126.5, 124.7, 123.2, 122.6, 121.2, 111.3, 102.0. LRMS calcd. for M⁺ C₁₄H₉BrO 272, found 272.

1-Methyl-2-(4-nitrophenyl)pyrrole (24):^[10a] 4-Nitrobenzenesulfonyl chloride (0.221 g, 1 mmol) and 1-methylpyrrole (0.243 g, 3 mmol) affords **24** in 92 % (0.186 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 8.26 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 6.82 (m, 1H), 6.42 (dd, *J* = 3.4, 1.7 Hz, 1H), 6.25 (t, *J* = 3.4 Hz, 1H), 3.75 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 145.9, 139.7, 132.4, 128.1, 126.6, 124.0, 111.5, 108.9, 35.7. LRMS calcd. for M⁺ C₁₁H₁₀N₂O₂ 202, found 202.

2-(4-Methoxyphenyl)-1-methylpyrrole (25):^[10a]. 4-Methoxybenzenesulfonyl chloride (0.206 g, 1 mmol) and 1-methylpyrrole (0.243 g, 3 mmol) affords **25** in 71 % (0.133 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.37 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.74 (m, 1H), 6.23 (t, *J* = 3.4 Hz, 1H), 6.20 (dd, *J* = 3.4, 1.7 Hz, 1H), 3.89 (s, 3H), 3.67 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 158.7, 134.4, 130.1, 126.0, 123.1, 113.9, 108.1, 107.6, 55.4, 35.0. LRMS calcd. for M⁺ C₁₂H₁₃NO 187, found 187.

2-(3-Bromophenyl)-1-methylpyrrole (26):^[25] 3-Bromobenzenesulfonyl chloride (0.255 g, 1 mmol) and 1-methylpyrrole (0.243 g, 3 mmol) affords **26** in 87 % (0.205 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.58 (s, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 6.75 (s, 1H), 6.30–6.20 (m, 2H), 3.69 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 135.5, 133.1, 131.4, 130.0, 129.7, 127.1, 124.5, 122.5, 109.5, 108.1, 35.2. LRMS calcd. for M⁺ C₁₁H₁₀BrN 235, found 235.

1-Benzyl-2-(4-nitrophenyl)pyrrole (27):^[10a] 4-Nitrobenzenesulfonyl chloride (0.221 g, 1 mmol) and 1-benzylpyrrole (0.471 g, 3 mmol) affords **27** in 80 % (0.222 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 8.21 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.40– 7.26 (m, 3H), 7.04 (dd, *J* = 7.4, 1.6 Hz, 2H), 6.91 (dd, *J* = 2.7, 1.8 Hz, 1H), 6.49 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.37 (dd, *J* = 3.7, 2.7 Hz, 1H), 5.25 (s, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 145.1, 138.5, 137.0, 131.5, 127.9, 127.3, 126.7, 125.1, 124.8, 122.8, 110.6, 108.4, 50.1. LRMS calcd. for M⁺ C₁₇H₁₄N₂O₂ 278, found 278.

1-(4-Fluorophenyl)-2-(4-nitrophenyl)pyrrole (28): 4-Nitrobenzenesulfonyl chloride (0.221 g, 1 mmol) and 1-(4-fluorophenyl)pyrrole (0.483 g, 3 mmol) affords **28** in 74 % (0.209 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 8.10 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.21–7.15 (m, 2H), 7.10 (t, *J* = 8.2 Hz, 2H), 7.00 (dd, *J* = 2.7, 1.7 Hz, 1H), 6.65 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.43 (dd, *J* = 3.6, 2.9 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 161.7 (d, *J* = 248.0 Hz), 145.6, 138.9, 136.0 (d, *J* = 3.2 Hz), 131.6, 127.7, 127.3 (d, *J* = 8.5 Hz), 126.9, 123.6, 116.3 (d, *J* = 22.8 Hz), 113.3, 110.2. Anal. Calcd for C₁₆H₁₁FN₂O₂ (282.27): C, 68.08; H, 3.93; N, 9.92; found C, 68.25; H, 3.99; N, 10.08.

3-(4-Nitrophenyl)selenophene (29):^[10c]. 4-Nitrobenzenesulfonyl chloride (0.221 g, 1 mmol) and selenophene (0.196 g, 1.5 mmol) affords **29** in 56 % (0.141 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 8.32 (dd, *J* = 2.5, 1.3 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 2H), 8.15 (dd, *J* = 5.5, 2.5 Hz, 1H), 7.71 (dd, *J* = 5.5, 1.3 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 146.7, 143.3, 142.4, 132.2, 129.1, 128.9, 127.1, 124.4. LRMS calcd. for M⁺ C₁₀H₇NO₂Se 253, found 253.

3-(4-Bromophenyl)selenophene (30):^[10c] 4-Bromobenzenesulfonyl chloride (0.255 g, 1 mmol) and selenophene (0.196 g, 1.5 mmol) affords **30** in 70 % (0.200 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 8.11 (dd, J = 2.5, 1.3 Hz, 1H), 8.09 (dd, J = 5.5, 2.5 Hz, 1H), 7.63 (dd, J = 5.5, 1.3 Hz, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 143.5, 136.2, 132.0, 131.4, 129.4, 128.3, 125.9, 121.1. LRMS calcd. for M⁺ C₁₀H₇BrSe 286, found 286.

3-(4-lodophenyl)selenophene (31):^[10c] 4-lodobenzenesulfonyl chloride (0.302 g, 1 mmol) and selenophene (0.196 g, 1.5 mmol)





affords **31** in 77 % (0.256 g) yield. ¹H NMR (400 MHz, CDCl₃): δ = 8.13–8.09 (m, 1H), 8.08 (dd, *J* = 5.5, 2.5 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.62 (dd, *J* = 5.5, 1.3 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 143.6, 137.9, 136.8, 131.4, 129.3, 128.6, 126.0, 92.5. LRMS calcd. for M⁺ C₁₀H₇ISe 334, found 334.

Supporting Information (see footnote on the first page of this article): Copies of ¹H and ¹³C NMR spectra of new compounds and ¹H NMR spectra of known compounds.

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Keywords: Palladium · Heterogeneous catalysis · Direct arylation · C–H bond functionalization · Desulfitative coupling

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Direct Arylation

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Direct Arylations of Heteroarenes
 with Benzenesulfonyl Chlorides Using Pd/C Catalyst



The potential of 10 % Pd/C catalyst in desulfitative direct arylation of heteroarenes was investigated. Electron-withdrawing as well as electron-donating substituents on the benzenesulfonyl

chlorides were tolerated. Notably, C-halo bonds including C–I bonds on the benzenesulfonyl chlorides remained untouched affording halo-substituted heteroaromatic derivatives.

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