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SpI Regiocontroled Palladium-Catalysed Direct Arylation at Carbon C2 of Benzofurans using Benzenesulfonyl Chlorides as the Coupling Partners

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The regioselective palladium-catalysed direct arylation of benzofurans with aryl halides is a challenging reaction because carbons C2 and C3 display similar reactivity. Such couplings generally lead to mixtures of C2 and C3 arylation products together with C2,C3 diarylation products. We found that the use of benzenesulfonyl chlorides instead of aryl halides as the coupling partner allows for controlling the regioselectivity of the palladium-catalysed arylation of benzofurans in favour of carbon C2. This method tolerates a variety of substituents on the benzenesulfonyl derivative.

Introduction

The arylation of heteroaromatics such as benzofurans is an important field of research in organic chemistry owing to the biological properties of some benzofuran derivatives (Figure 1). For example, saprisartan is an AT1 receptor antagonist and furaprofen is a non-steroidal anti-inflammatory drug.

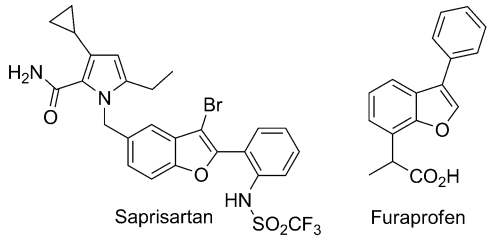

Figure 1. Examples of bioactive arylbenzofurans.

In 1990, Ohta and co-workers reported that the 2- or 5-arylation of several heteroaromatics including furans with aryl halides, through a C–H bond activation, proceeds in moderate to good yields using $Pd(PPh_3)_4$ as the catalyst.[1] Since these exciting results, the palladium-catalysed so-called direct arylation of heteroaryl derivatives has proved to be a very powerful method for the synthesis of a wide variety of arylated heterocycles.[2,3] However, relatively little effort has been expended towards developing such metal-catalysed direct arylation reactions for the synthesis of arylated benzofurans, and they are still often prepared by using more classical coupling procedures.[4,5]

The first example of a palladium-catalysed direct arylation at carbon C2 of benzofuran was reported by Ohta who obtained a low yield of 23% for its coupling with bromobenzene using $Pd(PPh_3)_4$ as the catalyst.[1] Similarly, Fagnou and co-workers reported the coupling of benzofuran with 2-bromotoluene using 2 mol% $Pd(OAc)_2$ and 4 mol% PCy_3 (Cy = cyclohexyl) as the catalyst, and again, the 2-arylated benzofuran was formed in a low yield of 29%.[6a] Higher yields of 41–53% were obtained by Mori and co-workers using $PdCl_2(PPh_3)_2$ as the catalyst associated to AgF as the base.[6c] It should be noted that an example of 2,3-diarylation of benzofuran in the presence of 5 mol% $Pd(OAc)_2$ and 10 mol% P*n*Bu(Ad)$_2$ (Ad = adamantyl) as the catalyst system has also been described by Chiong and Daugulis.[7] The Pd-catalysed synthesis of 2-arylbenzofurans using aryldiazonium trifluoroacetates or arylboronic acids as coupling partners,[8] or under oxidative coupling conditions[9] has also been reported. Recently, Glorius and co-workers prepared 2-arylbenzofurans through rhodium-catalysed oxidative arylation.[10]

The low yields often obtained for the Pd-catalysed coupling of aryl halides with benzofuran are attributable to the lack of reactivity and/or regioselectivity observed in the course of these couplings (Scheme 1). For example, we observed that the reaction of 4-bromobenzene with benzofuran in the presence of 2 mol% $Pd(OAc)_2$ using KOAc as the base in *N*,*N*-dimethylacetamide (DMA) led to a mixture of the mono-arylated benzofurans **1a** and **b** and also to the 2,3-diarylation product **1c** in a 50:17:33 ratio making this process unattractive. The use of other bases such as CsOAc, NaOAc, K_2CO_3 or K_3PO_4 led to lower conversions of benzofuran and also to mixtures of products.

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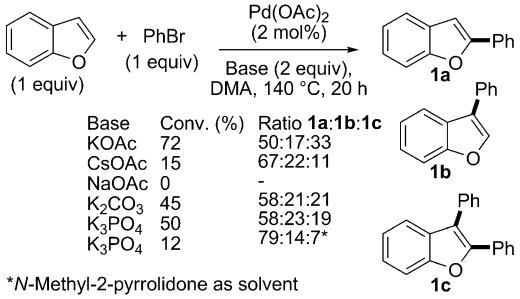
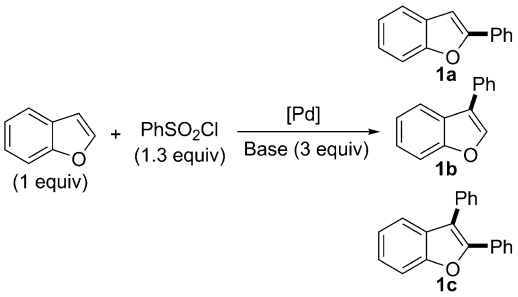


Scheme 1. Regioselectivity of the Pd-catalysed direct arylation of benzofuran with bromobenzene.



Scheme 2. Pd-catalysed direct arylation of benzofuran with benzenesulfonyl chloride.

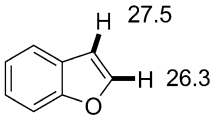


Figure 2. Benzofuran Gibbs free energies of activation (ΔG_{298K}) of the cleavage of C–H bonds in the CMD process using the $[Pd(C_6H_5)(PMe_3)(OAc)]$ catalyst.

According to Gorelsky calculations, in the concerted metallation deprotonation (CMD) process carbon 2 of benzofuran should be slightly more reactive than carbon 3 (energies: 26.3 and 27.5 kcal mol^{-1}, respectively, Figure 2).[11] This minor difference of energy of activation explains the poor regioselectivity observed for Pd-catalysed arylations that proceed through a CMD process.

Therefore, the discovery of a new process for the regioselective intermolecular direct coupling of benzofuran derivatives with arenes, especially using easily available catalyst, base and substrates, would be a considerable advantage.

Results and Discussion

In 2009, Dong and co-workers reported the Pd-catalysed coupling of 2-phenylpyridine with benzenesulfonyl chlorides to prepare sulfones.[12] In the course of this study, they also observed in one case a desulfitative[13] direct arylation of a quinoline derivative if using elevated temperatures in the presence of Ag_2CO_3 and CuBr. Then, the use of benzenesulfonyl chlorides[14–16] as the coupling partners for the palladium-catalysed desulfitative direct arylation has been extended to benzoxazoles derivatives by Cheng et al. using 10 mol% $Pd(OAc)_2$ catalyst, K_2CO_3 as a base and one equivalent of CuI as an additive to produce 2-arylbenzoxazoles in high yields.[17] We also recently reported the first palladium-catalysed desulfitative β-arylation of thiophene derivatives.[18] On the other hand, to our knowledge, the desulfitative direct arylation of benzofurans with benzenesulfonyl chlorides has not been reported. As the use of benzenesulfonyl chlorides instead of aryl halides drastically modifies the regioselectivity of palladium-catalysed direct arylations,[18] their behaviour in the presence of benzofurans needed to be investigated.

Herein, we describe a regioselective access to C2-arylated benzofurans using desulfitative palladium-catalysed C–H bond functionalisation of benzofurans with benzenesulfonyl chlorides as the coupling partners (Scheme 2). The influence of the benzenesulfonyl chloride substituents is reported.

Based on our previous results on palladium-catalysed desulfitative coupling with thiophene derivatives,[18] we first examined the influence of several reaction conditions on the products formation (Table 1). The reaction of 1.3 equivalents of benzenesulfonyl chloride with one equivalent of benzofuran in the presence of 5 mol% $Pd(OAc)_2$ catalyst and Li_2CO_3 as the base at 140 °C gave a mixture of products **1a** and **b** in a 26:1 ratio with a conversion of benzofuran of 87%; whereas no formation of diarylation product **1c** was detected by GC–MS analysis of the crude mixture (Table 1, entry 1). Then, we examined the influence of the palladium catalyst. The use of 5 mol% $PdCl_2$ led to similar results to the use of $Pd(OAc)_2$; whereas $PdCl(C_3H_5)$(dppb) (dppb = 1,4-bis(diphenylphosphino)butane was completely ineffective (entries 2 and 3). On the other hand, $PdCl_2(MeCN)_2$ catalyst gave the regioselective product **1a** (ratio **1a**:**b** 35:1) in 81% yield with full conversion of benzofuran (entry 4). The influence of the nature of the base was also examined. The use of Na_2CO_3, K_2CO_3, KOAc or K_3PO_4 led to low to

Table 1. Influence of the reaction conditions on the Pd-catalysed direct arylation of benzofuran with benzenesulfonyl chloride.[a]

	Catalyst (mol%)	Solvent	Base	Ratio **1a**:**b**:**c**	Conv. [%]	Yield [%]
1	$Pd(OAc)_2$ (5)	dioxane	Li_2CO_3	26:1:0	87	68
2	$PdCl_2$ (5)	dioxane	Li_2CO_3	35:1:0	70	60
3	$PdCl(C_3H_5)$(dppb) (5)	dioxane	Li_2CO_3	–	0	
4	$PdCl_2(CH_3CN)_2$ (5)	dioxane	Li_2CO_3	34:1:0	100	81
5	$PdCl_2(CH_3CN)_2$ (5)	dioxane	Na_2CO_3	60:1:0	50	
6	$PdCl_2(CH_3CN)_2$ (5)	dioxane	K_2CO_3	7:1:0	19	
7	$PdCl_2(CH_3CN)_2$ (5)	dioxane	KOAc	24:1:0	10	
8	$PdCl_2(CH_3CN)_2$ (5)	dioxane	K_3PO_4	15:1:5	37	
9	$PdCl_2(CH_3CN)_2$ (5)	pentan-1-ol	Li_2CO_3	sideproducts	18	
10	$PdCl_2(CH_3CN)_2$ (5)	Ethyl-benzene	Li_2CO_3	6:1:0	38	
11	$PdCl_2(CH_3CN)_2$ (5)	DMA	Li_2CO_3	–	0	
12	$PdCl_2(CH_3CN)_2$ (2.5)	dioxane	Li_2CO_3	27:1:0	90	73
13	$PdCl_2(CH_3CN)_2$ (5)	dioxane	Li_2CO_3	90:1:0	58[b]	

[a] Benzofuran (1 equiv), benzenesulfonyl chloride (1.3 equiv), base (3 equiv), 140 °C, 18 h, isolated yields, conversion of benzofuran. [b] 120 °C.

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moderate conversions of benzofuran and/or to lower regioselectivities than the use of Li_2CO_3 (entries 5–8). The influence of a few other solvents was then examined. Pentan-1-ol only gave unidentified side-products, and ethylbenzene afforded **1a** in low yield attributable to a lower regioselectivity of the arylation and a poor conversion of benzofuran (entries 9 and 10). The polar solvent DMA was completely ineffective for this coupling (entry 11). Then, we examined the influence of the catalyst loading and reaction temperature. With Li_2CO_3 as the base and dioxane as the solvent, a catalyst loading of 2.5 mol% of $PdCl_2(MeCN)_2$ gave **1a** in 73% yield with 90% conversion of benzofuran, but a reaction temperature of 120 °C instead of 140 °C was relatively ineffective (entries 12 and 13). Finally, we also studied the reactivity of benzenesulfinic acid sodium salt as the coupling partner instead of benzenesulfonyl chloride, because the Pd-catalysed synthesis of biaryls with such reactants was recently reported.[19a] However, no formation of desired products **1a**–**c** was detected by GC–MS analysis of the crude mixtures.[19b]

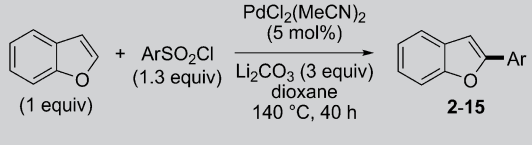
Then, the influence of the substituents on benzenesulfonyl chloride for the reaction with benzofuran was examined by using 5 mol% $Pd(MeCN)_2Cl_2$ catalyst in the presence of Li_2CO_3 in dioxane at 140 °C (Table 2). We initially employed electron-deficient benzenesulfonyl chlorides. Nitro-, cyano- and trifluoromethyl substituents at C4 of benzenesulfonyl chlorides gave very regioselectively the C2-arylated benzofurans **2**–**4** in 69–80% yields (Table 2 entries 1–3). High yield in **5** was also obtained from 4-chlorobenzenesulfonyl chloride (entry 4). It should be noted that no cleavage of the C–Cl bond was observed in the course of this reaction, allowing further transformations. From the slightly electron-deficient 4-fluorobenzenesulfonyl chloride, a good yield of 90% in **6** was also obtained (entry 5). Even the electron-rich 4-methylbenzenesulfonyl chloride gave the desired coupling product **7** in high yield and very high regioselectivity (entry 6). On the other hand, the use of the more electron-rich 4-methoxybenzenesulfonyl chloride gave **8** in only 39% yield attributable to a poor conversion of this reactant (entry 7).

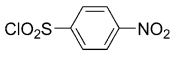
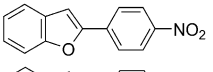
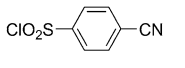
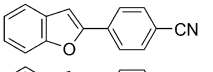
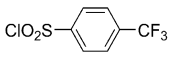
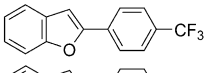
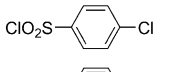
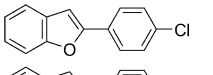
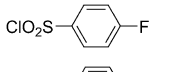
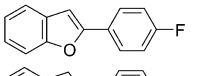
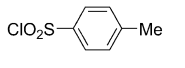
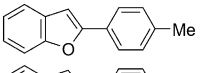
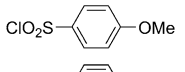
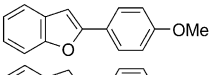
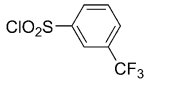
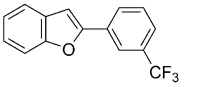
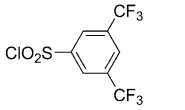
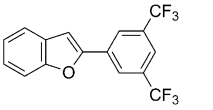
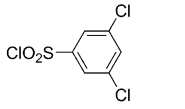
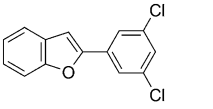
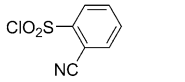
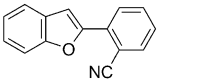
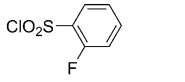
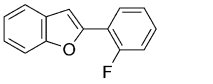
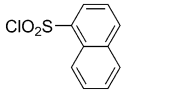
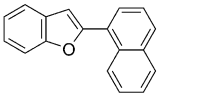
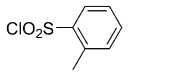
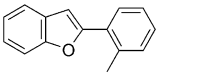
Then, we studied the influence of some *meta* and *ortho* substituents on the benzenesulfonyl derivative on the regioselectivity and yield for this coupling. *Meta* substituents have a minor influence on the reactivity of the benzenesulfonyl chlorides. 3-(Trifluoromethyl)benzenesulfonyl chloride gave **9** in 64% yield (Table 2, entry 8). High yields of **10** and **11** were also obtained from two di-*meta*-subtituted benzenesulfonyl chlorides (entries 9 and 10). Satisfactory result was also obtained from 2-cyanobenzenesulfonyl chloride to give **12** in 50% yield (entry 11). From 2-fluorobenzenesulfonyl chloride and naphthalene-1-sulfonyl chloride, the expected products **13** and **14** were obtained in 91% and 73% yields, respectively (entries 12 and 13). On the other hand, an *ortho*-methyl substituent on benzenesulfonyl chloride had a detrimental effect, as the desired product **15** was only observed as trace amount by GC–MS analysis (entry 14).

Consecutive arylations using 4-bromobenzenesulfonyl chloride were also studied (Scheme 3). Using the $Pd(MeCN)_2Cl_2$ catalyst in the presence of Li_2CO_3 in dioxane, 4-bromobenzenesulfonyl chloride was coupled at C2 position of benzofuran without cleavage of the C–Br bond to give **16** in 88% yield. Then, using $PdCl(C_3H_5)(dppb)$ catalyst[20a] with KOAc as the base in DMA and 2-ethyl-4-methylthiazole as the coupling partner, target product **17** was obtained in 88% yield.

The influence of a bromo substituent on benzofuran was also examined, because such substituent would allow the easy access to a variety of benzofuran derivatives (Scheme 4). Using 1.3 equivalents of differently substituted benzenesulfonyl chloride and 5 mol% $Pd(MeCN)_2Cl_2$ catalyst in the presence of

Table 2. Influence of the benzenesulfonyl chloride substituents on the Pd-catalysed direct C2-arylation of benzofuran.



	Benzenesulfonyl chloride	Product		Yield [%]
1			**2**	69
2			**3**	80
3			**4**	71
4			**5**	77
5			**6**	90
6			**7**	89
7			**8**	39
8			**9**	64
9			**10**	77
10			**11**	85
11			**12**	50
12			**13**	91
13			**14**	73
14			**15**	trace

[a] $PdCl_2(CH_3CN)_2$ (0.05 equiv), benzofuran (1 equiv), benzenesulfonyl chloride (1.3 equiv), Li_2CO_3 (3 equiv), dioxane, 140 °C, 40 h, isolated yields.

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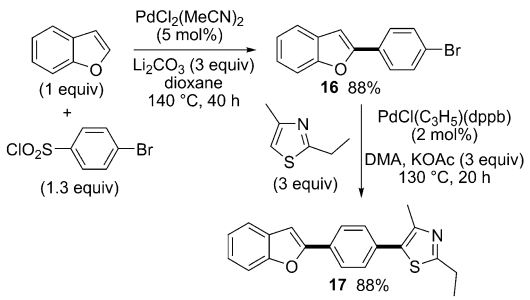
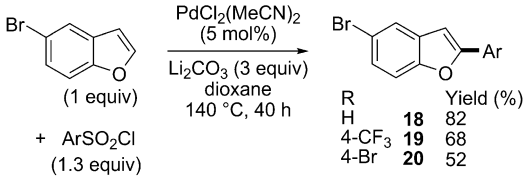


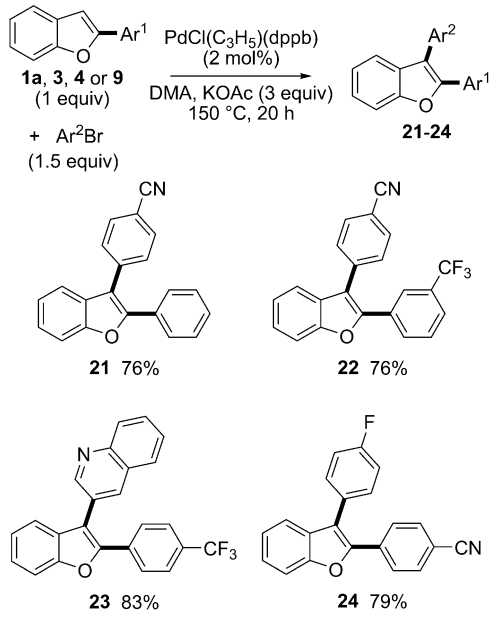
Scheme 3. Consecutive Pd-catalysed direct arylations using 4-bromobenzenesulfonyl chloride as the coupling partner.



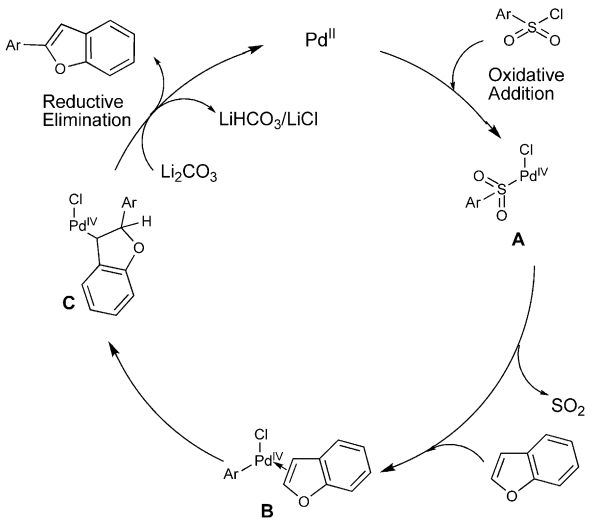
Scheme 4. Pd-catalysed direct arylation of 5-bromobenzofuran with benzenesulfonyl chlorides bearing different substituents R.

Li_2CO_3 in dioxane, the desired coupling products **18**–**20** were obtained in 52–82% yields without cleavage of the C–Br bond.

Finally, as the C3 position of benzofurans is known to be reactive for direct arylations with aryl halides using palladium catalysts with acetate bases in polar solvents,[20b] the reactivity of some of the prepared 2-arylbenzofurans for such couplings was examined (Scheme 5). **1a**, **3**, **4** and **9** were reacted with a set of aryl bromides in the presence of 2 mol% $PdCl(C_3H_5)$-(dppb) catalyst, KOAc as the base in DMA. Selective 3-arylations of these 2-arylbenzofurans were observed by using 4-bromobenzonitrile, 3-bromoquinoline or 4-bromofluorobenzene as the coupling partners to afford products **21**–**24** in 76–83% yields.



Scheme 5. Pd-catalysed direct C3-arylation of 2-arylbenzofurans with aryl bromides.



Scheme 6. Proposed catalytic cycle.

Although the mechanism cannot yet be elucidated, the catalytic cycle shown on Scheme 6 can be proposed. The first step of the catalytic cycle is probably the oxidative addition of the benzenesulfonyl chloride to Pd^{II} to afford the Pd^{IV} intermediate **A**. Such oxidative addition on Pd^{II} have been found to proceed even at room temperature.[12b] Then, after elimination of SO_2, coordination of benzofuran gives **B**. The migration of the aryl group to the α-carbon atom of benzofuran gives **C**. Finally, a proton abstraction assisted by the base gives the α-arylated benzofuran and regenerates the Pd^{II} species.

Conclusions

In summary, we report here the first palladium-catalysed desulfitative arylation of benzofuran derivatives. The reaction was found to provide very selectively the C2-arylated benzofurans, and proceeds with easily accessible ligand-free $Pd(MeCN)_2Cl_2$ catalyst and Li_2CO_3 as the base. Moreover, this procedure tolerates a variety of substituents on the benzenesulfonyl chloride. Owing to the wide availability of diversely functionalised benzenesulfonyl chlorides at an affordable cost, such simple reaction conditions (no expensive base and ligand) should be very attractive to synthetic chemists for gaining access to 2-arylbenzofurans. Moreover, from these 2-arylbenzofurans, a second palladium-catalysed C–H bond functionalization at carbon C3 of the benzofuran ring allows the synthesis of 2,3-diarylbenzofurans with two different aryl groups.

Experimental Section

General

All reactions were performed under an inert atmosphere with standard Schlenk techniques. HPLC grade 1,4-dioxane was used and stored under argon without further purification. ^1H NMR spectra

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were recorded on a Bruker GPX (400 MHz) spectrometer. Chemical shifts (δ) were reported in parts per million relative to residual chloroform (7.26 ppm for ^{1}H; 77.0 ppm for ^{13}C), constants were reported in Hertz. ^{1}H NMR assignment abbreviations were the following: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). ^{13}C NMR spectra were recorded at 100 MHz on the same spectrometer and reported in ppm. All reagents were weighed and handled in air.

General procedure for the synthesis of C2-arylated benzofurans

To a 25 mL oven-dried Schlenk tube, arylsulfonyl chloride (1.3 mmol), benzofuran derivative (1 mmol), Li_2CO_3 (0.222 g, 3 mmol), 1,4-dioxane (2 mL) and bis(acetonitrile)dichloropalladium(II) (12.9 mg, 0.05 mmol) were successively added. The reaction mixture was evacuated by vacuum–argon cycles (5 times) and stirred at 140 °C (oil bath temperature) for 18 or 40 h (see tables and schemes). After cooling the reaction at RT and concentration, the crude mixture was purified by silica column chromatography to afford the C2-arylated benzofurans.

2-Phenylbenzofuran (**1a**)[21]: Benzenesulfonyl chloride (0.230 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol), affords **1a** in 81% (0.157 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 7.8 Hz, 2H), 7.60 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.37 (t, J = 7.8 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.04 ppm (s, 1H).

2-(4-Nitrophenyl)-benzofuran (**2**)[22]: 4-Nitrobenzenesulfonyl chloride (0.287 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol) affords **2** in 69% (0.165 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, J = 7.8 Hz, 2H), 8.10 (d, J = 7.8 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.26 ppm (s, 1H).

4-Benzofuran-2-ylbenzonitrile (**3**)[22]: 4-Cyanobenzenesulfonyl chloride (0.263 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol) affords **3** in 80% (0.175 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 7.8 Hz, 2H), 7.72 (d, J = 7.8 Hz, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.18 ppm (s, 1H).

2-(4-Trifluoromethylphenyl)-benzofuran (**4**)[22]: 4-(Trifluoromethyl)-benzenesulfonyl chloride (0.318 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol) affords **4** in 71% (0.186 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): 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), 7.13 ppm (s, 1H).

2-(4-Chlorophenyl)-benzofuran (**5**)[23]: 4-Chlorobenzenesulfonyl chloride (0.274 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol) affords **5** in 77% (0.176 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.52 (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), 7.00 ppm (s, 1H).

2-(4-Fluorophenyl)-benzofuran (**6**)[24]: 4-Fluorobenzenesulfonyl chloride (0.252 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol) affords **6** in 90% (0.191 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (dd, J = 5.8, 5.5 Hz, 2H), 7.59 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.3 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.15 (t, J = 7.5 Hz, 2H), 6.95 ppm (s, 1H).

2-*p*-Tolylbenzofuran (**7**)[23]: 4-Methylbenzenesulfonyl chloride (0.248 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol) affords **8** in 89% (0.185 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, J = 7.8 Hz, 2H), 7.60 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 6.99 (s, 1H), 2.43 ppm (s, 3H).

2-(4-Methoxyphenyl)benzofuran (**8**)[22]: 4-Methoxybenzenesulfonyl chloride (0.269 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol) affords **9** in 39% (0.087 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 7.8 Hz, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 6.99 (d, J = 7.8 Hz, 2H), 6.90 (s, 1H), 3.87 ppm (s, 3H).

2-(3-Trifluoromethylphenyl)benzofuran (**9**)[25]: 3-(Trifluoromethyl)-benzenesulfonyl chloride (0.318 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol) affords **9** in 64% (0.168 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.65–7.52 (m, 4H), 7.34 (t, J = 7.8 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.10 ppm (s, 1H).

2-(3,5-Bis-trifluoromethylphenyl)benzofuran (**10**)[24]: 3,5-Bis(trifluoromethyl)benzenesulfonyl chloride (0.406 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol), affords **10** in 77% (0.254 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (s, 2H), 7.83 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.18 ppm (s, 1H).

2-(3,5-Dichlorophenyl)benzofuran (**11**)[26]: 3,5-Dichlorobenzenesulfonyl chloride (0.318 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol) affords **11** in 85% (0.223 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (s, 2H), 7.59 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.40–7.22 (m, 3H), 7.02 ppm (s, 1H).

2-Benzofuran-2-ylbenzonitrile (**12**)[27]: 2-Cyanobenzenesulfonyl chloride (0.263 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol) affords **12** in 50% (0.109 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.72 (s, 1H), 7.71–7.65 (m, 2H), 7.55 (d, J = 8.2 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.28 ppm (t, J = 8.0 Hz, 1H).

2-(2-Fluorophenyl)benzofuran (**13**)[28]: 2-Fluorobenzenesulfonyl chloride (0.252 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol) affords **13** in 91% (0.193 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (t, J = 7.7 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.68–7.24 (m, 5H), 7.19 ppm (dd, J = 8.6, 8.0 Hz, 1H).

2-Naphthalen-1-ylbenzofuran (**14**)[29]: Naphthalene-1-sulfonyl chloride (0.294 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol) affords **14** in 73% (0.178 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, J = 7.8 Hz, 1H), 7.95–7.87 (m, 3H), 7.68 (d, J = 7.8 Hz, 1H), 7.62–7.53 (m, 4H), 7.35 (t, J = 7.8 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.09 ppm (s, 1H).

2-(4-Bromophenyl)benzofuran (**16**)[30]: 4-Bromobenzenesulfonyl chloride (0.333 g, 1.3 mmol) and benzofuran (0.118 g, 1 mmol) affords **16** in 88% (0.240 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): 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 ppm (s, 1H).

5-(4-Benzofuran-2-ylphenyl)-2-ethyl-4-methylthiazole (**17**): 2-(4-Bromophenyl)benzofuran **16** (0.273 g, 1 mmol), 2-ethyl-4-methylthiazole (0.381 g, 3 mmol), KOAc (0.294 g, 3 mmol), DMA (2 mL) and $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) were successively added in a Schlenk tube. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 130 °C (oil bath temperature) for 20 h. After cooling the reaction to RT and concentration, the crude mixture was purified by silica column chromatography to afford product **17** in 88% (0.281 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$):

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$\delta = 7.90$ (d, $J = 8.3$ Hz, 2H), 7.60 (d, $J = 7.6$ Hz, 1H), 7.53 (d, $J = 7.6$ Hz, 1H), 7.50 (d, $J = 8.3$ Hz, 2H), 7.32 (t, $J = 7.6$ Hz, 1H), 7.22 (t, $J = 7.6$ Hz, 1H), 7.07 (s, 1H), 3.05 (q, $J = 7.6$ Hz, 2H), 2.52 (s, 3H), 1.42 ppm (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.3$, 154.9, 130.5, 129.6, 129.4 (m), 129.1, 125.1, 124.5, 123.0, 121.0, 111.2, 101.8, 26.9, 16.2, 14.3 ppm. Elemental analysis: calcd (%) for $C_{20}H_{17}NOS$ (319.42): C 75.20, H 5.36; found: C 75.34, H 5.19.

5-Bromo-2-phenylbenzofuran (**18**)[31]: Benzenesulfonyl chloride (0.230 g, 1.3 mmol) and 5-bromobenzofuran (0.197 g, 1 mmol) affords **18** in 82% (0.224 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.84$ (d, $J = 7.8$ Hz, 2H), 7.70 (s, 1H), 7.46 (t, $J = 7.8$ Hz, 2H), 7.42–7.35 (m, 3H), 6.95 ppm (s, 1H).

5-Bromo-2-(4-trifluoromethylphenyl)-benzofuran (**19**): 4-(Trifluoromethyl)benzenesulfonyl chloride (0.318 g, 1.3 mmol) and 5-bromobenzofuran (0.197 g, 1 mmol) affords **19** in 68% (0.232 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.88$ (d, $J = 7.8$ Hz, 2H), 7.71 (s, 1H), 7.70 (d, $J = 7.8$ Hz, 2H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.39 (d, $J = 8.0$ Hz, 1H), 7.03 ppm (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.4$, 153.8, 133.1, 130.7, 130.6 (q, $J = 31.0$ Hz), 127.9, 125.8 (q, $J = 4.6$ Hz), 125.1, 123.9 (q, $J = 272.0$ Hz), 123.8, 116.3, 112.7, 102.5 ppm. Elemental analysis: calcd (%) for $C_{15}H_8BrF_3O$ (341.12): C 52.81, H 2.36; found: C 53.00, H 2.17.

5-Bromo-2-(4-bromophenyl)benzofuran (**20**): 4-Bromobenzenesulfonyl chloride (0.333 g, 1.3 mmol) and 5-bromobenzofuran (0.197 g, 1 mmol) affords **20** in 52% (0.183 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.72$–7.66 (m, 3H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.38 (s, 2H), 6.95 ppm (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.1$, 153.6, 132.1, 128.8, 127.4, 126.5, 123.6, 123.1, 116.2, 112.6, 101.1 ppm. Elemental analysis: calcd (%) for $C_{14}H_8Br_2O$ (352.02): C 47.77, H 2.29; found: C 47.58, H 2.34.

Preparation of the $PdCl(C_3H_5)$(dppb) catalyst[20]

An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_2$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). Anhydrous dichloromethane (10 mL) were added, then the solution was stirred at RT for 20 min. The solvent was removed in vacuum. The yellow powder was used without purification. ^{31}P NMR (81 MHz, $CDCl_3$) $\delta = 19.3$ (s).

General procedure for the synthesis of C3-arylated benzofurans

To a 25 mL oven dried Schlenk tube, aryl bromide (1.5 mmol), 2-arylbenzofuran derivative (1 mmol), KOAc (0.294 g, 3 mmol), DMA (2 mL) and $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) were successively added. The reaction mixture was evacuated by vacuum–argon cycles (5 times) and stirred at 150 °C (oil bath temperature) for 20 h. After cooling the reaction at RT and concentration, the crude mixture was purified by silica column chromatography to afford the C3-arylated products.

4-(2-Phenylbenzofuran-3-yl)benzonitrile (**21**). 2-Phenylbenzofuran **1a** (0.194 g, 1 mmol) and 4-bromobenzonitrile (0.273 g, 1.5 mmol), affords **21** in 76% (0.224 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$ (d, $J = 7.8$ Hz, 2H), 7.63 (d, $J = 7.8$ Hz, 2H), 7.60–7.55 (m, 3H), 7.49 (d, $J = 7.8$ Hz, 1H), 7.40–7.33 (m, 4H), 7.29 ppm (d, $J = 7.8$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 154.1$, 151.6, 138.1, 132.7, 130.4, 129.9, 129.0, 128.7, 127.3, 125.2, 123.4, 119.4, 118.8, 115.7, 111.4, 111.2 ppm. Elemental analysis: calcd (%) for $C_{21}H_{13}NO$ (295.33): C 85.40, H 4.44; found: C 85.24, H 4.57.

4-[2-(3-Trifluoromethylphenyl)-benzofuran-3-yl]-benzonitrile (**22**): 2-(3-Trifluoromethylphenyl)benzofuran **9** (0.262 g, 1 mmol) and 4-bromobenzonitrile (0.273 g, 1.5 mmol) affords **22** in 76% (0.276 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.95$ (s, 1H), 7.78 (d, $J = 8.3$ Hz, 2H), 7.70 (d, $J = 7.9$ Hz, 1H), 7.65–7.56 (m, 4H), 7.50 (d, $J = 7.8$ Hz, 1H), 7.45 (t, $J = 7.2$ Hz, 1H), 7.43 (t, $J = 7.2$ Hz, 1H), 7.31 ppm (t, $J = 7.2$ Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 154.2$, 149.7, 137.4, 132.9, 131.4 (q, $J = 32.6$ Hz), 130.7, 130.3, 130.1, 129.1, 128.9, 125.8, 125.5 (q, $J = 4.0$ Hz), 123.9 (q, $J = 4.0$ Hz), 123.7, 123.6 (q, $J = 272.6$ Hz), 119.7, 118.6, 117.1, 111.8, 111.6 ppm. Elemental analysis: calcd (%) for $C_{22}H_{12}F_3NO$ (363.33): C 72.73, H 3.33; found: C 72.80, H 3.18.

3-[2-(4-Trifluoromethylphenyl)benzofuran-3-yl]quinoline (**23**): 2-(4-Trifluoromethylphenyl)-benzofuran **4** (0.262 g, 1 mmol) and 3-bromoquinoline (0.312 g, 1.5 mmol), affords **23** in 83% (0.323 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.99$ (s, 1H), 8.38 (s, 1H), 8.24 (d, $J = 8.3$ Hz, 1H), 7.89 (d, $J = 8.2$ Hz, 1H), 7.83 (t, $J = 8.0$ Hz, 1H), 7.76 (d, $J = 7.8$ Hz, 2H), 7.70–7.50 (m, 5H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.33 ppm (t, $J = 8.0$ Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 154.7$, 150.7, 150.4, 137.4, 133.7, 131.0 (q, $J = 32.0$ Hz), 130.9, 129.8, 129.1, 128.5, 128.2, 128.1, 127.4, 126.3, 126.1 (q, $J = 4.0$ Hz), 124.2 (q, $J = 272.6$ Hz), 124.1, 120.1, 115.7, 112.9, 111.9 ppm. Elemental analysis: calcd (%) for $C_{24}H_{14}F_3NO$ (389.37): C 74.03, H 3.62; found: C 74.18, H 3.74.

4-[3-(4-Fluorophenyl)benzofuran-2-yl]benzonitrile (**24**): 4-Benzofuran-2-ylbenzonitrile **3** (0.219 g, 1 mmol) and 4-bromofluorobenzene (0.263 g, 1.5 mmol) affords **24** in 79% (0.247 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$ (d, $J = 8.5$ Hz, 2H), 7.62–7.55 (m, 3H), 7.50–7.35 (m, 4H), 7.28 (t, $J = 7.0$ Hz, 1H), 7.21 ppm (t, $J = 7.0$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.7$ (d, $J = 248.7$ Hz), 154.2, 148.2, 134.7, 132.3, 131.3 (d, $J = 8.1$ Hz), 129.9, 127.9 (d, $J = 3.6$ Hz), 126.9, 126.0, 123.5, 120.3, 119.5, 118.6, 116.5 (d, $J = 21.3$ Hz), 111.5, 111.4 ppm. Elemental analysis: calcd (%) for $C_{21}H_{12}FNO$ (313.32): C 80.50, H 3.86; found: C 80.34, H 3.74.

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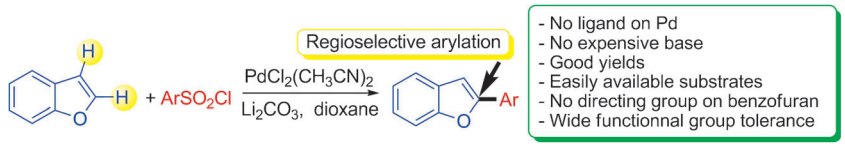
SpI **Regiocontroled Palladium-Catalysed Direct Arylation at Carbon C2 of Benzofurans using Benzenesulfonyl Chlorides as the Coupling Partners**



Low cost, high regioselectivity: The use of benzenesulfonyl chlorides as the coupling partner in the palladium-catalysed direct arylation of benzofurans allows for controlling the regioselectivity in favor of carbon C2. This method tolerates a variety of substituents on the benzenesulfonyl derivative.

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