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Graphical Abstract

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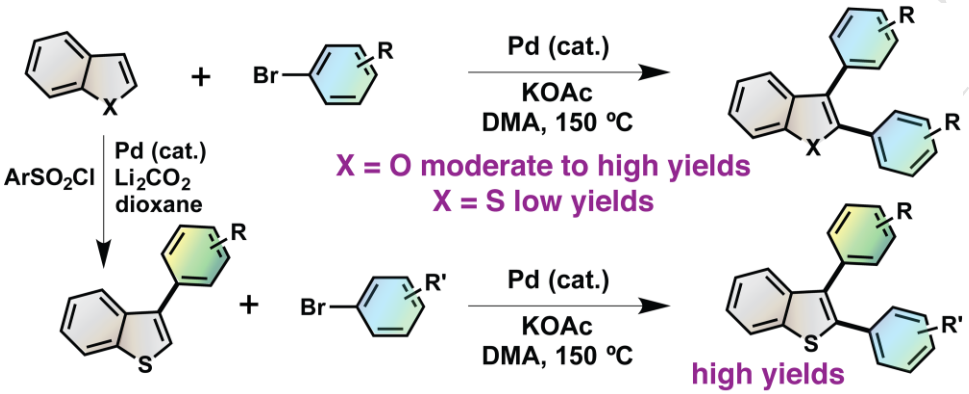

Reactivity of benzofuran and benzothiophene in palladium-catalysed direct C2,C3-diarylations

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ABSTRACT

The Pd-catalysed one pot direct diarylation of benzofuran and benzothiophene at both C2- and C3-positions was studied. In the presence of electron-deficient aryl bromides, the diarylation of benzofuran proceeded in good yields; whereas, with benzothiophene moderate yields were generally obtained, as the C3-position exhibits a poor reactivity. In order to obtain 2,3-diarylated benzothiophenes, its sequential arylation was examined. We found that the C3-arylation of benzothiophene followed by its C2-arylation provides a reliable methodology for the access to 2,3-diarylbenzothiophenes.

1. Introduction

The arylation of heteroaromatics such as benzofuran and benzothiophene is an important field for research in organic chemistry due to the biological properties of some of their derivatives. For example, Saprisartan is an AT1 receptor antagonist, Furaprofen is a non-steroidal anti-inflammatory drug and Raloxifene is used in the prevention of osteoporosis (Fig. 1).

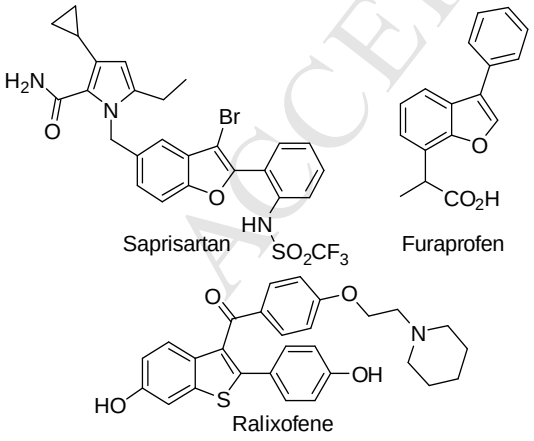


Figure 1. Examples of bioactive aryl-substituted benzofurans and benzothiophenes

In 1990, Ohta and co-workers reported that the C2-arylation of several heteroaromatics, including benzofuran and benzothiophene, with aryl bromides, *via* a C-H bond activation, proceed in moderate to good yields using $Pd(PPh_3)_4$ as the catalyst.[1] Since these seminal results, the palladium-catalysed so-called direct arylation of heteroaryl derivatives proved to be an extremely reliable method for the synthesis of a wide variety of arylated heterocycles.[2]

For the Pd-catalysed direct arylation of most 5-membered ring heterocycles, including benzofuran[3] and benzothiophene,[4] the reaction often proceeds *via* a concerted metallation deprotonation (CMD) mechanism.[5] According to Gorelsky calculations, in the CMD process, the carbon 2 of benzofuran should be slightly more reactive than carbon 3 (energies: 26.3 *vs* 27.5); whereas for benzothiophene C2-position is much more reactive than C3-position (energies: 26.5 *vs* 29.2) (Fig. 2).[6] Therefore, the one pot C2,C3-diarylation of these two heteroaromatic compounds should be possible, but benzothiophene is expected to be less reactive than benzofuran.

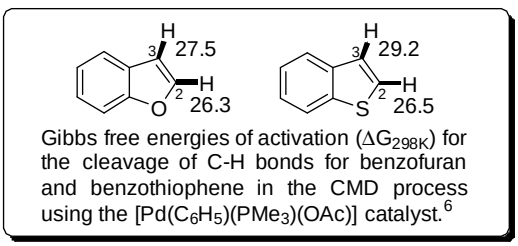
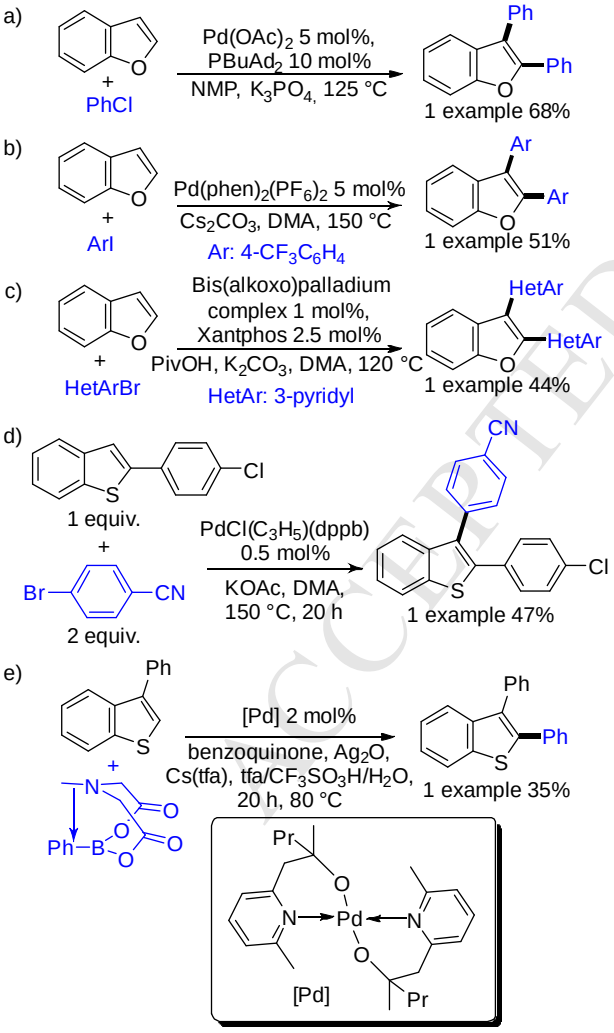


Figure 2. Benzofuran and benzothiophene Gibbs free energies of activation for CMD process.

So far, relatively little efforts have been expended toward developing such Pd-catalysed direct arylation reactions for the one pot synthesis of 2,3-diarylated benzofurans or

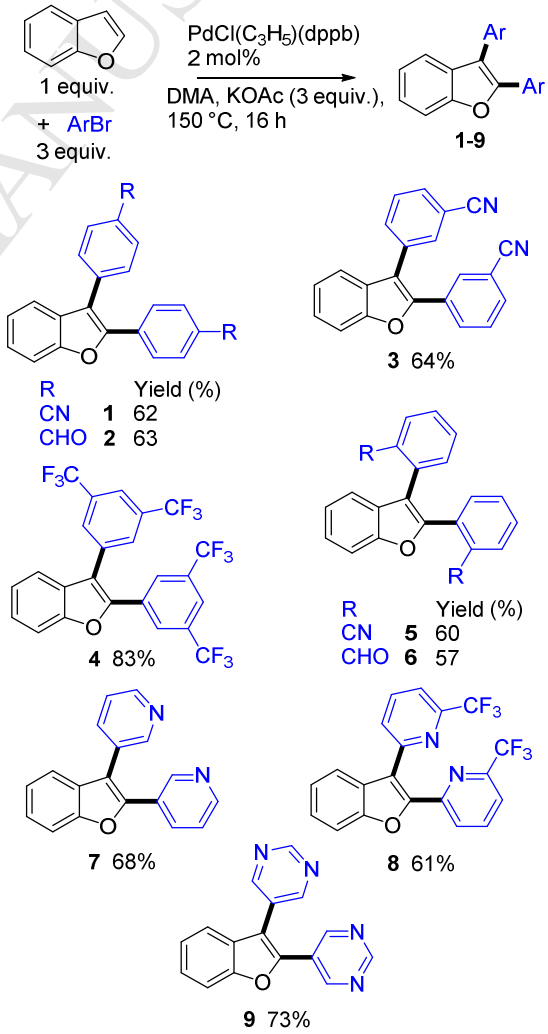
benzothiophenes.[7-9] These compounds are generally prepared *via* Suzuki reactions.[10,11] The first example of palladium-catalysed direct diarylation at carbons C2 and C3 of benzofuran was reported by Daugulis and Chiong in 2007. They prepared 2,3-diphenylbenzofuran in 68% yield, using chlorobenzene as the coupling partner and 5 mol% $Pd(OAc)_2$ associated to 10 mol% P*n*Bu(Ad)$_2$ as the catalyst system (Scheme 1, a).[7a] Similarly, Shibahara, Murai et al. reported in 2010 an example of 2,3-diarylation of benzofuran with 4-(trifluoromethyl)iodobenzene in 51% yield using 5 mol% $Pd(phen)_2(PF_6)_2$ catalyst (Scheme 1, b).[7b] The last example of diarylation of benzofuran was reported in 2015. Using 3-bromopyridine as aryl source and a bis(alkoxo)palladium complex as catalyst, the 2,3-diarylbenzofuran was obtained in 44% yield together with 47% of the mono-C2-arylated benzofuran (Scheme 1, c).[7c] A few examples of palladium-catalysed sequential diarylations of benzofuran have also been described.[8] Concerning benzothiophene, very few examples of C2,C3-diarylations have been reported. Schnürch et al. reported, in the course of their studies on benzothiophene C2-arylation reaction, that in some cases trace amount of diarylations were observed.[8b] So far, C2,C3-diarylated benzothiophenes have been prepared *via* successive Pd-catalysed direct arylations. Our laboratory reported in 2013 that from a 2-arylbenzothiophene and 4-bromobenzonitrile using $PdCl(C_3H_5)$(dppb) catalyst, the 2,3-diarylated benzothiophene could be obtained in 47% yield (Scheme 1, d).[9a] A procedure, using so-called MIDA boronate instead of aryl bromides as coupling partners for C2-arylation of 3-phenylbenzothiophene also led to a C2,C3-diarylated benzothiophene in moderate yield (Scheme 1, e).[9c]



Scheme 1. Reported Pd-catalysed direct diarylations of benzofuran and arylations of arylbenzothiophenes

2. Results and discussion

Based on our previous results on palladium-catalysed direct arylation of heteroarenes,[2m,9a] we first examined the reactivity of benzofuran in the presence of an excess of 4-bromobenzonitrile (Scheme 2). The reaction of 3 equiv. of this aryl bromide with 1 equiv. of benzofuran in the presence of 2 mol% $PdCl_2(C_3H_5)$(dppb) catalyst and 3 equiv. of KOAc as the base at 150 °C during 16 h gave the desired products **1** in 62%. The formation of mono-arylation products in low yield was also detected by GC/MS analysis of the crude mixture (Scheme 2).

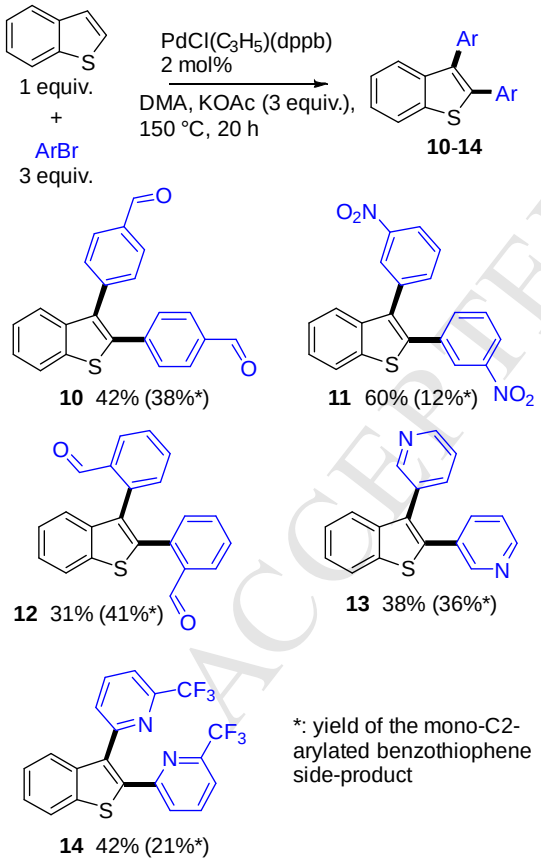


Scheme 2. Pd-catalysed direct diarylations of benzofuran

Then, the influence of the substituents on aryl bromide for diarylation of benzofuran, under these reaction conditions, was examined (Scheme 2). For this study, we initially employed *para*- and *meta*-substituted aryl bromides. Both 4-

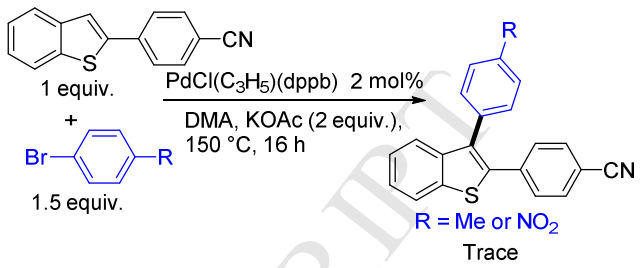
bromobenzaldehyde and 3-bromobenzonitrile gave the target diarylated benzofurans **2** and **3** in good yields. Trifluoromethyl substituents at both C3 and C5 positions of the aryl bromide gave the C2,C3-diarylated benzofuran **4** in 83% yield. Nitrile or formyl *ortho*-substituents on the aryl bromide were also tolerated as the desired products **5** and **6** were obtained in 60% and 57% yields, respectively. Pyridine is probably the most common heterocyclic motif found in pharmaceutically active compounds. It is also one of the most commonly employed motif in ligands used in organometallic chemistry. Therefore, the discovery of preparative methods of derivatives containing pyridines remain an essential research topic in organic synthesis. From benzofuran and 3 equiv. of 3-bromopyridine or 2-bromo-6-(trifluoromethyl)pyridine, the diarylated benzofurans **7** and **8** were obtained in 68% and 61% yields, respectively. 5-Bromopyrimidine was also tolerated as aryl source, with the formation of **9** in 73% yield.

The Pd-catalysed one pot direct C2,C3-diarylation of benzothiophene is more challenging as the C-H bond cleavage at C3-position *via* concerted metallation deprotonation requires an higher Gibbs free energy of activation (see Fig. 2). As expected, in most cases, sluggish reactions were observed with the formation of large amounts of the mono-C2-arylated benzothiophenes (12-41%) as side-products (Scheme 3). The best yield in C2,C3-diarylated benzothiophene was obtained for the coupling of 3-bromonitrobenzene with the formation of **11** in 60% yield; whereas, the reaction of bromobenzaldehydes or bromopyridines afforded **10** and **12-14** in 31-42% yields.



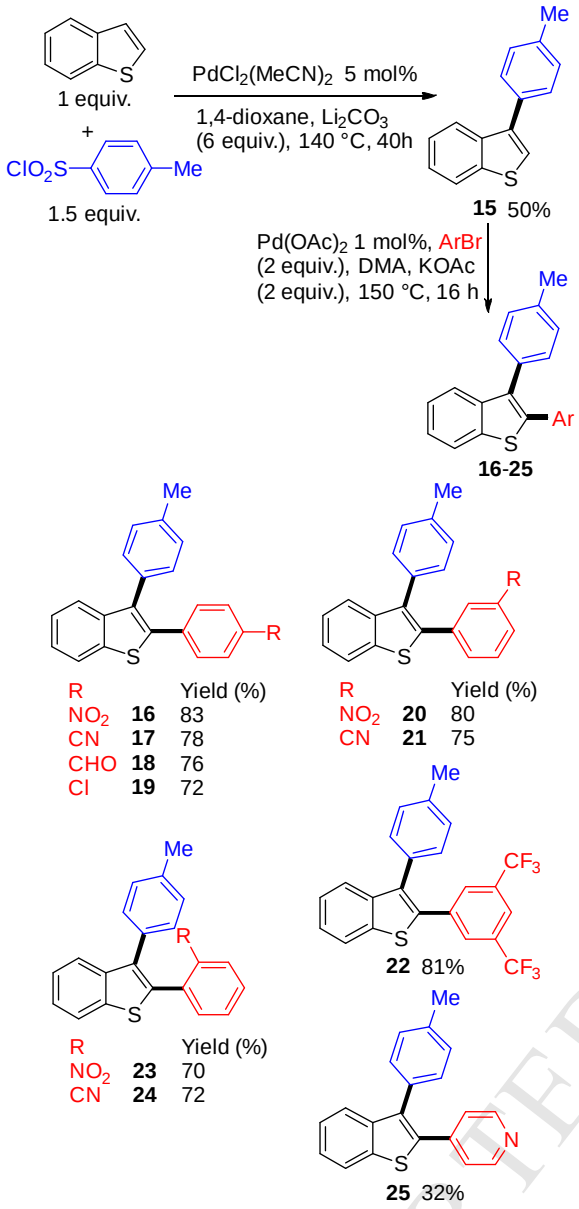
Scheme 3. Pd-catalysed direct diarylations of benzothiophene.

Consecutive arylations at C2-position followed by arylation at C3-position of benzothiophene could provide an alternative method for the preparation of 2,3-diarylthiophenes. We had previously reported a single example of C3-arylation of a 2-arylbenzothiophene (Scheme 1, d).[9a] However, the product was obtained in a moderate yield of 47%. Our attempts to extend this synthetic pathway to 4-(benzothiophen-2-yl)benzonitrile was not successful (Scheme 4). The reaction of this 2-arylbenzothiophene with 4-bromotoluene or 4-bromonitrobenzene afforded the desired coupling products in low yields (<25%) according to GC/MS analysis of the crude mixtures. Moreover, the separation of the mono- and di-arylated products was difficult.



Scheme 4. Attempts of sequential Pd-catalysed direct diarylations of benzothiophene.

Therefore, the access to 2,3-diarylated benzothiophenes *via* consecutive arylations at C3 position followed by arylation at C2-position was attempted (Scheme 5).



Scheme 5. Sequential Pd-catalysed direct diarylations of benzothiophene.

We have recently reported that the Pd-catalysed direct arylation of benzothiophene with benzenesulfonyl chlorides does not proceed via CMD pathway, but probably *via* the formation of a Pd(IV) intermediate, affording regioselectively C3-arylated benzothiophenes.[12,13] Using $Pd(MeCN)_2Cl_2$ catalyst in the presence of Li_2CO_3 in dioxane, and 4-methylbenzenesulfonyl chloride as aryl source, benzothiophene was regioselectively arylated at C3-position to give **15** in 50% yield (Scheme 5, top). Then, the C2-arylation of **15** *via* CMD process was attempted. Using 1 mol% $Pd(OAc)_2$ catalyst with KOAc as the base in DMA during 16 h, and a set of aryl bromides, the desired 2,3-diarylated benzothiophenes **16**-**25** were obtained in good to high yields. For example, the reaction of **15** with aryl bromides substituted at *para*-position by nitro, cyano, formyl or chloro groups gave **16**-**19** in 72-83% yields. Nitrile and formyl *meta*- or *ortho*-substituents on aryl bromides were also tolerated; whereas, the reaction with 4-bromopyridine afforded **25** in a lower yield.

3. Conclusion

In summary, we report here on the reactivity of benzofuran and benzothiophene in the palladium-catalysed one pot direct C2,C3-diarylation. With benzofuran, the reaction was found to provide quite selectively the C2,C3-diarylated benzofurans with a broad set of (hetero)aryl bromides, using 2 mol% $PdCl(C_3H_5)(dppb)$ catalyst and KOAc as base. Conversely, the one pot direct 2,3-diarylation of benzothiophene was sluggish due to a slow arylation at C3-position. However, from a 3-arylbenzothiophene, which could be easily obtained by Pd-catalysed desulfitative arylation, a second Pd-catalysed C-H bond functionalization at carbon C2 of the benzothiophene ring allows the synthesis of 2,3-diarylbenzothiophenes containing two different aryl groups in good yields. Moreover, this procedure tolerates a variety of substituents on the aryl bromide.

4. Experimental Section

General:

All reactions were carried out under an inert atmosphere with standard Schlenk techniques. ^1H NMR spectra were recorded on Bruker GPX (400 MHz) spectrometer. Chemical shifts (δ) were reported in parts per million relative to residual chloroform (7.26 ppm for ^1H; 77.0 ppm for ^{13}C), constants were reported in Hertz. ^1H 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. Compound **15** was prepared according to a reported procedure.[12]

Preparation of the $PdCl(C_3H_5)(dppb)$ catalyst:[14] 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). 10 mL of anhydrous dichloromethane were added, then, the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuum. The yellow powder was used without purification. ^{31}P NMR (81 MHz, $CDCl_3$) δ = 19.3 (s).

General procedure for one pot synthesis of C2,C3-diarylated benzofurans and benzothiophenes 1-14

To a 25 mL oven dried Schlenk tube, aryl bromide (3 mmol), benzofuran or benzothiophene (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 16 hours. After cooling the reaction at room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the diarylated benzofurans or benzothiophenes.

4,4'-(Benzofuran-2,3-diyl)dibenzonitrile (1)[8b]

From benzofuran (0.118 g, 1 mmol) and 4-bromobenzonitrile (0.546 g, 3 mmol), **1** was obtained in 62% (0.198 g) yield.

^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.69-7.62 (m, 5H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H).

4,4'-(Benzofuran-2,3-diyl)dibenzaldehyde (2)

From benzofuran (0.118 g, 1 mmol) and 4-bromobenzaldehyde (0.555 g, 3 mmol), **2** was obtained in 63% (0.205 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H), 10.00 (s, 1H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 191.3, 154.4, 149.6, 138.9, 135.9, 135.7, 130.5, 130.3, 129.9, 129.2, 128.0, 127.4, 126.0, 123.7, 120.1, 119.0, 111.5.

Elemental analysis: calcd (%) for $C_{22}H_{14}O_3$ (326.35): C 80.97, H 4.32; found: C 80.69, H 4.48.

3,3'-(Benzofuran-2,3-diyl)dibenzonitrile (3)

From benzofuran (0.118 g, 1 mmol) and 3-bromobenzonitrile (0.546 g, 3 mmol), **3** was obtained in 64% (0.205 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.80-7.69 (m, 4H), 7.67-7.57 (m, 3H), 7.48-7.39 (m, 3H), 7.31 (t, *J* = 7.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 149.2, 134.6, 134.2, 133.6, 132.6, 132.5, 131.9, 131.3, 131.0, 130.9, 130.2, 129.6, 126.7, 124.4, 120.4, 118.8, 118.7, 117.7, 114.3, 113.9, 112.2.

Elemental analysis: calcd (%) for $C_{22}H_{12}N_2O$ (320.35): C 82.49, H 3.78; found: C 82.60, H 3.64.

2,3-Bis(3,5-bis(trifluoromethyl)phenyl)benzofuran (4)

From benzofuran (0.118 g, 1 mmol) and 3,5-bis(trifluoromethyl)bromobenzene (0.879 g, 3 mmol), **4** was obtained in 83% (0.450 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 2H), 8.01 (s, 1H), 7.99 (s, 2H), 7.84 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 148.1, 134.1, 133.2 (q *J* = 33.7 Hz), 132.5 (q *J* = 33.7 Hz), 131.8, 129.8, 128.6, 126.9, 126.6 (m), 124.4, 122.2 (q, *J* = 272.2 Hz), 122.1 (q, *J* = 272.2 Hz), 119.9, 117.6, 112.0.

Elemental analysis: calcd (%) for $C_{24}H_{10}F_{12}O$ (542.32): C 53.15, H 1.86; found: C 53.24, H 2.00.

2,2'-(Benzofuran-2,3-diyl)dibenzonitrile (5)

From benzofuran (0.118 g, 1 mmol) and 2-bromobenzonitrile (0.546 g, 3 mmol), **5** was obtained in 60% (0.192 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.69 (m, 3H), 7.68-7.64 (m, 2H), 7.62-7.57 (m, 2H), 7.55-7.42 (m, 4H), 7.34 (t, *J* = 7.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 148.9, 135.4, 134.0, 133.8, 133.2, 133.1, 132.6, 131.5, 130.5, 129.3, 128.4, 128.1, 126.0, 123.6, 120.1, 114.5, 117.4, 117.3, 112.9, 111.7, 111.5.

Elemental analysis: calcd (%) for $C_{22}H_{12}N_2O$ (320.35): C 82.49, H 3.78; found: C 82.64, H 3.89.

2,2'-(Benzofuran-2,3-diyl)dibenzaldehyde (6)

From benzofuran (0.118 g, 1 mmol) and 2-bromobenzaldehyde (0.555 g, 3 mmol), **6** was obtained in 57% (0.186 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H), 9.90 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.65-7.56 (m, 2H), 7.53-7.35 (m, 7H), 7.30 (t, *J* = 7.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 191.0, 155.2, 150.8, 135.0, 134.9, 134.8, 134.7, 134.1, 132.3, 132.1, 131.4, 130.2, 129.9, 129.3, 129.2, 129.1, 126.4, 124.4, 120.6, 118.0, 112.2.

Elemental analysis: calcd (%) for $C_{22}H_{14}O_3$ (326.35): C 80.97, H 4.32; found: C 80.99, H 4.46.

3,3'-(Benzofuran-2,3-diyl)dipyridine (7)[7c]

From benzofuran (0.118 g, 1 mmol) and 3-bromopyridine (0.474 g, 3 mmol), **7** was obtained in 68% (0.185 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (bs, 1H), 8.78 (bs, 1H), 8.72 (bs, 1H), 8.57 (bs, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.48-7.25 (m, 4H).

6,6'-(Benzofuran-2,3-diyl)bis(2-(trifluoromethyl)pyridine) (8)

From benzofuran (0.118 g, 1 mmol) and 2-bromo-6-(trifluoromethyl)pyridine (0.678 g, 3 mmol), **8** was obtained in 61% (0.249 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.78-7.90 (m, 3H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 152.3, 149.5, 148.9, 147.3 (q, *J* = 34.8 Hz), 147.2 (q, *J* = 34.8 Hz), 137.9, 136.5, 129.1, 128.6, 126.2, 123.7, 123.6, 122.1, 121.0 (q, *J* = 274.2 Hz), 120.9 (q, *J* = 274.4 Hz), 120.3, 119.2 (m), 118.5 (m), 111.0.

Elemental analysis: calcd (%) for $C_{20}H_{10}F_6N_2O$ (408.30): C 58.83, H 2.47; found: C 58.92, H 2.58.

5,5'-(Benzofuran-2,3-diyl)dipyrimidine (9)[15]

From benzofuran (0.118 g, 1 mmol) and 5-bromopyrimidine (0.477 g, 3 mmol), **9** was obtained in 73% (0.200 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 9.20 (s, 1H), 8.97 (s, 2H), 8.92 (s, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.54-7.45 (m, 2H), 7.37 (t, *J* = 7.8 Hz, 1H).

4,4'-(Benzo[b]thiophene-2,3-diyl)dibenzaldehyde (10)

From benzothiophene (0.134 g, 1 mmol) and 4-bromobenzaldehyde (0.555 g, 3 mmol), **10** was obtained in 42% (0.144 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H), 9.98 (s, 1H), 7.97-7.90 (m, 3H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.44-7.38 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 191.6, 141.7, 140.1, 140.0, 139.5, 139.2, 135.7, 135.6, 133.7, 131.2, 130.4, 130.3, 130.0, 125.7, 125.3, 123.5, 122.5.

Elemental analysis: calcd (%) for $C_{22}H_{14}O_2S$ (342.41): C 77.17, H 4.12; found: C 77.14, H 4.21.

4-(Benzo[*b*]thiophen-2-yl)benzaldehyde[9a] was also isolated as side-product in 38% (0.090 g) yield: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.80-7.72 (m, 2H), 7.63 (s, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 1H).

2,3-Bis(3-nitrophenyl)benzo[b]thiophene (11)

From benzothiophene (0.134 g, 1 mmol) and 3-bromonitrobenzene (0.606 g, 3 mmol), **11** was obtained in 60% (0.225 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.0 Hz, 1H), 8.27 (s, 1H), 8.21 (s, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.70-7.42 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 148.5, 139.8, 139.2, 138.2, 136.6, 136.5, 135.5, 135.4, 132.4, 130.2, 129.9, 126.0, 125.5, 125.2, 124.5, 123.2, 123.1 (2C), 122.6.

Elemental analysis: calcd (%) for $C_{20}H_{12}N_2O_4S$ (376.39): C 63.82, H 3.21; found: C 63.87, H 3.14.

2-(3-Nitrophenyl)benzo[*b*]thiophene[16] was also isolated as side-product in 12% (0.030 g) yield: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.90-7.80 (m, 2H), 7.68 (s, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.44-7.32 (m, 2H).

2,2'-(Benzo[b]thiophene-2,3-diyl)dibenzaldehyde (12)

From benzothiophene (0.134 g, 1 mmol) and 2-bromobenzaldehyde (0.555 g, 3 mmol), **12** was obtained in 31% (0.106 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (s, 1H), 9.75 (s, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 7.0 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.60-7.38 (m, 8H), 7.31 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 190.8, 140.6, 139.9, 137.7, 136.6, 135.2, 134.9, 134.5, 134.0, 133.7, 132.8, 132.5, 132.2, 129.8, 129.3, 128.8, 128.6, 126.1, 125.9, 123.8, 122.7.

Elemental analysis: calcd (%) for $C_{22}H_{14}O_2S$ (342.41): C 77.17, H 4.12; found: C 77.21, H 4.02.

2-(Benzo[*b*]thiophen-2-yl)benzaldehyde[17] was also isolated as side-product in 41% (0.097 g) yield: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.25 (s, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 7.0 Hz Hz, 1H), 7.82 (d, J = 7.0 Hz Hz, 1H), 7.70-7.60 (m, 2H), 7.53 (d, *J* = 7.0 Hz, Hz, 1H), 7.45-7.36 (m, 2H), 7.28 (s, 1H).

3,3'-(Benzo[b]thiophene-2,3-diyl)dipyridine (13)

From benzothiophene (0.134 g, 1 mmol) and 3-bromopyridine (0.474 g, 3 mmol), **13** was obtained in 38% (0.110 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.58 (dd, *J* = 4.8, 1.5 Hz, 2H), 8.52 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.92 (d, *J* = 7.0 Hz, 1H), 7.67 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.61-7.55 (m, 2H), 7.47-7.33 (m, 3H), 7.25-7.20 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 150.3, 149.2, 149.1, 140.2, 139.4, 137.9, 137.2, 136.9, 131.1, 131.0, 130.0, 125.5, 125.2, 123.8, 123.5, 123.2, 122.5.

Elemental analysis: calcd (%) for $C_{18}H_{12}N_2S$ (288.37): C 74.97, H 4.19; found: C 75.10, H 4.11.

3-(Benzo[*b*]thiophen-2-yl)pyridine[18] was also isolated as side-product in 36% (0.076 g) yield: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (s, 1H), 8.57 (d, *J* = 4.6 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.60 (s, 1H), 7.38-7.34 (m, 3H).

6,6'-(Benzo[b]thiophene-2,3-diyl)bis(2-(trifluoromethyl)pyridine) (14)

From benzothiophene (0.134 g, 1 mmol) and 2-bromo-6-(trifluoromethyl)pyridine (0.678 g, 3 mmol), **14** was obtained in 42% (0.178 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (t, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.46-7.35 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 152.6, 148.3 (q, *J* = 34.8 Hz), 147.8 (q, *J* = 34.8 Hz), 140.5, 139.8, 139.6, 137.7, 137.6, 133.6, 128.3, 125.8, 125.4, 125.0, 123.5, 122.2, 121.2 (q, *J* = 274.4 Hz), 120.9 (q, *J* = 272.8 Hz), 119.0, 118.8.

Elemental analysis: calcd (%) for $C_{20}H_{10}F_6N_2S$ (424.36): C 56.61, H 2.38; found: C 56.80, H 2.30.

2-(Benzo[*b*]thiophen-2-yl)-6-(trifluoromethyl)pyridine[19] was also isolated as side-product in 21% (0.058 g) yield: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.91-7.81 (m, 4H), 7.57 (dd, *J* = 2.2 and 6.4 Hz, 1H), 7.42-7.36 (m, 2H).

General procedure for synthesis of C2,C3-diarylated benzothiophenes 16-25

To a 25 mL oven dried Schlenk tube, aryl bromide (2 mmol), 3-(*p*-tolyl)benzothiophene **15** (0.224 g, 1 mmol), KOAc (0.196 g, 2 mmol), DMA (2 mL) and $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 °C (oil bath temperature) for 16 hours. After cooling the reaction at room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the diarylated benzothiophenes.

2-(4-Nitrophenyl)-3-(*p*-tolyl)benzo[b]thiophene (16)

From 3-(*p*-tolyl)benzothiophene **15** (0.224 g, 1 mmol) and 4-bromonitrobenzene (0.404 g, 2 mmol), **16** was obtained in 83% (0.286 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 141.4, 140.9, 139.4, 138.1, 136.3, 136.1, 131.8, 130.3, 130.2, 129.9, 125.6, 125.0, 124.2, 123.8, 122.3, 21.5.

Elemental analysis: calcd (%) for $C_{21}H_{15}NO_2S$ (345.42): C 73.02, H 4.38; found: C 73.10, H 4.50.

4-(3-(*p*-Tolyl)benzo[b]thiophen-2-yl)benzonitrile (17)

From 3-(*p*-tolyl)benzothiophene **15** (0.224 g, 1 mmol) and 4-bromobenzonitrile (0.364 g, 2 mmol), **17** was obtained in 78% (0.253 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.41-7.32 (m, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 139.4, 139.2, 137.9, 136.7, 135.6, 132.2, 131.8, 130.2, 130.1, 129.9, 125.5, 124.9, 124.1, 122.3, 118.8, 111.1, 21.5.

Elemental analysis: calcd (%) for $C_{22}H_{15}NS$ (325.43): C 81.20, H 4.65; found: C 81.41, H 4.47.

4-(3-(*p*-Tolyl)benzo[b]thiophen-2-yl)benzaldehyde (18)

From 3-(*p*-tolyl)benzothiophene **15** (0.224 g, 1 mmol) and 4-bromobenzaldehyde (0.370 g, 2 mmol), **18** was obtained in 76% (0.249 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 2.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.8, 141.0, 140.9, 139.3, 137.8, 137.5, 135.4, 135.2, 132.1, 130.3, 130.2, 129.8, 129.7, 125.3, 124.8, 124.0, 122.3, 21.5.

Elemental analysis: calcd (%) for $C_{22}H_{16}OS$ (328.43): C 80.46, H 4.91; found: C 80.47, H 5.04.

2-(4-Chlorophenyl)-3-(*p*-tolyl)benzo[b]thiophene (19)

From 3-(*p*-tolyl)benzothiophene **15** (0.224 g, 1 mmol) and 4-bromochlorobenzene (0.382 g, 2 mmol), **19** was obtained in 72% (0.240 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.5 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.32-7.22 (m, 8H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0, 138.9, 137.9, 137.4, 133.9, 133.8, 133.1, 132.3, 130.9, 130.3, 129.7, 128.7, 124.9, 124.7, 123.7, 122.2, 21.5.

Elemental analysis: calcd (%) for $C_{21}H_{15}ClS$ (334.86): C 75.32, H 4.52; found: C 75.17, H 4.34.

2-(3-Nitrophenyl)-3-(*p*-tolyl)benzo[b]thiophene (20)

From 3-(*p*-tolyl)benzothiophene **15** (0.224 g, 1 mmol) and 3-bromonitrobenzene (0.404 g, 2 mmol), **20** was obtained in 80% (0.276 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (t, *J* = 2.0 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.47-7.37 (m, 3H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 140.0, 138.2, 137.1, 135.5, 135.2, 134.6, 134.5, 130.7, 129.3, 129.0, 128.5, 124.5, 124.0, 123.5, 123.1, 121.5, 121.4, 20.6.

Elemental analysis: calcd (%) for $C_{21}H_{15}NO_2S$ (345.42): C 73.02, H 4.38; found: C 73.00, H 4.21.

3-(3-(*p*-Tolyl)benzo[b]thiophen-2-yl)benzonitrile (21)

From 3-(*p*-tolyl)benzothiophene **15** (0.224 g, 1 mmol) and 3-bromobenzonitrile (0.364 g, 2 mmol), **21** was obtained in 75% (0.244 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.65-7.61 (m, 2H), 7.58-7.51 (m, 2H), 7.47-7.33 (m, 3H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 138.9, 137.8, 136.1, 136.0, 135.0, 133.8, 132.9, 131.5, 131.0, 130.1, 129.7, 129.2, 125.2, 124.8, 123.8, 122.2, 118.5, 112.7, 21.4.

Elemental analysis: calcd (%) for $C_{22}H_{15}NS$ (325.43): C 81.20, H 4.65; found: C 81.14, H 4.60.

2-(3,5-Bis(trifluoromethyl)phenyl)-3-(*p*-tolyl)benzo[b]thiophene (22)

From 3-(*p*-tolyl)benzothiophene **15** (0.224 g, 1 mmol) and 3,5-bis(trifluoromethyl)bromobenzene (0.586 g, 2 mmol), **22** was obtained in 81% (0.353 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.72 (s, 3H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1, 139.4, 138.6, 137.1, 136.5, 135.6, 132.1 (q, *J* = 33.4 Hz), 131.7, 130.4, 130.3, 129.8 (m), 126.0, 125.4, 124.5, 123.5 (q, *J* = 273.0 Hz), 122.1, 121.4 (m), 21.7.

Elemental analysis: calcd (%) for $C_{23}H_{14}F_6S$ (436.42): C 63.30, H 3.23; found: C 63.47, H 3.08.

2-(2-Nitrophenyl)-3-(*p*-tolyl)benzo[b]thiophene (23)

From 3-(*p*-tolyl)benzothiophene **15** (0.224 g, 1 mmol) and 2-bromonitrobenzene (0.404 g, 2 mmol), **23** was obtained in 70% (0.241 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.50-7.34 (m, 4H), 7.12 (s, 4H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 140.1, 140.0, 137.8, 136.4, 134.3, 133.8, 132.8, 131.4, 130.3, 129.9, 129.7, 129.5, 125.4, 125.1, 124.9, 124.1, 122.7, 21.7.

Elemental analysis: calcd (%) for $C_{21}H_{15}NO_2S$ (345.42): C 73.02, H 4.38; found: C 73.12, H 4.47.

2-(3-(*p*-Tolyl)benzo[b]thiophen-2-yl)benzonitrile (24)

From 3-(*p*-tolyl)benzothiophene **15** (0.224 g, 1 mmol) and 2-bromobenzonitrile (0.364 g, 2 mmol), **24** was obtained in 72% (0.234 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.45-7.36 (m, 3H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 139.4, 138.2, 137.1, 136.8, 133.9, 133.2, 132.2, 132.1, 131.0, 130.1, 129.0, 128.2, 125.0, 124.5, 123.7, 122.1, 117.6, 113.7, 21.1.

Elemental analysis: calcd (%) for $C_{22}H_{15}NS$ (325.43): C 81.20, H 4.65; found: C 81.24, H 4.87.

4-(3-(*p*-Tolyl)benzo[b]thiophen-2-yl)pyridine (25)

From 3-(*p*-tolyl)benzothiophene **15** (0.224 g, 1 mmol) and 4-bromopyridine (0.316 g, 2 mmol), **25** was obtained in 32% (0.096 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (bs, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.25-7.20 (m, 4H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 142.4, 140.7, 138.9, 137.7, 136.0, 135.3, 131.5, 129.8, 129.6, 125.3, 124.6, 123.8, 123.5, 122.1, 21.2.

Elemental analysis: calcd (%) for $C_{20}H_{15}NS$ (301.41): C 79.70, H 5.02; found: C 79.61, H 4.88.

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ACCEPTED MANUSCRIPT

- The reactivity of benzofuran and benzothiophene in C2,C3-diarylation was studied

- A simple one pot access to C2,C3-diarylated benzofuranes is described

- An effective sequential access to C2,C3-diarylated benzothiophene is reported