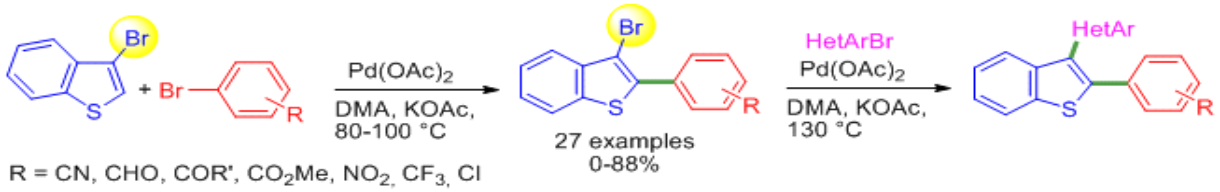
Conditions for the Palladium-Catalysed Direct 2-Arylation of 3-Bromobenzo[b]thiophene Tolerant of the Benzothienyl Carbon-Bromine Bond

Imen Smari, Hamed Ben Ammar, Bechir Ben Hassine, Jean-François Soulé, Henri Doucet

Graphical Abstract



Conditions for Palladium-Catalysed Direct 2-Arylation of 3-Bromobenzothiophene Derivatives Tolerant to the Benzothienyl C-Br bond

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Abstract: Phosphine-free $Pd(OAc)_2$ catalyst was found to promote the direct 2-arylation of 3-bromobenzothiophene without cleavage of the benzothienyl C-Br bond, allowing the synthesis in only one step of 2-aryl-3-bromobenzothiophenes. The best results were generally obtained using a low loading of the palladium catalyst (0.5 mol%), quite low reaction temperatures (80-120°C) and short reaction times (0.5-2h). The reaction proceeds with electron-deficient *para*- *meta*- and *ortho*-substituted aryl bromides and also heteroaryl bromides. The benzothienyl C-Br bond has been profitably employed for further palladium-catalysed functionalizations. This strategy allows straightforward synthesis of 2,3-di(hetero)arylated benzothiophenes with two different (hetero)aryl units *via* sequential catalytic arylations.

Key words: Aryl halides, Catalysis, C–H activation, Benzothiophenes, Palladium.

1. Introduction

The arylation of heteroaromatics such as benzothiophenes for the access to 2-arylbenzothiophene derivatives is an important research field in organic synthesis due to the biological and physical properties of such compounds. For example, Raloxifene is used in the prevention of osteoporosis and breast cancer, and Arzoxifene also exhibits anti-osteoporosis properties (Fig. 1).[1]

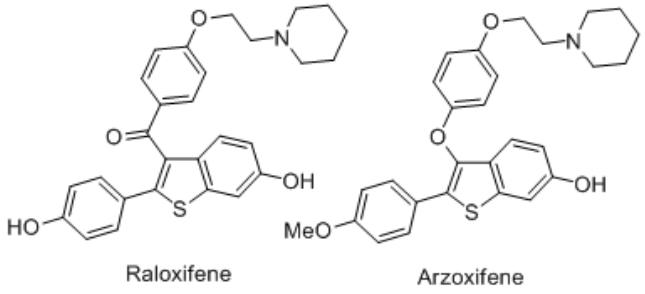
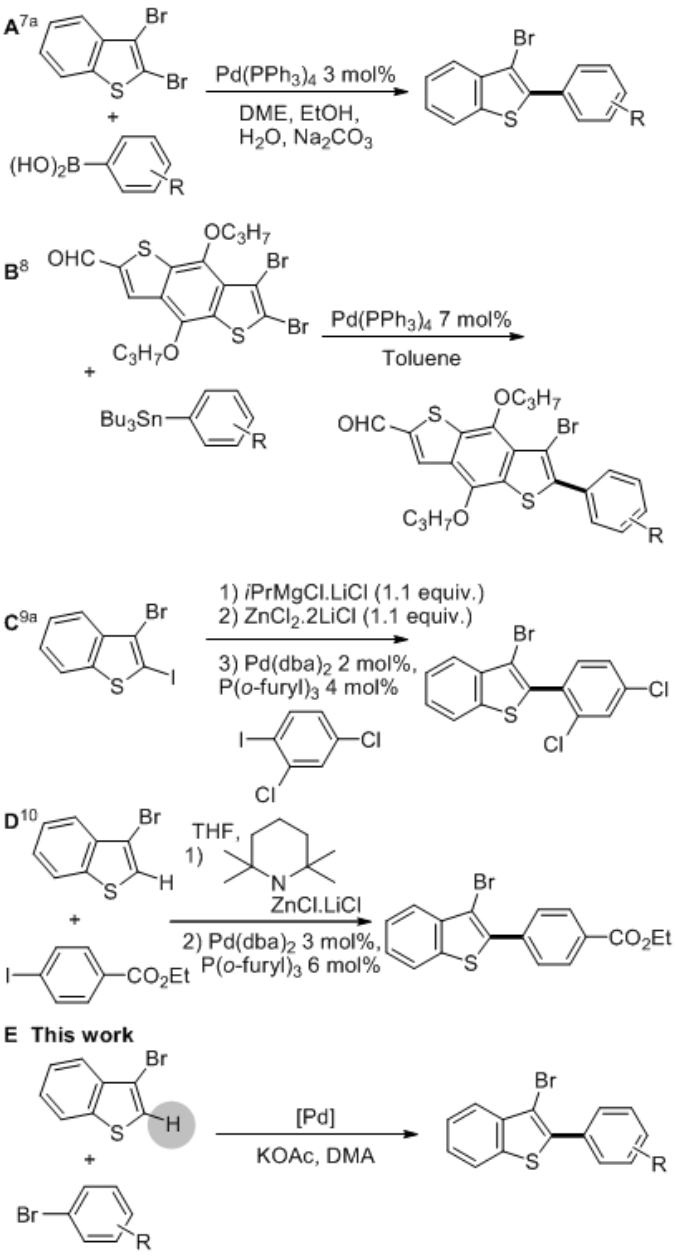


Figure 1 Examples of bioactive 2-arylbenzothiophene derivatives

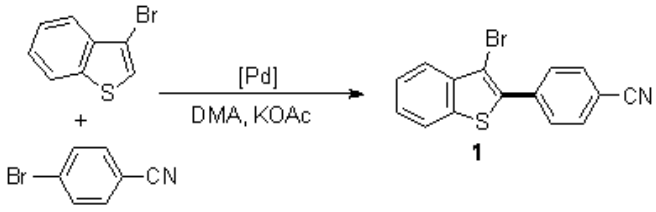
In 1985-1992, Ohta et al. reported the arylation of several heteroarenes such as thiophenes, furans or thiazoles with aryl halides, *via* a C–H bond activation, in moderate to good yields using $Pd(PPh_3)_4$ as the catalyst.[2a,2b] Since these results, the palladium-catalysed direct arylation of heteroaryl derivatives with aryl halides or triflates has proved to be a very effective method for a simpler and "greener" access to arylated heterocycles, due to the reduced number of steps, reduced amount of waste, and to the wider diversity of available compounds.[2,3] Presently, one of the major drawbacks of this reaction is the functional group tolerance. For example, the use of 3-bromobenzothiophenes for direct C2-arylations, without cleavage of the C-Br bond, would be very useful as it would give a simple access to a wide variety of 3-substituted 2-arylbenzothiophenes useful for pharmaceutical applications. To our knowledge, except our preliminary result which was limited to one specific substrate,[4] no example of palladium catalysed direct arylations of 3-bromobenzothiophenes has been described (Fig. 1). So far the 2-aryl-3-bromobenzothiophenes were generally prepared *via* bromination of 2-arylbenzothiophenes using Br_2.[5] The other methods to prepare such compounds employ the classical palladium-catalysed cross-coupling procedures[6] such as Suzuki (Scheme 1, **A**),[7] Stille (Scheme 1, **B**)[8] or Negishi (Scheme 1, **C**)[9] reactions using 2,3-dihalobenzothiophenes (Scheme 1). The Pd-catalysed 2-arylation of 3-bromobenzothiophene with an aryl iodide in the presence of a strong base has also been reported (Scheme 1, **D**).[10] As palladium-catalysed direct arylation of easily available 3-bromobenzothiophene would provide a simpler access to 2-aryl-3-bromobenzothiophenes, we decided to investigate its reactivity for such couplings (Scheme 1, **E**).



Scheme 1. Reported procedures for Pd-catalysed synthesis of 2-aryl-3-bromobenzothiophenes from 3-bromobenzothiophenes

2. Results and discussion

First, we studied the coupling of 3-bromobenzothiophene with 4-bromobenzonitrile using several reaction conditions (Scheme 2, table 1). We have recently reported that the phosphine-free $Pd(OAc)_2$ catalyst reaction conditions allowed the successful coupling of several aryl bromides with simple thiophene derivatives.[11] Employing 1 mol% $Pd(OAc)_2$ as the catalyst and KOAc as the base in DMA (DMA: *N*,*N*-dimethylacetamide) during 20h at 140 °C, we observed the formation of the desired 2-arylated benzothiophene **1** in low yield (Scheme 2, Table 1, entry 1). A similar yield was obtained using $PdCl(C_3H_5)$(dppb) catalyst[12] [dppb: 1,4-bis(diphenylphosphino)butane] (Table 1, entry 2). These low yields are probably due to the quite high reactivity of the benzothienyl C-Br bond in the presence of a palladium catalyst at this elevated temperature. After the oxidative addition of 3-bromobenzothiophene (or of **1**) to palladium, the coupling at C2 of 3-bromobenzothiophene might produce bis-benzothiophene derivatives as side-products. On the other hand, a reaction time reduced to 2h allowed to increase the yield in **1** to 36% with a complete conversion of 4-bromobenzonitrile (Table 1, entry 3). Then, several reactions were performed at 120 °C. The best result was obtained using 1 mol% $Pd(OAc)_2$ catalyst and 0.5h as reaction time (Table 1, entries 4-7). A further decrease of the reaction temperature to 100 °C and 80 °C allowed to increase the yield in **1** to 72% and 87%, respectively (Table 1, entries 8 and 9).



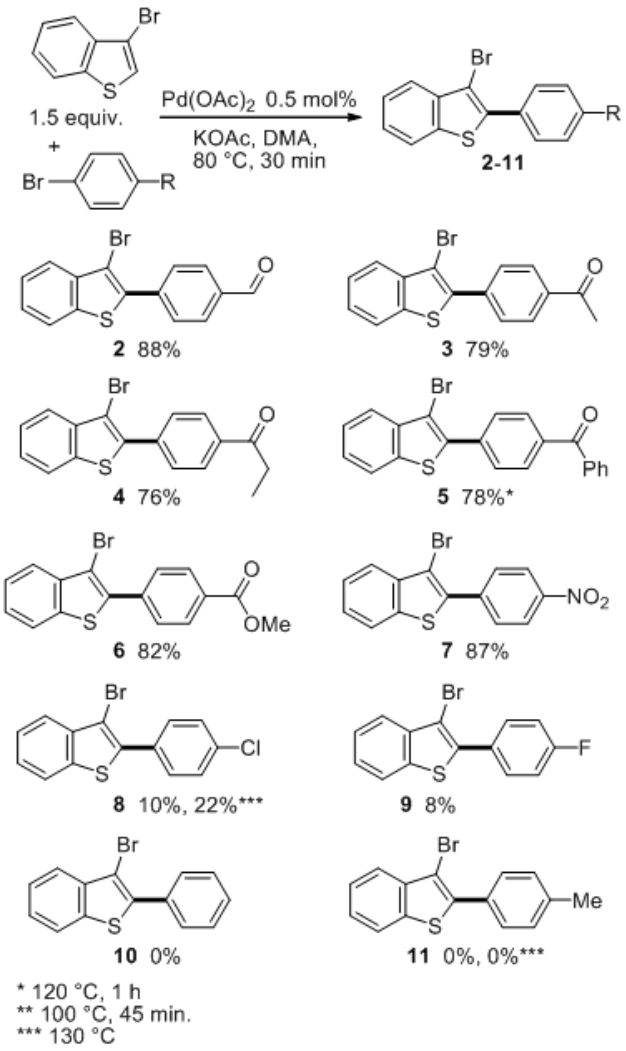
Scheme 2. Influence of the reaction conditions for the coupling of 4-bromobenzonitrile and 3-bromobenzothiophene

Table 1. Influence of the reaction conditions for the coupling of 4-bromobenzonitrile and 3-bromobenzothiophene (Scheme 2)

Entry	Catalyst (mol%)	Temp. (°C)	Time (h)	Conv. (%)	Yield in **1** (%)
1	$Pd(OAc)_2$ (1)	140	20	100	25
2	$PdCl(C_3H_5)$ (dppb) (1)	140	20	100	23
3	$Pd(OAc)_2$ (1)	140	2	100	36
4	$Pd(OAc)_2$ (1)	120	1	100	57
5	$Pd(OAc)_2$ (1)	120	1	100	48[a]
6	$Pd(OAc)_2$ (0.5)	120	1	92	49
7	$Pd(OAc)_2$ (1)	120	0.5	100	62
8	$Pd(OAc)_2$ (1)	100	0.5	100	72
9	$Pd(OAc)_2$ (1)	80	0.5	100	87 (84)

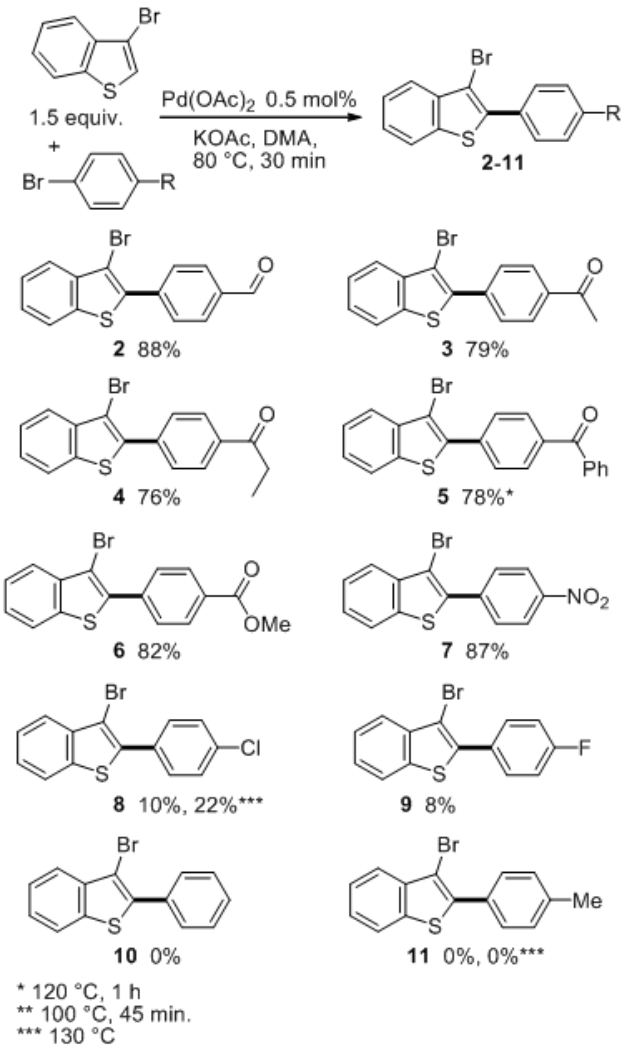
Conditions: 4-bromobenzonitrile (1 mmol), 3-bromobenzothiophene (1.5 mmol), KOAc (2 mmol), DMA, under argon, GC and NMR yields, yields in parentheses is isolated. [a] 4-bromobenzonitrile (1.1 mmol), 3-bromobenzothiophene (1 mmol).

Next, we examined the scope and limitations of this reaction using *para*-, *meta*- or *ortho*-substituted aryl bromides and also heteroaryl bromides (Schemes 3-5). 4-Bromobenzaldehyde, 4-bromoacetophenone, 4-bromopropiophenone, 4-bromobenzophenone and methyl 4-bromobenzoate gave the desired coupling products **2**-**6** in 76-88% yields (Scheme 2, top). 4-Bromonitrobenzene was also a suitable substrate affording **7** in 87% yield. On the other hand, at 80 °C the coupling with 4-bromofluorobenzene and 4-bromochlorobenzene only afforded very low yields in **8** and **9**. The use of higher reaction temperatures (100 and 130 °C) allowed to slightly improve the yield in **8** to 22%. In the presence of bromobenzene or with the electron-rich 4-bromotoluene, no formation of the desired products **10** and **11** was observed even at a higher reaction temperature (Scheme 3, bottom).



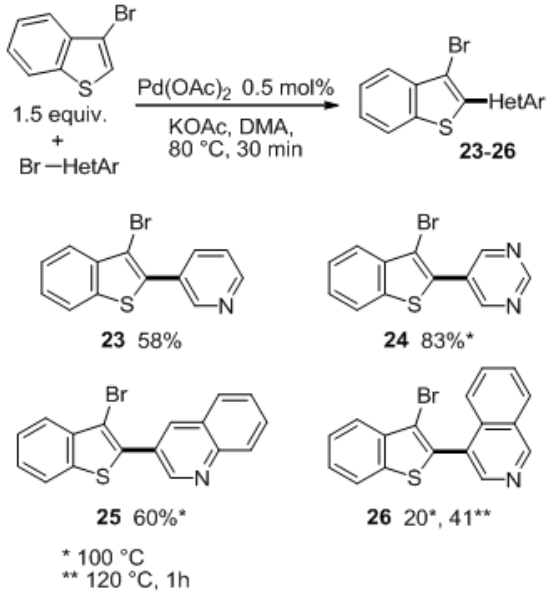
Scheme 3. Scope of the direct 2-arylation of 3-bromobenzothiophene with *para*-substituted aryl bromides

Then, the reactivity of a few *meta*-substituted aryl bromides was investigated (Scheme 4). 3-Bromonitrobenzene, 3-bromobenzonitrile, 3-bromoacetophenone and 3-bromobenzalhedyde also gave the expected 2-arylated benzothiophenes **12**-**15** in 67-83% yields. However, with 3-bromonitrobenzene a longer reaction time had to be employed, as after 0.5 h, only a partial conversion this aryl bromide was observed. From the 3,4-disubstituted aryl bromide, 4-bromo-1-nitro-2-(trifluoromethyl)benzene, the product **17** was also obtained in high yield. Again, fluoro-substituted 3-bromofluorobenzene exhibited a poor reactivity, and **18** was only produced in 12% yield. No significant steric effect was observed in the presence of the sterically demanding aryl bromides, 2-bromobenzaldehyde and 2-bromobenzonitrile, as **19** and **20** were obtained in 80% and 88% yields, respectively. Next, we tried to evaluate the difference of reactivity between mono- and di-*ortho*-substituted aryl bromides, and we were pleased to find that the reaction proceeded efficiently with both 1-bromonaphthalene and 9-bromoanthracene to afford **21** and **22** in 61 and 64% yields, respectively.



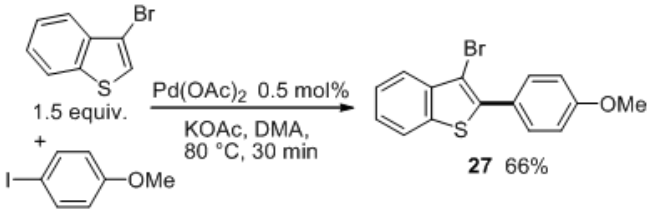
Scheme 4. Scope of the direct 2-arylation of 3-bromobenzothiophene with *meta*- or *ortho*-substituted aryl bromides

Pyridines are probably the most common heterocyclic motif found in pharmaceutically active compounds.[13] Therefore, preparative methods of biheteroaryl derivatives containing pyridines remain an essential research topic in organic synthesis.[14] 3-Bromopyridine and 5-bromopyrimidine were also found to react nicely with 3-bromobenzothiophene to give the coupling products **23** and **24** in high yields (Scheme 5). 3-Bromoquinoline also affords the desired product **25** in good yield. Due to a lower reactivity of 4-bromoquinoline, the coupling reaction was performed at 120 °C during 1h to give **26** in 41% yield. At 100 °C, a lower yield of 20% was obtained.



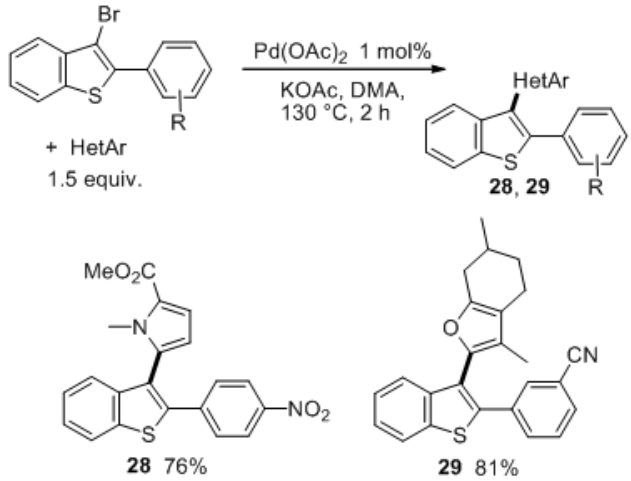
Scheme 5. Scope of the direct 2-arylation of 3-bromobenzothiophene with heteroaryl bromides

In the presence of electron-rich aryl bromides such as 4-bromotoluene, disappointing results had been obtained due to complete decomposition of the reagents (see scheme 2). As the oxidative addition of aryl iodides to palladium generally requires lower reaction temperatures than aryl bromides; the reactivity of 4-iodoanisole was examined. At 80 °C, this aryl iodide nicely reacts with 3-bromobenzothiophene to afford the desired product **27** in 66% yield (Scheme 6).



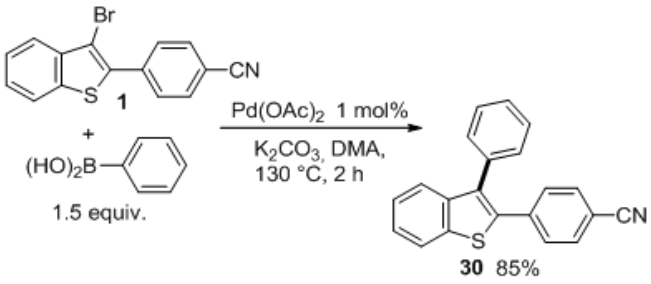
Scheme 6. Scope of the direct 2-arylation of 3-bromobenzothiophene

Then, in order to demonstrate the synthetic potential of the 2-aryl-3-bromobenzothiophenes, we investigated the reactivity of **7** and **13** in Pd-catalysed direct arylations using pyrrole and furan derivatives as the coupling partners (Scheme 7). The expected compounds **28** and **29** were obtained in 76% and 81% yields using 1 mol% $Pd(OAc)_2$ catalyst at 130 °C. No significant influence of the aryl substituents of the 2-aryl-3-bromobenzothiophenes was observed.



Scheme 7. Pd-catalysed direct arylations of 2-aryl-3-bromobenzothiophenes

In order to further demonstrate the potential of 2-aryl-3-bromobenzothiophenes, a Suzuki coupling reaction[6,7] between 4-(3-bromobenzo[b]thiophen-2-yl)benzonitrile **1** and benzeneboronic acid was performed. At 130 °C, the reaction proceeds nicely to afford **30** in 85% yield.



Scheme 8. Suzuki coupling with a 2-aryl-3-bromobenzothiophene

3. Conclusion

In summary, we have demonstrated that using appropriate reaction conditions, a variety of aryl halides can be successfully coupled with 3-bromobenzothiophene *via* a palladium catalysed direct arylation without cleavage of the benzothienyl C-Br bond. Using as little as 0.5 mol% of $Pd(OAc)_2$ as the catalyst precursor at 80-130 °C, the direct 2-arylation of 3-bromobenzothiophene generally proceeds in high yields with aryl bromides that possess electron withdrawing groups such as cyano, nitro, propionyl, ester, acetyl, formyl, benzoyl or trifluoromethyl. Satisfactory results were also obtained using heteroaryl bromides. With 3-bromobenzothiophene, moderate reaction temperatures are mandatory to avoid unwanted oligomerization processes. This procedure which employs a quite low loading of an air-stable commercially available catalyst and an inexpensive base is economically and environmentally attractive. The major by-products are AcOH/KBr instead of metallic salts with more classical cross-coupling procedures such as Suzuki, Stille or Negishi reactions. Moreover, no preparation of an organometallic derivative is required, reducing the number of steps and consequently the amount of waste to prepare these compounds.

Experimental Section

General Remarks: All reactions were run under argon in Schlenk tubes using vacuum lines. DMA analytical grade was not distilled before use. Potassium acetate (99+) were used. Commercial aryl bromides and 3-bromobenzothiophene were used without purification. ^1H and ^{13}C spectrum were recorded with Bruker 400 MHz spectrometer in $CDCl_3$ solutions. Chemical shift are reported in ppm relative to $CDCl_3$ (7.25 for ^1H NMR and 77.0 for ^{13}C NMR). Flash chromatography were performed on silica gel (230-400 mesh).

General procedure

As a typical experiment, the reaction of the aryl bromide (1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) at 80-130 °C (see tables or schemes) during 0.5-2h (see tables or schemes) in DMA (4 mL) in the presence of $Pd(OAc)_2$ (see tables or schemes) under argon affords the corresponding product after evaporation of the solvent and filtration on silica gel (pentane:ether 1:2 except for **7**, **12** and **23-26** 1:10).

4-(3-Bromobenzo[b]thiophen-2-yl)benzonitrile (1)[15]

4-Bromobenzonitrile (0.182 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **1** in 84% (0.264 g) isolated yield as a white solid (mp: 92-94 °C).

^1H NMR (400 MHz, $CDCl_3$): δ 7.93-7.87 (m, 3H), 7.85 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.52 (t, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H).

4-(3-Bromobenzothiophen-2-yl)benzaldehyde (2)

4-Bromobenzaldehyde (0.185 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **2** in 88% (0.279 g) isolated yield as a white solid (mp: 118-122 °C).

^1H NMR (400 MHz, $CDCl_3$): δ 10.08 (s, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.95 (d, J = 8.2 Hz, 2H), 7.94-7.87 (m, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 139.1, 137.9, 136.5, 135.9, 130.2, 129.8, 126.1, 125.5, 124.0, 122.2, 106.4.

elemental analysis: calcd (%) for $C_{15}H_9BrOS$ (317.20): C 56.80, H 2.86; found: C 56.98, H 2.87.

1-(4-(3-Bromobenzothiophen-2-yl)phenyl)ethanone (3)

4-Bromoacetophenone (0.199 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80°C during 0.5h affords the product **3** in 79% (0.261 g) isolated yield as a white solid (mp: 97-100 °C).

^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.2 Hz, 2H), 7.96-7.80 (m, 4H), 7.49 (t, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 2.66 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 139.1, 137.8, 137.7, 136.8, 136.7, 129.8, 128.5, 126.0, 125.5, 123.9, 122.2, 106.1, 26.7.

elemental analysis: calcd (%) for $C_{16}H_{11}BrOS$ (331.23): C 58.02, H 3.35; found: C 58.22, H 3.47.

1-(4-(3-Bromobenzo[b]thiophen-2-yl)phenyl)propan-1-one (4)

4-Bromopropiophenone (0.213 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **4** in 76% (0.262 g) isolated yield as a white solid (mp: 130-133 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.2 Hz, 2H), 7.92-7.80 (m, 4H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 3.06 (t, *J* = 7.6 Hz, 2H), 1.27 (q, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 139.1, 137.8, 137.5, 136.9, 136.6, 129.8, 128.2, 125.9, 125.4, 123.9, 122.2, 106.0, 31.9, 8.2.

elemental analysis: calcd (%) for $C_{17}H_{13}BrOS$ (345.25): C 59.14, H 3.80; found: C 59.34, H 4.04.

(4-(3-Bromobenzothiophen-2-yl)phenyl)(phenyl)methanone (5)

4-Bromobenzophenone (0.261 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 120 °C during 1h affords the product **5** in 78% (0.306 g) isolated yield as a yellow solid (mp: 111-114 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.80 (m, 8H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.55-7.46 (m, 3H), 7.43 (t, *J* = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 139.1, 137.8, 137.5, 137.4, 137.1, 136.9, 132.6, 130.3, 130.0, 129.5, 128.4, 125.9, 125.5, 123.9, 122.2, 106.1.

elemental analysis: calcd (%) for $C_{21}H_{13}BrOS$ (393.30): C 64.13, H 3.33; found: C 64.29, H 3.27.

Methyl 4-(3-bromobenzo[b]thiophen-2-yl)benzoate (6)

Methyl 4-bromobenzoate (0.215 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **6** in 82% (0.284 g) isolated yield as a yellow solid (mp: 76-80 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.2 Hz, 2H), 7.93-7.80 (m, 4H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 3.96 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 139.1, 137.8, 137.6, 136.9, 130.1, 129.8, 129.6, 125.9, 125.4, 123.9, 122.2, 106.0, 52.3.

elemental analysis: calcd (%) for $C_{16}H_{11}BrO_2S$ (347.23): C 55.34, H 3.19; found: C 55.20, H 3.28.

3-Bromo-2-(4-nitrophenyl)benzothiophene (7)

4-Bromonitrobenzene (0.202 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **7** in 87% (0.291 g) isolated yield as a yellow solid (mp: 150-153 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.2 Hz, 2H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.55-7.35 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 139.6, 139.0, 137.9, 135.3, 130.4, 126.4, 125.7, 124.2, 123.8, 122.3, 107.1.

elemental analysis: calcd (%) for $C_{14}H_8BrNO_2S$ (334.19): C 50.32, H 2.41; found: C 50.17, H 2.50.

3-Bromo-2-(4-chlorophenyl)benzothiophene (8)

4-Bromochlorobenzene (0.192 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 130 °C during 0.5h affords the product **8** in 22% (0.071 g) isolated yield as a white solid (mp: 155-158 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.55-7.35 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 137.6, 136.8, 134.9, 131.5, 130.9, 128.9, 125.7, 125.4, 123.8, 122.2, 105.4.

elemental analysis: calcd (%) for $C_{14}H_8BrClS$ (323.64): C 51.96, H 2.49; found: C 51.78, H 2.60.

3-Bromo-2-(4-fluorophenyl)benzo[b]thiophene (9)

4-Bromofluorobenzene (0.175 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **9** in 8% (0.025 g)

isolated yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.73 (dd, *J* = 8.2, 5.8 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 8.2 Hz, 2H).

3-Bromo-2-(3-nitrophenyl)benzothiophene (12)

3-Bromonitrobenzene (0.202 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 2h affords the product **12** in 83% (0.277 g) isolated yield as a yellow solid (mp: 100-103 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 138.8, 137.8, 135.5, 135.1, 134.8, 129.6, 126.3, 125.7, 124.5, 124.1, 123.4, 122.3, 106.8.

elemental analysis: calcd (%) for $C_{14}H_8BrNO_2S$ (334.19): C 50.32, H 2.41; found: C 50.08, H 2.24.

3-(3-Bromobenzothiophen-2-yl)benzonitrile (13)[7d]

3-Bromobenzonitrile (0.182 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **13** in 69% (0.217 g) isolated yield as a pink solid (mp: 98-102 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H).

1-(3-(3-Bromobenzothiophen-2-yl)phenyl)ethanone (14)

3-Bromoacetophenone (0.199 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **14** in 67% (0.222 g) isolated yield as a pink solid (mp: 118-122 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 2.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 139.0, 137.7, 137.4, 136.9, 134.0, 133.6, 129.6, 129.0, 128.4, 125.8, 125.4, 123.8, 122.2, 105.8, 26.7.

elemental analysis: calcd (%) for $C_{16}H_{11}BrOS$ (331.23): C 58.02, H 3.35; found: C 58.31, H 3.01.

3-(3-Bromobenzo[b]thiophen-2-yl)benzaldehyde (15)

3-Bromobenzaldehyde (0.185 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **15** in 67% (0.212 g) isolated yield as a white solid (mp: 99-102 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.11 (s, 1H), 8.26 (s, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 138.9, 137.7, 136.7, 136.5, 135.3, 134.2, 131.0, 129.6, 129.4, 125.9, 125.5, 123.9, 122.3, 106.0.

elemental analysis: calcd (%) for $C_{15}H_9BrOS$ (317.20): C 56.80, H 2.86; found: C 56.74, H 2.64.

2-(3,5-Bis(trifluoromethyl)phenyl)-3-bromobenzothiophene (16)

From 3,5-bis(trifluoromethyl)bromobenzene (0.293 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **16** in 80% (0.340 g) isolated yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 2H), 7.93 (s, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 137.8, 135.3, 134.4, 132.3 (q, *J* = 33.0 Hz), 129.7, 126.5, 125.8, 124.3, 123.1 (q, *J* = 272.6 Hz), 122.3, 122.2, 107.3.

elemental analysis: calcd (%) for $C_{16}H_7BrF_6S$ (425.19): C 45.20, H 1.66; found: C 45.00, H 1.51.

3-Bromo-2-(4-nitro-3-(trifluoromethyl)phenyl)benzothiophene (17)

4-Bromo-1-nitro-2-(trifluoromethyl)benzene (0.270 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **17** in 83% (0.333 g) isolated yield as a yellow solid (mp: 97-99 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 138.9, 138.3, 138.0, 133.8, 133.7, 129.0 (q, *J* = 5.4 Hz), 126.9, 126.0, 125.7, 124.5, 124.4 (q, *J* = 34.2 Hz), 122.5, 121.6 (q, *J* = 273.9 Hz), 108.1.

elemental analysis: calcd (%) for $C_{15}H_7BrF_3NO_2S$ (402.19): C 44.80, H 1.75; found: C 45.07, H 1.81.

3-Bromo-2-(3-fluorophenyl)benzothiophene (18)

3-Bromofluorobenzene (0.175 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **18** in 12% (0.037 g) isolated yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.55-7.38 (m, 5H), 7.13 (t, *J* = 7.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (d, *J* = 247.0 Hz), 158.0, 139.1, 137.7, 130.1 (d, *J* = 8.3 Hz), 125.8, 125.4 (m), 123.8, 122.2, 116.6 (d, *J* = 23.0 Hz), 115.7 (d, *J* = 21.2 Hz), 105.6.

elemental analysis: calcd (%) for $C_{14}H_8BrFS$ (307.18): C 54.74, H 2.63; found: C 54.70, H 2.89.

2-(3-Bromobenzo[b]thiophen-2-yl)benzaldehyde (19)

2-Bromobenzaldehyde (0.185 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **19** in 80% (0.254 g) isolated yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.57-7.52 (m, 2H), 7.45 (t, *J* = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 138.5, 138.0, 136.1, 134.5, 133.9, 133.6, 132.0, 129.7, 127.8, 126.1, 125.7, 123.7, 122.2, 109.8.

elemental analysis: calcd (%) for $C_{15}H_9BrOS$ (317.20): C 56.80, H 2.86; found: C 56.89, H 2.94.

2-(3-Bromobenzo[b]thiophen-2-yl)benzonitrile (20)[4]

2-Bromobenzonitrile (0.182 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 2h affords the product **20** in 88% (0.276 g) isolated yield as a white solid (mp: 161-163 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H).

3-Bromo-2-(naphthalen-1-yl)benzo[b]thiophene (21)

1-Bromonaphthalene (0.207, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 120 °C during 1h affords the product **21** in 61% (0.207 g) isolated yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.64-7.43 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 138.3, 136.9, 133.5, 131.8, 130.5, 129.7, 129.3, 128.4, 126.7, 126.2, 126.0, 125.5, 125.3, 125.1, 123.5, 122.2, 108.5.

elemental analysis: calcd (%) for $C_{18}H_{11}BrS$ (339.25): C 63.73, H 3.27; found: C 63.80, H 3.51.

2-(Anthracen-9-yl)-3-bromobenzothiophene (22)

9-Bromoanthracene (0.257, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **22** in 64% (0.249 g) isolated yield as a yellow solid (mp: 105-108 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 8.2 Hz, 1H), 8.46 (s, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.55-7.45 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 138.1, 132.2, 131.7, 130.6, 129.4, 128.6, 127.6, 127.2, 126.3, 125.6, 125.4, 124.0, 122.3, 122.2, 110.8.

elemental analysis: calcd (%) for $C_{22}H_{13}BrS$ (389.31): C 67.87, H 3.37; found: C 67.99, H 3.50.

3-(3-Bromobenzo[b]thiophen-2-yl)pyridine (23)

3-Bromopyridine (0.158 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **23** in 58% (0.168 g) isolated yield as a yellow solid (mp: 119-122 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (bs, 1H), 8.69 (bs, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.50-7.43 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 149.6, 139.0, 138.0, 137.1, 134.3, 126.1, 125.7, 124.0, 122.4, 106.7.

elemental analysis: calcd (%) for $C_{13}H_8BrSN$ (290.18): C 53.81, H 2.78; found: C 53.70, H 2.99.

5-(3-Bromobenzothiophen-2-yl)pyrimidine (24)

5-Bromopyrimidine (0.159 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 100 °C during 0.5h affords the product **24** in 83% (0.241 g) isolated yield as a white solid (mp: 136-140 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (s, 1H), 9.15 (s, 2H), 7.91 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 156.7, 138.7, 138.1, 130.4, 127.5, 126.5, 125.8, 124.2, 122.4, 107.8.

elemental analysis: calcd (%) for $C_{12}H_7BrN_2S$ (291.17): C 49.50, H 2.42; found: C 49.75, H 2.51.

3-(3-Bromobenzothiophen-2-yl)quinoline (25)

3-Bromoquinoline (0.208 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 100 °C during 0.5h affords the product **25** in 60% (0.204 g) isolated yield as a pink solid (mp: 81-84 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (s, 1H), 8.53 (d, J = 1.8 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.5 Hz, 2H), 7.87 (d, J = 8.5 Hz, 1H), 7.80 (t, J = 8.0 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 147.2, 138.9, 138.0, 136.8, 134.4, 130.5, 129.2, 128.2, 127.5, 126.6, 126.0, 125.6, 123.9, 122.3, 106.8.

elemental analysis: calcd (%) for $C_{17}H_{10}BrNS$ (340.24): C 60.01, H 2.96; found: C 60.24, H 3.09.

4-(3-Bromobenzo[b]thiophen-2-yl)isoquinoline (26)

4-Bromoisoquinoline (0.208 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 120 °C during 1h affords the product **26** in 41% (0.139 g) isolated yield as a yellow solid (mp: 90-93 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (s, 1H), 8.65 (s, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.79 (t, J = 8.0 Hz, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5, 143.2, 138.8, 138.2, 134.9, 132.4, 132.0, 128.4, 128.2, 126.1, 125.6, 125.2, 123.7, 122.3, 109.9.

elemental analysis: calcd (%) for $C_{17}H_{10}BrNS$ (340.24): C 60.01, H 2.96; found: C 60.17, H 3.11.

3-Bromo-2-(4-methoxyphenyl)benzo[b]thiophene (27)[15]

4-Iodoanisole (0.234 g, 1 mmol), 3-bromobenzothiophene (0.320 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) in DMA at 80 °C during 0.5h affords the product **27** in 66% (0.211 g) isolated yield as a yellow solid (mp: 78-82 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.47 (t, J = 7.7 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.01 (d, J = 8.2 Hz, 2H), 3.88 (s, 3H).

Methyl 1-methyl-5-(2-(4-nitrophenyl)benzo[b]thiophen-3-yl)-pyrrole-2-carboxylate (28)

3-Bromo-2-(4-nitrophenyl)benzothiophene **7** (0.334 g, 1 mmol), methyl 1-methylpyrrole-2-carboxylate (0.208 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) at 130 ° during 2h in DMA (4 mL) in the presence of $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) under argon affords the corresponding product **28** after evaporation of the solvent and filtration on silica gel (pentane:ether 1:10) in 76% (0.298 g) yield as a yellow solid (mp: 72-75 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.2 Hz, 2H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.50-7.35 (m, 4H), 7.12 (d, *J* = 4.0 Hz, 1H), 6.27 (d, *J* = 4.0 Hz, 1H), 3.86 (s, 3H), 3.48 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 141.6, 139.1, 130.9, 130.1, 129.7, 128.9, 125.4, 124.8, 123.9, 123.8, 123.7, 122.2, 118.5, 117.2, 111.6, 51.2, 34.0.

elemental analysis: calcd (%) for $C_{21}H_{16}N_2O_4S$ (392.43): C 64.27, H 4.11; found: C 64.30, H 4.12.

3-(3-(3,6-Dimethyl-4,5,6,7-tetrahydrobenzofuran-2-yl)benzo[b]thiophen-2-yl)benzonitrile (29)

3-(3-Bromobenzothiophen-2-yl)benzonitrile **13** (0.314 g, 1 mmol), menthofuran (0.225 g, 1.5 mmol) and KOAc (0.196 g, 2 mmol) at 130 °C during 2h in DMA (4 mL) in the presence of $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) under argon affords the corresponding product **29** after evaporation of the solvent and filtration on silica gel (pentane:ether 1:2) in 81% (0.310 g) yield as a white solid (mp: 156-159 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90-7.82 (m, 1H), 7.78-7.73 (m, 1H), 7.65-7.60 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.48-7.36 (m, 3H), 2.75-2.65 (m, 1H), 2.40-2.10 (m, 3H), 2.17 (s, 3H), 2.00-1.70 (m, 2H), 1.50-1.20 (m, 1H), 1.12 (d, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 140.9, 140.2, 138.5, 138.4, 136.2, 132.9, 132.1, 131.0, 129.3, 125.2, 124.9, 124.3, 122.1, 119.0, 118.9, 118.5, 112.7, 31.5, 31.2, 29.6, 21.5, 20.1, 8.8.

elemental analysis: calcd (%) for $C_{25}H_{21}NOS$ (383.51): C 78.30, H 5.52; found: C 78.25, H 5.68.

4-(3-Phenylbenzo[b]thiophen-2-yl)benzonitrile (30)

The reaction of 4-(3-bromobenzo[b]thiophen-2-yl)benzonitrile **1** (0.314 g, 1 mmol), phenylboronic acid (0.183 g, 1.5 mmol) and K_2CO_3 (0.276 g, 2 mmol) at 130 °C during 2h in DMA (4 mL) in the presence of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) under argon affords the corresponding product **30** after evaporation of the solvent and filtration on silica gel (pentane:ether 1:2) in 85% (0.264 g) isolated yield as a white solid (mp: 200-204 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.48-7.28 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 139.1, 139.0, 136.9, 135.3, 134.8, 132.1, 130.2, 130.0, 129.0, 128.0, 125.4, 124.8, 123.8, 122.2, 118.6, 111.1.

elemental analysis: calcd (%) for $C_{21}H_{13}NS$ (311.40): C 81.00, H 4.21; found: C 80.69, H 4.01.

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